OMEROS

OMEROS CORPORATION

CLINICAL PROTOCOL

PROTOCOL NO. OMS721-TMA-001
Amendment 11.1

EUDRACT Number: 2014-001032-11

Investigational New Drug
OMS721

PHASE2

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

01 **June** 2020

APPROVED BY:

[redacted]

[redacted]
Date

1.1. Investigator Agreement

I have read Omeros Protocol No. OMS721-TMA-001 Amendment 11.1 and agree to conduct the study, as described in this protocol, and provide the necessary assurances that this study will be conducted according to the stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and International Conference on Harmonisation (ICH) guidelines.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1.2. Contact Information

Sponsor Medical Monitor

PSI Medical Monitor

Novotech Medical Monitor

1.3. Amendments

Amendment	Date	Abbreviated Summary of Change
01	21 Mar 2014	• Added text that if Grade 3 or higher adverse events occur in any patient in a cohort, then safety information will be provided to the United States Food and Drug Administration 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
02	31 Mar 2014	• The safety data will be reviewed by a clinical study monitoring team • Added text that adverse events of Grade 3 or higher will be reviewed carefully with respect to number and causality when determining if dose escalation is appropriate • Added text on how dose selection will occur for Stage 2 • Added text to provide stopping rules for the study
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.
04	16 Apr 2014	• Section 7.4 was amended to remove the limitation on the stopping rule to "treatment-related" adverse events and now includes all adverse events
05	21 Nov 2014	• Inclusion criteria No. 4 was amended to clarify and re-define hematopoietic stem cell transplant-associated thrombotic microangiopathy and refractory thrombotic thrombocytopenic criteria • Exclusion criteria No. 5 was amended to change the upper limit of resting heart rate from 100 to 115 beats per minute • Exclusion criteria 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 criteria No. 14 was added to include hypersensitivity to product constituents • The early termination criteria were amended to remove the requirement to discontinue patients who have received a prohibited concomitant therapy
06	04 Feb 2015	• Changed refractory thrombotic thrombocytopenic purpura to thrombotic thrombocytopenic purpura and added biopsy-diagnosed post-renal transplant thrombotic microangiopathy • Removed the time requirement in atypical hemolytic uremic syndrome screening inclusion criteria • Added thrombotic thrombocytopenic purpura inclusion criteria for platelet count and microangiopathic hemolysis • Removed inclusion criteria pertaining to failure to attain a treatment response • Added screening criteria of mycobacterial or significant fungal infection
07	26 Mar 2015	• Removed post-renal transplant as a patient population • Added Standard of Care treatment regimen • [redacted]

Amendment	Date	Abbreviated Summa1·y of Change
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- • 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 atypical hemolytic uremic syndrome patients from 4 weeks to 12 weeks • Added detection of AEs that occur at an incidence of at least 7.5% in the separate coho1is • Removed text around stopping rnles and added periodic review by Data Monitoring Committee
09	20Apr 2017	• [redacted] Note: Amendment 09 was not implemented
	12 Oct 2018	• Closed enrollment of thrombotic thrombocytopenic pwpura and atypical hemolytic uremic syndrome patients • Changed the dose to 370 mg IV weekly x 4 for HSCT-TMA patients • Added Amendment Summa1y of Changes • Updated the nonclinical experience and rationale for selection of dose • Updated patient enrollment nwnbers for ongoing clinical studies
11.1	28May 2020	• Provided for collection of additional data for patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy • Changed the primary and secondary objectives to focus on hematopoietic stem cell transplant-associated thrombotic microangiopathy • Defined criteria by which to detennine clinical response to treatment • Changed all reference to individuals with disease from "subject" to "patient" Note: Amendment 11 was signed but not submitted when an e1TOr in the secondaiy objectives was discovered and removed in Amendment 11.1
11.1	01 Jun 2020	• Removed "renal function in patients who had renal dysfunction at baseline" from the seconda1y objectives as this was not intended to be included in Amendment 11

2. SYNOPSIS

Name of Sponsor/Company: Omeros Corporation	
Name of Investigational Product: OMS721	
Name of Active Ingredient: OMS721 (MASP-2 monoclonal antibody)	
Protocol Number: OMS721-TMA-001	
Title of Study: 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	
Planned Number of Clinical Study Center(s): [redacted]	
Expected Duration of Study: Approximately 48 months (first patient visit to last patient visit)	**Phase of Development:** Phase 2

Objectives:

The purpose of this Phase 2 study is to evaluate the safety, efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of OMS721 in patients with thrombotic microangiopathies (TMA). As of Protocol Amendment 11, the primary and secondary endpoints are modified to provide for evaluation of response in patients with hematopoietic stem cell transplant (HSCT)-associated TMA.

The co-primary objectives of this study are to:

- Assess the safety and tolerability of multiple-dose administration of OMS721 in patients with TMA (this will be assessed in patients with HSCT-TMA as well as in patients with atypical hemolytic uremic syndrome [aHUS] or thrombotic thrombocytopenic purpura [TTP])
- Evaluate the efficacy of OMS721 in patients with HSCT-TMA by response defined as:
  - Improvement in TMA laboratory markers of platelet count and lactate dehydrogenase (LDH), and
  - Improvement in clinical status

Methodology:

This is a Phase 2, uncontrolled, 3-stage, ascending-dose-escalation study in patients with 1 of 3 forms of TMA: aHUS, TTP, or HSCT-TMA.

In Stage 1 of the study, OMS721 was administered to 3 cohorts (Cohorts 1, 2, and 3), with dose escalation by cohort to identify the optimal dosing regimen. After enrollment and treatment of each cohort, there was a safety review to determine whether dose escalation should proceed. In Stage 2, the dose selected in the first stage was administered to expanded cohorts initially planned to be 40 patients per cohort with distinct etiologies (aHUS alone in 1 cohort, and TTP or HSCT-TMA in the other cohort). As of Amendment 10 of this protocol, enrollment of aHUS and TTP patients was closed. As of Amendment 11 of this protocol,

enrollment in the study has been completed. Patients completing Stage 2 may be eligible for continued treatment in Stage 3 if they have tolerated OMS721 treatment and derived clinical benefit.

OMS721 is to be used in conjunction with standard of care treatments. Standard of care treatments are not to be delayed or withheld from patients entering this study. These treatments should be initiated according to local standard of care. For example, plasma exchange should not be delayed while waiting for initiation of OMS721 treatment if local standard of care is to administer plasma exchange.

OMS721 will be administered by intravenous (IV) infusion. The cohorts and treatments are provided below.

For patients with HSCT-TMA enrolled under Amendment 10 or earlier versions of this protocol, additional data will be collected. These data will include supplemental data on patient demographics and baseline conditions, donor characteristics, the transplant procedure, concomitant medications, TMA-related laboratory measures, transfusions, transplant complications, and outcomes. These data will be derived 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) following the first dose of OMS721, whichever comes first. These data were requested by regulatory authorities because patients who have undergone HSCT typically have complicated post-transplant courses, and these additional data will provide the needed information to draft patient narratives, including the full patient profile, and allow for better understanding of OMS721 response and outcomes.

As of Amendment 11, enrollment in the study has been completed, and the additional data will be collected until a predetermined data cutoff date for those patients who have not reached 2 years after first OMS721 dose.

Cohort (Number)	Stage	Treatment
1 (N = 3)	1	OMS721 Dose 0.675 mg/kg IV weekly x 4
2 (N = 3)	1	OMS721 Dose 2.0 mg/kg IV weekly x 4
3 (N = 3)	1	OMS721 Dose 4.0 mg/kg IV weekly x 4
4 (N = 40 aHUS) As of Amendment 10, Cohort 4 is closed	2	OMS721 Dose 4.0 mg/kg IV weekly x 12
4 (N ≤ 40 aHUS) As of Amendment 10, Cohort 4 is closed	3	OMS721 Dose 4.0 mg/kg IV weekly x 12
5 (N = 40 TTP or HSCT-TMA) As of Amendment 10, TTP enrollment is closed	2	OMS721 Dose 4.0 mg/kg IV weekly x 4 As of Amendment 10, the dose is changed to 370 mg IV weekly x 4
5 (N ≤ 40 TTP or HSCT-TMA) As of Amendment 10, TTP enrollment is closed	3	OMS721 Dose 4.0 mg/kg IV weekly x 4 As of Amendment 10, the dose is changed to 370 mg IV weekly x 4

Abbreviations: aHUS = atypical hemolytic uremic syndrome; HSCT-TMA = hematopoietic stem cell transplant-associated thrombotic microangiopathy; IV = intravenous; TTP = thrombotic thrombocytopenic purpura.

The **Stage 1** study schedule included 9 visits across 3 periods. Stage 1 is complete.

Period 1 – Screening (Visit 1, up to 4 weeks)

Period 2 – Treatment (Visit 2 to Visit 5, 4 weeks)

Period 3 – Follow-up (Visit 6 to Visit 9, 8 weeks)

The length of time for individual patient participation was approximately 12 to 16 weeks.

The **Stage 2** study schedule for the **aHUS** cohort (Cohort 4) included 17 visits across 3 periods:

Period 1 – Screening (Visit 1, up to 4 weeks)

Period 2 – Treatment (Visit T-1 to Visit T-12, 12 weeks)

Period 3 (if patient did not continue to Stage 3) – Follow-up (Visit F-1 to Visit F-4, 6 weeks)

The length of time for individual aHUS patient participation in Stage 2 was approximately 18 to 22 weeks, depending on the time from screening to the first dose of OMS721 administration. Patients entering Stage 3 did not undergo the follow-up visits in Stage 2. The **Stage 3** study schedule for the **aHUS** cohort included 16 visits across 2 periods.

Period 2 (continued from Stage 2) – Treatment (Visit T-13 to Visit T-24, 12 weeks)

Period 3 – Follow-up (Visit F-1 to Visit F-4, 6 weeks)

The length of time for individual aHUS patient participation in Stage 3 was approximately 18 weeks, and the total length of time in Stage 2 and Stage 3 was approximately 30 to 34 weeks, depending on the time from screening to the first dose of OMS721 administration in Period 2.

As of Amendment 10 of this protocol, Cohort 4 was closed. As of Amendment 11 of this protocol, enrollment in the study has been completed.

The **Stage 2** study schedule for the **TTP/HSCT-TMA** cohort (Cohort 5) includes 9 visits across 3 periods:

Period 1 – Screening (Visit 1, up to 4 weeks)

Period 2 – Treatment (Visit T-1 to Visit T-4, 4 weeks)

Period 3 (if patient does not continue to Stage 3) – Follow-up (Visit F-1 to Visit F-4, 10 weeks)

The length of time for individual TTP/HSCT-TMA patient participation in Stage 2 (if he or she does not continue to Stage 3) will be approximately 14 to 18 weeks, depending on the time from screening to the first dose of OMS721 administration. Patients entering Stage 3 will not undergo the Follow-up visits in Stage 2.

The **Stage 3** study schedule for the **TTP/HSCT-TMA** cohort includes 8 visits across 2 periods:

Period 2 (continued from Stage 2) – Treatment (Visit T-5 to Visit T-8, 4 weeks)

Period 3 – Follow-up (Visit F-1 to Visit F-4, 6 weeks)

The length of time for individual TTP/HSCT-TMA patient participation in Stage 3 will be approximately 10 weeks, and the total length of time in Stage 2 and Stage 3 will be

approximately 14 to18 weeks, depending on the time from screening to the first dose of OMS721 administration in Period 2.

As of Amendment 10 of this protocol, TTP enrollment was closed. As of Amendment 11 of this protocol, enrollment in the study has been completed.

The coronavirus associated lockdown situation in various countries has created uncertainty in the ability to collect all follow-up data and resolve all queries on a few patients enrolled in the study. When adequate data on the primary and secondary endpoints is available, the database will be locked for interim analyses and creation of an interim CSR to enable regulatory submission for drug approval. Efforts will continue to collect additional follow-up data and resolve any outstanding queries.

Number of Patients (Planned):

Approximately 60

Diagnostic Criteria and Main Criteria for Inclusion:

Patients may be included in the study only if they meet all of the following criteria:

1. Competent to provide informed consent.
2. 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 study.
3. Are age ≥ 18 at screening (Visit 1).
4. Have a diagnosis of one of the following TMAs:
    - As of Amendment 10 of this protocol, enrollment of aHUS patients was closed. Primary aHUS, diagnosed clinically and having ADAMTS13 activity > 10% in plasma. Patients are eligible with or without a documented complement mutation or anti-complement factor H (anti-CFH) antibody. Patients are categorized according to their response to plasma therapy (plasma exchange or plasma infusion):
        - Plasma therapy-resistant aHUS patients must have all of the following: 1) screening platelet count < 150,000/μL despite at least 4 plasma therapy treatments prior to screening; 2) evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > upper limit of normal [ULN], haptoglobin < lower limit of normal [LLN]); and 3) serum creatinine > ULN.
        - Chronic plasma therapy-responsive aHUS patients (plasma therapy-sensitive) must require at least once-per-week plasma therapy for 4 weeks before first dose of OMS721 with serum creatinine > ULN.
    - As of Amendment 10 of this protocol, enrollment of TTP patients was closed. TTP defined as having all of the following:
        - Platelet count < 150,000/μL
        - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < LLN)

    - ADAMTS13 activity ≤ 10% during the current episode of TTP or historically
  - Persistent HSCT-associated TMA 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/μL
    - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < LLN)
    - Renal dysfunction (doubling of serum creatinine from pre-transplant).
5. No clinically apparent alternative explanation for thrombocytopenia and anemia.
6. If sexually active and of childbearing potential, must agree to practice a highly effective method of birth control until the end of the study, defined as one which 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, or vasectomized partner.

Exclusion Criteria:

Patients will be excluded from the study for any of the following reasons:

1. Had eculizumab therapy within 3 months prior to screening.
2. Have Shiga toxin-producing *Escherichia* coli-associated hemolytic uremic syndrome.
3. Have a positive direct Coombs test.
4. Have an active systemic bacterial or fungal infection requiring antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed).
5. Baseline resting hea1t rate< 45 beats per minute or> 115 beats per minute.
6. Baseline QTcF > 470 milliseconds.
7. Have malignant hype1tension (diastolic blood pressure> 120 1Ilill Hg with bilateral hemonhages or "cotton-wool" exudates on funduscopic examination).
8. Have a poor prognosis with a life expectancy of less than 3 months in the opinion of the Investigator.
9. Are pregnant or lactating.
10. Have received treatment with an investigational dmg or device within 4 weeks prior to screemng.
11. Have abno1mal liver ftmction tests defined as alanine aminotransferase or aspaitate aminotransferase> 5 times ULN.
12. Have a positive test for human immunodeficiency vims antibodies.
13. Are an employee of Omeros, an Investigator, a study staff member, or their illllllediate family member.
14. Have a known hypersensitivity to any constituent of the product.
15. Presence of any condition that the Investigator believes would put the patient at risk.

Duration of Treatment:

Stage I -Four weekly doses. As of Amendment 11 of this protocol, Stage 1 is complete.
Stage 2-Twelve weekly doses for aHUS. As of Amendment 10 of this protocol, aHUS emollment was closed.

Stage 2 – Four weekly doses for TTP/HSCT-TMA. As of Amendment 10 of this protocol, TTP enrollment was closed.

Stage 3 – Additional 12 weekly doses for aHUS. As of Amendment 10 of this protocol, aHUS enrollment was closed.

Stage 3 – Additional 4 weekly doses for TTP/HSCT-TMA. As of Amendment 10 of this protocol, TTP enrollment was closed.

As of Amendment 11 of this protocol, enrollment in the study has been completed.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable

Study Endpoints:

The co-primary endpoints are:

- Safety as assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and clinical laboratory tests (includes patients with HSCT-TMA, aHUS, and TTP)
- For HSCT-TMA patients, response to OMS721 treatment. A responder is defined as a patient with HSCT-TMA who demonstrates improvement in laboratory TMA markers (platelet count and LDH) and clinical benefit (either improvement in organ function or reduction in transfusion burden). The specific criteria are defined as follows:
  - Improvement in laboratory TMA markers:
    - Platelet count:
      - For patients with baseline platelet count ≤ 20,000/μL:
        - Tripling of baseline platelet count

          and
        - Post baseline platelet count > 30,000/μL

          and
        - No platelet transfusions 2 days before and on the day of the platelet count collection
      - For patients with baseline platelet count > 20,000/μL
        - Increase in platelet count ≥ 50%

          and
        - Post baseline platelet count > 75,000/μL

          and
        - No platelet transfusions 2 days before and on the day of the platelet count collection

    and

- LDH:
  - LDH < 1.5 x ULN

and

– Improvement in clinical status:

- Improvement in organ function as evidenced by any of the following:
  - Improvement in renal function:
    - Reduction of creatinine > 40%

      or
    - Creatinine < ULN and reduction of creatinine > 20%

      or
    - Discontinuation of renal replacement therapy (RRT)

  or

  - Improvement in pulmonary function:
    - Extubation and discontinuation of ventilator support

      or
    - Discontinuation of non-invasive mechanical ventilation (continuous positive pressure ventilation)

  or

  - Improvement in neurological function:
    - Improvement in reversible neurological conditions (e.g., cessation of seizures)

      or
    - Stabilization of irreversible neurological conditions (e.g., stability of neurological deficits following stroke without further deterioration or subsequent strokes)

  or

  - Improvement in gastrointestinal function (gastrointestinal HSCT-TMA will require diagnosis by tissue biopsy):
    - Improvement measured by improvement in the gastrointestinal measures in the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria

or

- Freedom from transfusion (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 OMS721 dose date)

The secondary endpoints of this study are to evaluate the following in patients with HSCT-TMA treated with OMS721:

- 100-day survival, from the date of TMA diagnosis
- Overall survival, from the date of TMA diagnosis
- Duration of response defined as the number of days from the first response date to the first relapse date
- 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 within the 2 weeks prior to or on the first OMS721 dose date)
- Freedom from red blood cell (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 within the 2 weeks prior to or on the first OMS721 dose date)
- Change from baseline in platelet count (post baseline platelet counts without platelet transfusions 2 days before and on the day of the platelet count collection will be 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 (Hgb) (post baseline Hgb without RBC and whole blood transfusions 6 days before and on the day of the Hgb collection will be used) over time using central laboratory values
- Change from baseline in creatinine over time using central laboratory values
- The PK of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The PD of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The immunogenicity of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)

Statistical Methods:

Sample Size

In Stage 1 of the study, 3 patients per dose-escalation cohort is a common scheme and is considered to be sufficient in combination with data from the Phase 1 study to allow selection of a dose for Stage 2.

In Stage 2, the sample size for each cohort (aHUS and HSCT-associated TMA/TTP) is 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 [Legendre 2013]. This sample size is considered adequate in these orphan diseases to identify treatment effects in uncontrolled studies.

It is expected that approximately 28 HSCT-TMA patients enrolled before Protocol Amendment 11 will be included to support a regulatory approval. The width of the exact 95% confidence interval (CI) for the response rate based on 28 HSCT-TMA patients ranges from 12.3% to 38.7%. If the observed response rate is 50%, the exact 95% CI is 30.6% to 69.4%.

Efficacy

A patient is a responder if this patient meets the responder criteria at any time post baseline during the study. Analysis of the primary efficacy endpoint will use a non-responder imputation to impute missing or incomplete data to evaluate response. The number and percentage of responders will be summarized with exact 95% CI (Clopper-Pearson) for the Full Analysis Set (FAS) and Per-protocol Analysis Set (PAS) populations. The FAS population will include all HSCT-TMA patients who receive any amount of study drug. The PAS population will include all HSCT-TMA patients who received at least 4 weeks of study treatment (treatment period is greater than or equal to 28 days). Each criteria of the response will also be summarized in the same fashion.

Pharmacokinetic Analyses

Plasma concentrations of OMS721 and PD measures will be provided in listings. These data will be used in integrated population PK/PD analyses across studies. A PK/PD analysis plan will document the analyses.

Anti-Drug Antibody Response

The number and percentage of patients with anti-drug antibody (ADA) will be summarized by disease, dose, Drug Product formulation, and time. Potential effects of ADA on PK and PD will be evaluated in integrated population PK/PD analyses, which will be documented in the PK/PD analysis plan.

Pharmacodynamic Analyses

The PD effect will be assayed *ex vivo* by quantifying lectin pathway activity and summarized by disease, dose, and time.

Pharmacokinetic/Pharmacodynamic Relationship

The correlation of serum concentration of OMS721 and PD effect will be evaluated.

Safety Analyses

All patients who receive any study drug will be included in the safety analyses. The safety data, including AEs, vital signs, laboratory data, and reasons for withdrawal from study, will

be descriptively summarized by disease and dose. Adverse events will be coded according to preferred term and system/organ class using the Medical Dictionary for Regulatory Activities AE coding dictionary.

3. TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	anti-drug antibody
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under time-concentration curve
BIW	twice weekly
BP	blood pressure
BTD	Breakthrough Therapy Designation
C3	Complement component 3
C3a	complement component 3a
C5a	complement component 5a
C5b-9	complement components 5b-9, also known as the membrane attack complex
CFH	complement factor H
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAH	diffuse alveolar hemorrhage
DMC	Data Monitoring Committee
ECG	electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVHD	graft-versus-host disease
Hgb	hemoglobin
HIPAA	Health Insurance and Portability and Accountability Act
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
HUS	hemolytic uremic syndrome
ICH	International Conference on Harmonisation
IgAN	immunoglobulin A nephropathy
IgG4	immunoglobulin G4
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
IV	intravenous
λz	elimination rate constant
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MASP	mannan-binding lectin-associated serine protease
MBL	mannan-binding lectin
MedRA	Medical Dictionary for Regulatory Activities
nM	nanomolar
NOAEL	no observed adverse effect level
OS	overall survival
PAS	Per-protocol Patient Set
PD	pharmacodynamic
PK	pharmacokinetic
QW	once weekly
RBC	red blood cell
RR	respiratory rate
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	System Organ Class
STEC	Shiga toxin-producing E. coli
$t_{½}$	elimination half-life
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
VOD	veno-occlusive disease

5. INTRODUCTION

5.1. Background

This study was originally designed to provide preliminary information on the safety and potential efficacy of OMS721 for the treatment of thrombotic microangiopathies (TMAs). As originally designed, this study included 3 types of TMA—hematopoietic stem cell transplant-associated TMA (HSCT-TMA), atypical hemolytic uremic syndrome (aHUS), and thrombotic thrombocytopenic purpura (TTP)—and included 2 stages: a dose-escalation stage and a cohort expansion stage. A separate Phase 3 study has been initiated for patients with aHUS (Study OMS721-HUS-002); therefore, patients with aHUS are no longer being enrolled in Study OMS721-TMA-001. Patients with TTP are also no longer being enrolled in this study because it was difficult to observe a treatment effect over the current standard of care.

Improvements in laboratory TMA markers have been observed in patients with HSCT-TMA in this ongoing study, and marked unexpected improvements were observed in some patients with life-threatening disease. In support of an application for Breakthrough Therapy Designation (BTD) from the United States Food and Drug Administration (FDA), Omeros Corporation (Omeros, Sponsor) compared survival in OMS721-treated patients with a literature-based historical control. A substantial survival improvement was observed, and BTD was granted by FDA for the treatment of patients with HSCT-TMA who have persistent TMA despite modification of immunosuppressive therapy. The Sponsor has had continued discussions with regulatory agencies internationally regarding approval of OMS721 for the treatment of HSCT-TMA. These discussions have focused on approval based on patients with HSCT-TMA treated in this study as well as patients with HSCT-TMA treated under compassionate use or expanded-access protocols. Efficacy will be assessed by response to treatment evaluated by organ function or transfusion burden and laboratory measures of TMA.

Amendment 11 of this protocol provides for collection of additional data for OMS721-treated patients with HSCT-TMA to determine patient responses and longer-term outcomes and to support marketing authorization applications. The additional data to be collected are limited to patient demographics and baseline conditions, donor characteristics, the transplant procedure, concomitant medications, TMA-related laboratory measures, transfusions, transplant complications, and outcomes (see Section 19.4 for additional detail).

5.1.1. Description of OMS721

Omeros Corporation (Omeros, Sponsor) is developing OMS721, a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) to mannan-binding lectin-associated serine protease 2 (MASP-2), for the treatment of lectin complement pathway-mediated diseases.

The primary function of the complement system is to protect the host against infectious agents [Ricklin 2010]. This complex system targets immune and inflammatory responses to surfaces that display molecular patterns not usually present on healthy host cells. Activation of the complement system initiates a series of proteolytic steps that culminate in the formation of a membrane attack complex, which disrupts the membranes of targeted cells causing lysis and cell death. In addition, complement activation triggers opsonization and the recruitment of phagocytic cells to further engage the infectious agents.

Three pathways activate complement in response to distinct initiating events: the classical, lectin, and alternative pathways. The classical pathway is triggered by immune complexes and mediates important immune effector functions. The lectin pathway can be activated by specific types of cell-surface carbohydrate patterns that are usually found on microbes, but not on healthy host cell surfaces. These carbohydrate patterns are also found on injured host tissue. Lectin pathway activation is initiated by members of the MASP enzyme family. These proteases are synthesized as proenzymes that, in blood, form a complex with lectins, such as mannan-binding lectin (MBL), ficolins, and collectins. These lectins bind to carbohydrate patterns on foreign or injured host cell surfaces, targeting MASPs to their site(s) of action and leading to activation of MASPs. There are 3 known MASPs: MASP-1, MASP-2, and MASP-3 [Yongqing 2012]. MASP-2 is thought to be the key enzyme responsible for activation of the lectin pathway; upon activation, it cleaves its substrates, complement component 2 and complement component 4, both of which contribute to the formation of the complement component 3 (C3) convertase, which is a central component of complement activation.

OMS721 blocks the action of MASP-2, thereby inhibiting the lectin pathway of complement activation. The alternative pathway, by contrast, is continuously activated at a low level and is kept in check by a series of regulatory proteins. The alternative pathway also acts as an amplification loop, increasing the host immune response following activation of the classical and/or the lectin pathways. While the complement system supports innate host defense against pathogens, mutations in the genome or tissue damage can cause inappropriate activation and lead to serious disease, e.g., TMA, in which endothelial damage as well as fibrin and platelet-rich thrombi in the microvasculature lead to end-organ damage.

OMS721 is a fully human IgG4 mAb directed against MASP-2. OMS721 avidly binds to recombinant MASP-2 (apparent equilibrium dissociation constant approximately 100 picomolar) and exhibits greater than 5000-fold selectivity over the homologous proteins complement component 1s, complement component 1r, and MASP-1. In functional assays, OMS721 inhibits the human lectin pathway with nanomolar (nM) potency (concentration leading to 50% inhibition of approximately 3 nM) but has no significant effect on the classical or alternative complement pathways. OMS721 administered either by intravenous (IV) or subcutaneous (SC) injection to mice, non-human primates, and humans resulted in high plasma concentrations that were associated with suppression of lectin pathway activation in an *ex vivo* assay. OMS721 treatment reduced complement components 5b-9 (C5b-9, also known as the membrane attack complex) deposition and thrombus formation in *in vitro* models of TMA and inhibited thrombus formation in a mouse model of TMA, thus demonstrating that OMS721 is a potential candidate for the treatment of diseases that result from inappropriate lectin pathway activation.

5.1.2. Indication – Thrombotic Microangiopathies

Based on mechanism of action and results of nonclinical studies, OMS721 is in development for the treatment of TMA and other diseases potentially mediated by the lectin pathway of complement. Thrombotic microangiopathy is a descriptive name for histologic abnormalities consisting of thickening of arteriole and capillary walls with endothelial damage, subendothelial accumulation of protein and debris, and fibrin and platelet-rich thrombi occluding vessel lumina. The disorders that are associated with TMA are characterized by systemic or intrarenal aggregation of platelets, thrombocytopenia, and mechanical injury to erythrocytes.

Thrombotic microangiopathies may present as a primary condition or in association with other diseases. The classification scheme for TMA has evolved as the etiology and pathophysiology of distinct patient populations have been established [Besbas 2006]. Thrombotic microangiopathies can present with several clinical presentations, including TTP, aHUS, HSCT-TMA, and TMA caused by cancer chemotherapy, calcineurin inhibitor administration, and systemic lupus erythematosus.

5.1.2.1. Atypical Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) occurs primarily in children following a diarrheal illness and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. A major category of TMA is Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome (STEC-HUS), which has also been referred to as diarrhea + HUS or typical HUS. Another type of HUS is atypical HUS (aHUS), which is a recurrent illness often associated with complement dysregulation.

Atypical HUS is a rare, life-threatening disease that, if left untreated, results in end-stage renal disease in 50% of patients within 1 year of diagnosis [Loirat 2011]. Dysregulation of the complement system is central to aHUS pathogenesis, and genetic abnormalities in complement genes have been identified in more than 60% of all aHUS patients. Certain mutant variants of the genes encoding complement factor H, factor I, factor B, and C3 have been identified as major risk factors; these alleles lead to increased complement activity. This complement hyperactivity is linked, by a mechanism that is not well understood, to a procoagulant phenotype on kidney endothelial cells that promotes the formation of microthrombi in the renal microvasculature and results in rapidly declining renal function in about half of affected individuals. Familial studies have shown that aHUS has incomplete penetrance and that approximately 50% of the carriers of the high-risk alleles develop the condition [Sullivan 2010]. It is thought that certain precipitating factors are needed to trigger aHUS. Such precipitating factors include infection, malignancies, use of endothelium-damaging drugs, transplantation, and pregnancy. Many of these precipitating factors are linked to endothelial cell activation, stress, or injury. Atypical HUS is treated with plasma therapy (plasma exchange or plasma infusion) or eculizumab, an anti-C5 mAb.

5.1.2.2. Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura was initially described as a syndrome that occurs primarily in adults characterized by a pentad of signs and symptoms consisting of thrombocytopenia, microangiopathic hemolytic anemia, neurologic and renal abnormalities, and fever. Thrombotic thrombocytopenic purpura is characterized by a severe deficiency of the von Willebrand factor-cleaving protease termed ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

In practice, the clinical distinction between TTP and HUS is not always clear [Moake 2002]. Thrombotic thrombocytopenic purpura has many of the same clinical and laboratory features as aHUS but is associated with low ADAMTS13 activity (≤ 5% to 10% of normal depending on the assay) due to genetic mutations or autoantibodies to the protein [George 2006]. It is typically associated with lower platelet counts, which can be severe. Plasma exchange is the standard treatment for TTP, with some patients requiring the addition of corticosteroids and/or rituximab to achieve an adequate response.

5.1.2.3. Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy

Hematopoietic stem cell transplant-associated TMA is a serious multisystem disease affecting post-transplant outcomes [Jodele 2015]. The kidney is the most commonly affected organ, but the disease also occurs in the lung, central nervous system, gastrointestinal tract, and serosal tissues. The reported incidence of HSCT-TMA varies in retrospective and pathological reviews, but a prospective study of 100 pediatric patients found an incidence of 39%, 79% of which had features portending a poor prognosis [Jodele 2014a]. A recent large retrospective chart review of adult patients also reported an incidence of 39% [Postalcioglu 2018].

Hematopoietic stem cell transplantation induces substantial endothelial injury [Vion 2015]. This injury results from toxic conditioning regimes, immunosuppressive drugs, infections, and graft-versus-host disease (GVHD) [Khosla 2017]. This endothelial injury is believed to contribute to many serious post-HSCT complications, including veno-occlusive disease (VOD) (also known as sinusoidal obstructive syndrome), GVHD, capillary leak syndrome, diffuse alveolar hemorrhage (DAH), and TMA [Akil 2015, Carreras 2011, Khosla 2017, Vion 2015]. Preconditioning endothelial health and the degree of post-transplant endothelial injury measured by serum biomarkers are associated with both the development and severity of post-transplant complications [Cooke 2008, Dietrich 2013, Gloude 2017, Lindas 2014]. Suppression of tumorigenicity-2, a marker of endothelial injury, has been demonstrated to correlate with the risk of GVHD, TMA, and death following HSCT [Abu Zaid 2017, Rotz 2017a, Vander Lugt 2013]. The association of TMA and steroid-refractory GVHD has also been observed clinically and linked to endothelial injury [Rotz 2017a, Zeisbrich 2017]. Thus, TMA appears to be one manifestation of endothelial cell injury associated with HSCT. Limiting endothelial injury would be expected to reduce the severity of related clinical syndromes, such as TMA, as well as other complications related to endothelial cell injury.

Endothelial injury activates the lectin pathway of complement on the endothelial cell surface [Collard 2000]. Complement activation induces formation of complement component 3a (C3a) and complement component 5a (C5a). Preclinically, C3a and C5a have induced endothelial activation associated with endothelial injury and pro-inflammatory changes, leukocyte recruitment, and endothelial apoptosis [Mahajan 2016, Wu 2016, Zhang 2010]. Complement activation further leads to formation of C5b-9 on the cell surface. While membrane-bound, it can cause cell lysis. Even when sublytic, C5b-9 causes additional cell injury that induces secretion of prothrombotic factors, platelet activation, upregulation of adhesion molecules, and dysfunctional morphological changes in the endothelium [Kerr 2012]. These complement-mediated activities may amplify endothelial injury and dysfunction, causing or worsening clinical conditions.

Complement activation has been demonstrated in HSCT-TMA and GVHD [Cherry 2015, Rotz 2017b]. Eculizumab, a C5 inhibitor, has been reported to improve survival in patients with HSCT-TMA having features portending a poor prognosis [Bohl 2017, de Fontbrune 2015, Jodele 2014b]. Inhibition of the lectin pathway could limit endothelial cell injury by inhibiting both C3a and C5a, without increasing infection risk associated with classical pathway inhibition.

There are no approved products indicated for the treatment of HSCT-TMA. First-line management of HSCT-TMA includes modification or cessation of any immunosuppressive regimen, appropriate treatment of infections and/or GVHD if present, aggressive control of hypertension, and other supportive therapy as deemed appropriate by the treating physician

[Khosla 2017]. Plasma therapy is thought to have no utility in this patient population [Khosla 2017, Rosenthal 2016]. Patients who do not respond to modification of their immunosuppression have a poor prognosis. Adult m01iality has been repo1ted to be as high as 100% (4 out of 4 patients, all of whom died within 69 days from diagnosis) [Worel 2007]. In a larger and more recent series, only 17% of adult patients (4 out of 24) who unde1went immunosuppression modification and received treatment with plasmapheresis, defibrotide, or rituximab survived 1 year [Bohl 2017]. Eculizumab has been repo1ied to treat HSCT-TMA effectively with a 90% response rate when used off-label in 1 adult study; however, there was a high rate of infection-related m01iality following eculizumab treatment [Bohl 2017]. These data demonstrate that HSCT-TMA is a life-threatening condition and, with the lack of effective treatment options, represents a significant l1lllnet medical need.

5.1.3. Scientific Rationale

The lectin pathway acts as an innate immune sensor of tissue injmy and has a dominant role in activating complement in settings of endothelial cell stress or injmy [Collard 1999]. Therefore, the lectin pathway likely plays a key role in initiating and pe1petuating complement activation in TMA, and inhibition of the lectin pathway may address both TMA and complement-mediated organ injmy related to TMA.

The role ofMASP-2 activity in promoting TMA following endothelial injmy has been conoborated in experimental animal models. Intravital microscopy studies have shown that, while lipopolysaccharide-induced microvascular injmy leads to extensive microvascular coagulation in the affected blood vessel of wild-type mice, these microthrombi are completely absent in MASP-2-deficient mice [Manuel DN et al unpublished obse1vation]. Moreover, treatment of no1mal mice with OMS721 reduced microthrombi fo1mation compared to isotype controls in a fluorescein isothiocyanate-labeled dextran photo-activation model [described in the Investigator's Brochure, **Section 4.1.2.1].** Also, *in vitro* studies have demonstrated that OMS721 inhibits C5b-9 deposition or thrombus fo1mation on endothelial cells activated with human sera from patients having aHUS in both the active and remission states.

[redacted]

6. STUDY PURPOSE AND OBJECTIVES

The pmpose of this Phase 2 study is to evaluate the safety, efficacy, PK, PD, and immunogenicity of OMS721 in patients with TMA. As of Amendment 11 of this study protocol, the prima1y and seconda1y endpoints are modified to provide for evaluation of response in patients with HSCT-associated TMA.

6.1. Primary Study Objectives

The co-prima1y objectives of this study are to:

- Assess the safety and tolerability of multiple-dose administration of OMS721 in patients with TMA (this will be assessed in patients with HSCT-TMA as well as in patients with aHUS or TTP)
- Evaluate the efficacy of OMS721 in patients with HSCT-TMA by response defined as:
  - Improvement in TMA laborat01y markers of platelet count and lactate dehydrogenase (LDH), and
  - Improvement in clinical status

6.2. Secondary Study Objectives

The secondary objectives of this study are to evaluate the following in patients with HSCT-TMA treated with OMS721:

- Duration of response
- 100-day survival
- Overall survival (OS)
- Platelet count change from baseline
- Lactate dehydrogenase change from baseline
- Haptoglobin change from baseline
- Hemoglobin (Hgb) change from baseline
- 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 OMS721 dose
- Freedom from red blood cell (RBC) transfusion in patients who received at least 1 RBC transfusion within 2 weeks of the first OMS721 dose
- The PK of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The PD of multiple-dose administration of OMS721(this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The immunogenicity of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)

6.3. Exploratory Objectives

The exploratory objectives of this study are to:

- Assess the effect of baseline circulating MBL levels on PK and PD measures
- Assess the effect of baseline circulating MASP-2 levels on PK and PD measures
- Describe the effect of OMS721 on TMA laboratory markers in patients with aHUS and TTP

7. STUDY DESIGN AND PROCEDURES

7.1. Summary of Study Design

This is a Phase 2, uncontrolled, three-stage, ascending-dose-escalation study in patients with TMA: aHUS, TTP, or HSCT-TMA. As originally designed, the primary outcomes to be measured were safety and clinical activity. The secondary outcomes to be measured were PK,

PD, and immunogenicity (i.e., presence of ADA response). Amendment 10 discontinued enrollment of patients with aHUS and TTP. Amendment 11 provides for collection of additional data from patients with HSCT-TMA, changes the primary and secondary objectives to focus on HSCT-TMA, and defines criteria by which to determine clinical response to treatment. Amendment 11 also provides for collection of PK and PD measures for analysis within integrated population PK and PD analyses across different studies.

OMS721 is to be used in conjunction with standard of care treatments. Standard of care treatments are not to be delayed or withheld from patients entering this study. These treatments should be initiated according to local standard of care. For example, plasma exchange should not be delayed while waiting for initiation of OMS721 treatment if local standard of care is to administer plasma exchange.

In Stage 1 of the study, OMS721 was administered to 3 cohorts (Cohort 1, Cohort 2, and Cohort 3), with dose escalation by cohorts to identify the optimal dosing regimen. After enrollment and treatment of each cohort, there was a safety review to determine whether dose escalation should proceed. In Stage 2, the dose selected in the first stage was administered to expanded cohorts initially planned to be 40 patients per cohort with distinct etiologies (aHUS alone in 1 cohort and TTP or HSCT-TMA in the other cohort). As of Amendment 10 of this protocol, enrollment of aHUS and TTP patients was closed. As of Amendment 11 of this protocol, enrollment in the study has been completed.

Each patient in Stage 1 received 4 weekly doses of OMS721. Prior to Amendment 10, patients in Stage 2 with aHUS received 12 weekly doses, and patients with TTP or HSCT-TMA received 4 weekly doses. Patients in Stage 2 who demonstrate improvement in TMA signs during their initial treatment period may be eligible for Stage 3, which provides continued treatment under this protocol. Patients in the aHUS cohort were eligible for an additional 12 weekly doses. Patients in the HSCT-TMA cohort may be eligible for an additional 4 weekly doses. The patient's treating Investigator and the Sponsor's medical monitor will determine eligibility for Stage 3 based upon the patient's response to therapy, safety, and tolerability prior to the last scheduled treatment visit in Stage 2 in order to determine the appropriate PK draws following that visit. (Note: patients entering Stage 3 will not undergo the Stage 2 follow-up visits.) Follow-up visits are planned to allow adequate time for ADA assessment and/or at least 6 weeks of follow-up after the last dose to allow adequate time for OMS721 elimination, whichever is longer. As of Amendment 10 of this protocol, enrollment of aHUS and TTP patients was closed. As of Amendment 11 of this protocol, enrollment in the study has been completed.

Different treatment durations for the different cohorts in Stage 2 and Stage 3 are provided because the natural history and response to treatment of each disease state is different. For example, plasma therapy for acute episodes of TTP typically is stopped when remission is achieved. Relapses occur, but generally not immediately. Also, HSCT-TMA often resolves within a few weeks of calcineurin inhibitor modification. These diseases could be effectively treated with relatively short-term treatment. On the other hand, treatment for aHUS is often chronic, and relapses are common following discontinuation of treatment. Therefore, the treatment duration for the TTP/HSCT-TMA cohort is shorter than the treatment duration of the aHUS cohort.

OMS721 will be administered by IV infusion. The planned enrollment is up to approximately 60 patients overall. The stages, cohorts, and treatments are provided in Table 1.

Table 1: OMS721-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

Abbreviations: aHUS = atypical hemolytic uremic syndrome; HSCT-TMA = hematopoietic stem cell transplant-thrombotic microangiopathy; IV = intravenous.

[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.

As of Amendment 11 of this protocol, enrollment in the study has been completed.

For patients with HSCT-TMA enrolled under Amendment 10 or earlier versions of this protocol, additional data will be collected. Notification and consent of patients (or legal representatives for deceased patients) for this additional data collection are being collected according to local rules and regulations.

These additional data are outlined in this amendment in Section 19.4. These data will include supplemental data on patient demographics and baseline conditions, donor characteristics, the transplant procedure, concomitant medications, TMA-related laboratory measures, transfusions, transplant complications, and outcomes. These data will be derived 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 OMS721 dose, whichever is earlier. These data were requested by regulatory authorities because patients who have undergone HSCT typically have complicated post-transplant courses, and these additional data will allow for better understanding of OMS721 response and outcomes. As of Amendment 11, enrollment in the study has been completed, and the additional data will be collected until a predetermined data cutoff date for those patients who have not reached 2 years after first OMS721 dose.

7.1.1. Stage 1

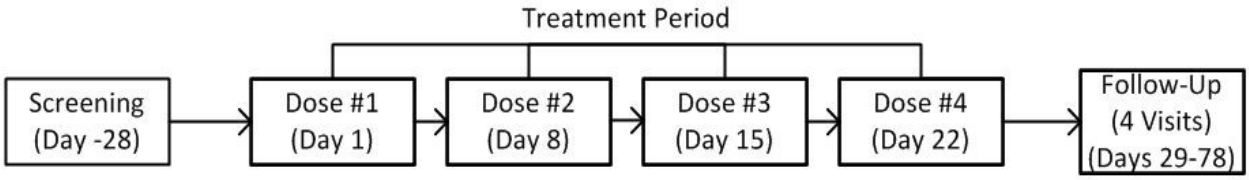
In Stage 1, eligible patients were enrolled to sequential cohorts without regard to etiology of TMA. Dose escalation was guided by safety monitoring through at least 1 week after the last patient in the cohort had completed treatment. It may have been necessary to change the number of cohorts and dose levels based on emerging PK and PD data, which would have been

implemented by a protocol amendment. The safety, PK, and PD data from the first stage were reviewed to set the dose for the second stage.

As of Amendment 11 of this protocol, Stage 1 is complete.

The Stage 1 study design is illustrated in Figure 1.

Figure 1: Stage 1 Study Design Schematic



The Stage 1 study schedule includes 9 visits across 3 periods:

Period 1 – Screening (Visit 1, up to 4 weeks)

Period 2 – Treatment (Visit 2 to Visit 5, 4 weeks)

Period 3 – Follow-up (Visit 6 to Visit 9, 8 weeks)

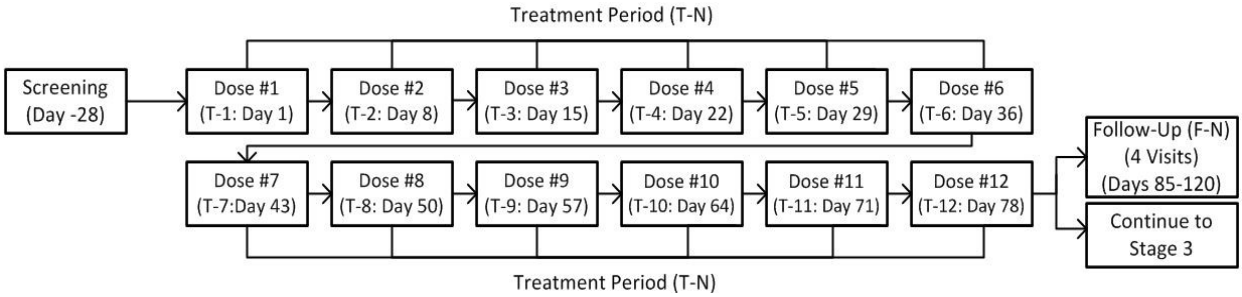
The length of time for individual patient participation in Stage 1 was approximately 12 to 16 weeks, depending on the time from screening to the first dose of OMS721 administration.

7.1.2. Stage 2 and Stage 3

aHUS Cohort

The Stage 2 and Stage 3 study designs are illustrated in Figure 2 and Figure 3 for the aHUS cohorts. As of Amendment 10 of this protocol, enrollment of aHUS patients was closed.

Figure 2: Stage 2 Study Design Schematic (aHUS Cohort)



The Stage 2 study schedule for the aHUS cohort (Cohort 4) includes 17 visits across 3 periods:

Period 1 – Screening (Visit 1, up to 4 weeks)

Period 2 – Treatment (Visit T-1 to Visit T-12, 12 weeks)

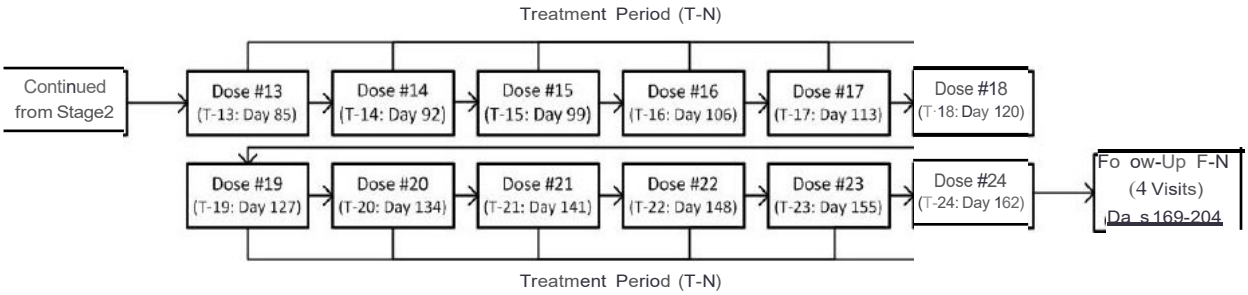
Period 3 (if patient does not continue to Stage 3) – Follow-up (Visit F-1 to Visit F-4, 6 weeks)

The length of time for individual aHUS patient participation in Stage 2 (if he or she did not continue to Stage 3) was approximately 18 to 22 weeks, depending on the time from screening to

the first dose of OMS721 administration. Follow-up visits for patients who did not continue to Stage 3 occurred on Day 85, Day 92, Day 106, and Day 120.

Patients with aHUS who completed Stage 2 treatment may have been eligible for an additional 12 weeks of treatment if the Investigator believed the patient was at risk for relapse of TMA, the patient tolerated OMS721 treatment, and the patient had no conditions that increase the risk of OMS721 treatment (e.g., serious active infection). The patient's treating Investigator and the Sponsor's medical monitor determined eligibility for Stage 3 based upon the patient's response to therapy and safety and tolerability prior to the last scheduled treatment visit in Stage 2 in order to dete1mine the appropriate PK draws following that visit. Patients entering Stage 3 did not undergo the Follow-up visits in Stage 2.

Figure 3: Stage 3 Study Design Schematic (aHUS Cohort)



The **Stage 3** study schedule for the aHUS cohort (Coho1t 4) includes 16 visits across 2 periods:

Period 2 (continued from Stage 2)-Treatment (Visit T-13 to Visit T-24, 12 weeks)

Period 3 - Follow-up (Visit F-1 to Visit F-4, 6 weeks)

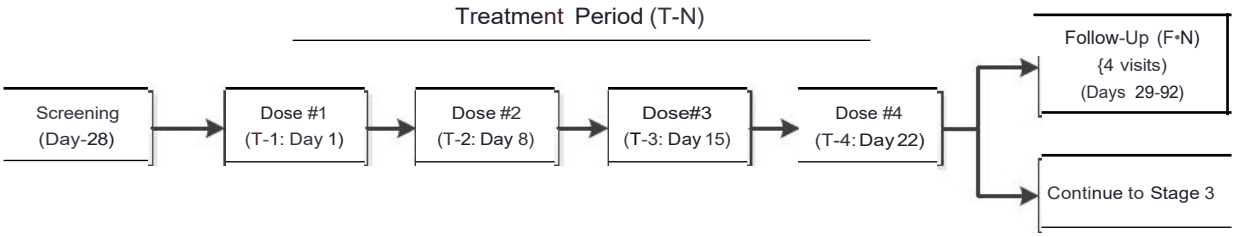
The length of time for individual aHUS patient paiticipation in Stage 3 was approximately 18 weeks and the total length of time in Stage 2 and Stage 3 was approximately 30 to 34 weeks. Follow-up visits occuned on Day 169, Day 176, Day 190, and Day 204.

The overall study was planned to take approximately 48 months to complete (from first patient visit to last patient visit).

TTP/HSCT-TMA Cohort

The Stage 2 and Stage 3 study designs are illustrated in Figure 4 and Figure 5 for the HSCT-TMA coho1t. As of Amendment 10 of this protocol, enrollment of TTP patients was closed. As of Amendment 11 of this protocol, enrollment in the study has been completed.

Figure 4: Stage 2 Study Design Schematic (HSCT-TMA Cohort)



The **Stage 2** study schedule for the HSCT-TMA coho1t (Coho1t 5) includes 4 doses with up to 9 visits across 3 periods:

Period 1- Screening (Visit 1, up to 4 weeks)

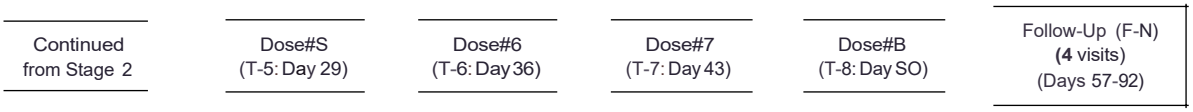
Period 2-Treatment (Visit T-1 to Visit T-4, 4 weeks)

Period 3 (if patient does not continue to Stage 3)-Follow-up (Visit F-1 to Visit F-4, 10 weeks)

The length of time for individual HSCT-TMA patient paiticipation in Stage 2 (if he or she does not continue to Stage 3) was approximately 14 to 18 weeks, depending on the time from screening to the first dose of OMS721 administration. Follow-up visits for patients who do not continue to Stage 3 will occur on Day 29, Day 36, Day 50, and Day 92.

Patients with HSCT-TMA who have completed the Stage 2 treatment period may be eligible for an additional 4 weeks of treatment if the Investigator believes the patient is at risk for relapse of TMA or has not responded to the initial 4 weeks of treatment, the patient tolerated OMS721 treatment, and the patient has no conditions that increase the risk of OMS721 treatment (e.g., serious active infection). The patient's treating Investigator and the Sponsor's medical monitor will detennine eligibility for Stage 3 based upon the patient's response to therapy and safety and tolerability prior to the last scheduled treatment visit in Stage 2 in order to detennine the appropriate PK draws following that visit. Patients entering Stage 3 will not undergo the Follow-up visits in Stage 2.

Figure 5: Stage 3 Study Design Schematic (HSCT-TMA Cohort)



The **Stage 3** study schedule for the HSCT-TMA coho1t (Coho1t 5) includes 8 visits across 2 periods:

Period 2 (continued from Stage 2)- Treatment (Visit T-5 to Visit T-8, 4 weeks)

Period 3 -Follow-up (Visit F-1 to Visit F-4, 6 weeks)

Follow-up visits in Stage 3 for the HSCT-TMA cohort will occur on Day 57, Day 64, Day 78, and Day 92. The length of time for individual TTP/HSCT-TMA patient paiticipation in Stage 3 will be approximately 10 weeks, and the total length of time in Stage 2 and Stage 3 will be approximately 14 to 18 weeks.

7.2. Study Rationale

This is the first study of OMS721 in patients with TMA. In addition to evaluating safety, tolerability, PK, PD, and immunogenicity, clinical activity in patients with TMA is to be obtained. Results from nonclinical toxicity studies of OMS721, Phase 1 studies in healthy volunteers, a Phase 2 study in glomernlonephropathies, and data collected in this study as of the time of this amendment indicate that there is a positive benefit/risk ratio to conduct this study at

the proposed doses in patients with TMA. Patients previously emolled thus far in this study have tolerated OMS721 well. The treatment period is being extended because the non-human primate chronic toxicity study has been completed without treatment-related adverse findings, patients previously emolled in this study have demonstrated improvement in laborato1y measmes of TMA, and continued treatment has been requested. Inclusion of patients in this ongoing protocol provides for better safety and efficacy evaluation than expanded access across Investigators. The difference in treatment dmations reflects the different courses of the TMA subpopulations included in this study.

[redacted]

[redacted]

7.3. Study Endpoints

7.3.1. Primary Endpoints

The co-primary endpoints are:

- Safety as assessed by adverse events (AEs), vital signs, ECGs, and clinical laboratory tests (includes patients with HSCT-TMA, aHUS, and TTP)
- For HSCT-TMA patients, response to OMS721 treatment. A responder is defined as a patient with HSCT-TMA who demonstrates improvement in laboratory TMA markers (platelet count and LDH) and clinical benefit (either improvement in organ function or reduction in transfusion burden). The specific criteria are defined as follows:
  - Improvement in laboratory TMA markers:
    - Platelet count:
      - For patients with baseline platelet count ≤ 20,000/μL:
        - Tripling of baseline platelet count

          and
        - Post baseline platelet count > 30,000/μL

          and
        - No platelet transfusions 2 days before and on the day of the platelet count collection
      - For patients with baseline platelet count > 20,000/μL
        - Increase in platelet count ≥ 50%

          and
        - Post baseline platelet count > 75,000/μL

          and
        - No platelet transfusions 2 days before and on the day of the platelet count collection

      and
    - LDH:
      - LDH < 1.5 x upper limit of normal (ULN)

  and
  - Improvement in clinical status:
    - Improvement in organ function as evidenced by any of the following:
      - Improvement in renal function:

- Reduction of creatinine > 40%

  or

- Creatinine < ULN and reduction of creatinine > 20%

  or

- Discontinuation of renal replacement therapy (RRT)

or

- Improvement in pulmonary function:
  - Extubation and discontinuation of ventilator support

  or

  - Discontinuation of non-invasive mechanical ventilation (continuous positive pressure ventilation)

or

- Improvement in neurological function:
  - Improvement in reversible neurological conditions (e.g., cessation of seizures)

  or

  - Stabilization of irreversible neurological conditions (e.g., stability of neurological deficits following stroke without further deterioration or subsequent strokes)

or

- Improvement in gastrointestinal function (gastrointestinal HSCT-TMA will require diagnosis by tissue biopsy):
  - Improvement measured by improvement in the gastrointestinal measures in the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria

or

- Freedom from transfusion (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 OMS721 dose date)

7.3.2. Secondary Endpoints

The secondary endpoints are to evaluate the following in patients with HSCT-TMA treated with OMS721:

- Duration of response, defined as the number of days from the first response date to the first relapse date

- 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 OMS721 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 OMS721 dose date)
- Change from baseline in platelet count (post baseline platelet counts without platelet transfusions 2 days before and on the day of the platelet count collection will be 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 Hgb (post baseline Hgb without RBC and whole blood transfusions 6 days before and on the day of the Hgb collection will be used) over time using central laboratory values
- Change from baseline in creatinine over time using central laboratory values
- The PK of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The PD of multiple-dose administration of OMS721(this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The immunogenicity of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)

7.3.3. Exploratory Endpoints

The exploratory endpoints are:

- Assess the effect of baseline circulating MBL levels on PK and PD measures in patients with HSCT-TMA, aHUS, and TTP
- Assess the effect of baseline circulating MASP-2 levels on PK and PD measures in patients with HSCT-TMA, aHUS, and TTP
- Describe the effect of OMS721 on TMA laboratory markers in patients with aHUS and TTP

7.4. Study Extension

Patients completing the treatment period of Stage 2 may be eligible for continued OMS721 treatment in Stage 3. Patients may be eligible for extension of their treatment with OMS721 in

Stage 3 if they are deriving clinical benefit, have not displayed any signs or symptoms of serious toxicity, and the Investigator and Sponsor's medical monitor agree that the patient may derive benefit from continuing treatment in Stage 3. The primary objective of the Stage 3 extension is to provide a treatment option that may be better than alternative treatments. A secondary objective of this extension is to assess safety and efficacy parameters of OMS721 during extended treatment.

The decision to offer extended treatment will be made on a case-by-case basis and will be implemented under the following guidelines:

- The patient provides informed consent for further treatment.
- The benefit-to-risk assessment is positive for the patient.

The patient's treating Investigator and the Sponsor's medical monitor will determine eligibility for Stage 3 based upon the patient's response to therapy and safety and tolerability prior to the last scheduled treatment visit in Stage 2 in order to determine the appropriate PK draws following that visit.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

1. Competent to provide informed consent.
2. Voluntarily provide informed consent in accordance with regulations and governing ethics committee requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.
3. Are age ≥ 18 years at screening (Visit 1).
4. Have a diagnosis of TMA in accordance with one of the following 3 categories:
    - As of Amendment 10 of this protocol, enrollment of aHUS patients was closed. Primary aHUS, diagnosed clinically and having ADAMTS13 activity > 10% in plasma. Patients are eligible with or without a documented complement mutation or anti-complement factor H (anti-CFH) antibody. Patients are categorized according to their response to plasma therapy (plasma exchange or plasma infusion):
        - Plasma therapy-resistant aHUS patients must have all of the following:
            - Screening platelet count < 150,000/μL despite at least 4 plasma therapy treatments prior to screening
            - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < lower limit of normal [LLN])
            - Serum creatinine > ULN

    - Chronic plasma therapy-responsive aHUS patients (plasma therapy-sensitive) must require at least once-per-week plasma therapy for 4 weeks before first dose of OMS721 with serum creatinine > ULN.
  - As of Amendment 10 of this protocol, enrollment of TTP patients was closed. TTP defined as having all of the following:
    - Platelet count < 150,000/μL
    - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < LLN)
    - ADAMTS13 activity ≤ 10% during the current episode of TTP or historically
  - Persistent HSCT-associated TMA 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/μL
    - Evidence of microangiopathic hemolysis (presence of schistocytes, serum LDH > ULN, or haptoglobin < LLN)
    - Renal dysfunction (doubling of serum creatinine from pre-transplant)
5. No clinically apparent alternative explanation for thrombocytopenia and anemia.
6. If sexually active and of childbearing potential, must agree to practice a highly effective method of birth control until the end of the study, 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, or vasectomized partner.

8.2. Patient Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

1. Had eculizumab therapy within 3 months prior to screening.
2. Have STEC-HUS.
3. Have a positive direct Coombs test.
4. Have an active systemic bacterial or fungal infection requiring antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed).
5. Baseline resting heart rate < 45 beats per minute or > 115 beats per minute.
6. Baseline QTcF > 470 milliseconds.
7. Have malignant hypertension (diastolic blood pressure [BP] > 120 mm Hg with bilateral hemorrhages or “cotton-wool” exudates on funduscopic examination).
8. Have a poor prognosis with a life expectancy of less than 3 months in the opinion of the Investigator.
9. Are pregnant or lactating.

10. Have received treatment with an investigational drug or device within 4 weeks prior to screening.
11. Have abnormal liver function tests defined as ALT or aspartate aminotransferase (AST) > 5 times ULN.
12. Have a positive test for human immunodeficiency virus (HIV) antibodies.
13. Are an employee of Omeros, an Investigator, a study staff member, or their immediate family member.
14. Have a known hypersensitivity to any constituent of the product.
15. Presence of any condition that the Investigator believes would put the patient at risk.

8.3. Patient Withdrawal Criteria

8.3.1. Early Discontinuation of Study Drug Administration

Patients may voluntarily withdraw from the study at any time for any reason without prejudice to further treatment. A patient must permanently discontinue study drug under any of the following circumstances:

- The patient becomes pregnant. Study drug must be discontinued immediately and the pregnancy reported to the Sponsor.
- The patient wishes to discontinue study drug treatment for any reason.
- The patient experiences a medical emergency that necessitates discontinuing study drug treatment.
- The patient receives a prohibited concomitant therapy.
- The Investigator, Sponsor, or patient's primary care physician decides to discontinue treatment for medical reasons or due to the patient's noncompliance with the protocol.

The reason for termination of study drug before study completion must be recorded in the patient's Case Report Form (CRF). The patient should complete all scheduled study Follow-Up visits provided written consent to do so has not been withdrawn. Patients who discontinue study drug prematurely will not be replaced.

8.3.2. Patient Withdrawal from the Study

A patient must be withdrawn from the study and discontinue study drug under the following circumstances:

- The patient wishes to withdraw consent to participate in the study.
- The Investigator or patient's primary care physician decides that the patient should be withdrawn from the study.
- The Sponsor decides that the patient should be withdrawn or the Sponsor discontinues the study for any reason.

The reason for withdrawal must be recorded in the patient's CRF. The patient should complete the evaluations scheduled for the last follow-up visit (dependent on the patient's cohort and Stage), provided written consent to do so has not been withdrawn. Patients who are withdrawn may be replaced at the discretion of the Sponsor in consultation with the Investigator in order to meet study objectives.

8.3.3. Notification of Withdrawal

When a study participant, voluntarily or involuntarily, is withdrawn from the study , the Sponsor and the ethics committee (as applicable, in accordance with Institutional Review Board [IRB]/Independent Ethics Committee [IEC] requirements) will be notified and provided with the reasons for patient's withdrawal from this study.

9. STUDY DRUG AND TREATMENT OF PATIENTS

OMS721 is manufactured using current Good Manufacturing Practices for investigational use. OMS721 is a human IgG4 mAb directed against MASP-2. Two formulations are available, the higher concentration drug product (185 mg/mL) and the lower concentration drug product (100 mg/mL), depending on which amendment patients were enrolled under (see Section 9.1.3).

9.1. OMS721 Drug Product

OMS721 100 mg/mL Injection Solution is a clear, colorless to yellow-brown liquid. It consists of 2 mL OMS721 Drug Substance, formulated in 20 mM sodium acetate, 5% sorbitol, and 0.01% polysorbate 80, pH 5.0 ± 0.8, at a concentration of 100 mg/mL, and supplied in a single-use 5 mL sterile, clear-glass vials. Each vial contains 2 mL of 100 mg/mL Injection Solution. As of Amendment 10 of this protocol, the 100 mg/mL formulation will not be used for newly enrolled patients.

Drug Product, OMS721 185 mg/mL is a clear, colorless to yellow-brown liquid. It contains OMS721 Drug Substance (nominal concentration of 185 mg/mL), formulated at pH 5.8, in citrate (20 mM), arginine (200 mM), and polysorbate 80 (0.01%). The Drug Product is supplied in a single-use type I glass 2 mL vial containing 2 mL of solution.

The OMS721 Drug Product (185 mg/mL) will be further diluted for IV administration in accordance with the preparation instructions described below.

9.1.1. Packaging and Labeling of Drug Product

OMS721 100 mg/mL Injection Solution is packaged in 5 mL clear-glass vials containing 2 mL of OMS721. As of Amendment 10 of this protocol, the 100 mg/mL formulation will not be used for newly enrolled patients.

Drug Product, OMS721 185 mg/mL is packaged in 2 mL clear-glass vials containing 2 mL of OMS721. This formulation will come packaged in a single vial per single carton.

The vials and single outer cartons will be labeled in accordance with applicable regulations, including, at a minimum, the following information:

- Name of the drug product (OMS721 100 mg/mL Injection Solution or Drug Product, OMS721 185 mg/mL)
- Product identification number
- Regulatory cautionary statement regarding investigational or clinical trial use

9.1.2. Blinding

No blinding is necessary in this study.

9.1.3. Study Drug Dose Preparation

Prior to preparation, the study drug should be inspected for any particulate matter or discoloration. If any particulate matter or discoloration is observed, the vial should not be used. As of Amendment 10 of this protocol, only the Drug Product, OMS721 185 mg/mL formulation will be used. The refrigerated vials (Drug Product, OMS721 185 mg/mL) must be used within 4 hours following septum piercing. Do not shake or heat the OMS721. Avoid exposure to direct sunlight.

As of Amendment 10 of this protocol, the dose is changed to a fixed dose of 370 mg.

For dispensing, Drug Product OMS721 185 mg/mL is removed from refrigerated storage and allowed to come to room temperature undisturbed for a minimum of 30 minutes and then used to prepare the appropriate dosing solution.

The appropriate calculated volume of Drug Product, OMS721 185 mg/mL will be withdrawn from the vial using polypropylene syringes for dose preparation.

The measured OMS721 dose will be added to a polyvinyl chloride or polyolefin infusion bag containing a minimum of 50 mL D5W or normal saline for injection solution and mixed by gentle inversion about 10 times. The infusion preparation should not be shaken. The prepared infusion bag should be properly labeled, including the date and time of preparation, and kept at room temperature until ready for administration. The infusion bag should be administered within 4 hours of preparation. If the infusion bag is not used within 4 hours, then it should be discarded and the disposition recorded under drug accountability.

The diluted study drug should be infused intravenously over approximately a 30-minute period.

9.1.3.1. Supplemental Drug Administration for Patients Receiving Plasma Therapy

If the patient is receiving plasma exchange or plasma infusion on the day of study drug administration, then the study drug should be started within 3 hours after completion of plasma therapy.

If plasma exchange is performed at any time prior to the next scheduled dose, then a supplemental dose of study drug (50% of assigned dose) should be administered within 1 hour after completion of each plasma exchange up to 4 supplemental doses per week. The total weekly dose should not exceed 300% of the assigned dose.

If plasma infusion is performed at any time prior to the next scheduled dose, then a supplemental dose (50% of assigned dose) should be administered before each plasma infusion up to

4 supplemental doses per week. The total weekly dose should not exceed 300% of the assigned dose.

9.1.4. Storage and Handling of Drug Product

OMS721 Drug Product vials are to be stored according to the Investigator's Brochure.

- As of Amendment 10 of this protocol, 100 mg/mL Injection Solution will no longer be used for newly enrolled patients. Any remaining vials of OMS721 100 mg/mL Injection Solution should be returned or destroyed as described in Section 9.1.5 and Section 9.2.
- Drug Product, OMS721 185 mg/mL is stored at 2°C to 8°C.

Allow Drug Product, OMS721 185 mg/mL to come to room temperature without manipulation (i.e., warming up in your hands or putting the vial in hot water is not allowed) for a minimum of 30 minutes, and then use it to prepare the appropriate dosing solution. The OMS721 Drug Product must be used to prepare the appropriate dosing solution within 4 hours after piercing of the vial septum. Drug Product that has not been punctured can be at room temperature for 24 hours.

9.1.5. Study Drug Accountability

In compliance with the US FDA, European Medicines Agency (EMA), and other applicable regulations, records will be maintained by the Investigator and/or pharmacist designee for OMS721 study Drug Product delivery to the site, the inventory at the site, the use of each vial, and the return of used and unused Drug Product, including dates and quantities. The Investigator and/or pharmacist designee will maintain the investigative site's study drug accountability documentation. The documentation should include the identification of the Drug Product used, Drug Product, OMS721 100 mg/mL Injection Solution or Drug Product, 185 mg/mL. After the study has been completed, a copy of the Investigator/pharmacy drug accountability records will be provided to the Sponsor. The original drug accountability records will be retained by the site.

9.2. Return of Drug Product

At the end of the study, the Sponsor will inform the site as to disposition of unused Drug Product. If instructed, unused supplies may be destroyed at the site according to local laws, regulations, and the institution's standard operating procedures.

10. STUDY PROCEDURES

The Schedule of Events for each cohort and Stage is summarized in Section 19.

10.1. Study Schedule

10.1.1. Stage 1

As of Amendment 11 of this protocol, Stage 1 is complete.

Study procedures were performed at Screening (Visit 1, Day –28 to 0), at each of the dosing days during the Treatment Period (Visit 2 to Visit 5, Day 1 to Day 25), and during the Follow-up Period (Visit 6 to Visit 9, Day 29 to Day 78).

10.1.1.1. Stage 1 Screening Visit (Visit 1, Up to Day –28)

Screening evaluations will occur within 28 days prior to dosing (Day 1). Before any of the screening evaluations are performed for the specific purpose of this study, the patient must provide informed consent for this study in compliance with regulations and governing ethics committee requirements. The procedures listed below will be performed and documented to determine patient eligibility prior to treatment assignment.

1. A medical history, including directed questioning regarding prior mycobacterial infection or significant fungal infection, will be taken, and demographics will be recorded.
2. The history of TMA will be recorded, including the following information:
    - Type of TMA (aHUS, TTP, or HSCT-TMA). As of Amendment 10 of this protocol, enrollment of aHUS and TTP patients is closed.
    - Date of diagnosis (for HSCT-TMA, interval from time of transplantation)
    - History of previous episodes of TMA (record dates for prior episodes)
    - Family history of TMA
    - History of kidney transplantation for TMA-induced renal failure
    - Symptoms related to current episode of TMA
    - Diagnostic evaluations for TMA, e.g., Shiga toxin testing, complement genetic testing, ADAMTS13, Coombs test
    - Description of the type and frequency of plasma therapy during current episode
    - Description of frequency of dialysis during current episode
    - Immune suppressive medications to treat current episode
    - If taking calcineurin inhibitors chronically, changes, if any, to the dose and regimen during current episode
3. Use of prior and concomitant medications will be obtained.
4. Vital signs will be taken, including BP, pulse rate, respiratory rate (RR), and temperature (after at least 5 minutes of rest in the supine position).
5. A complete physical examination will be performed, including height and weight. If diastolic BP is > 120 mm Hg, then a funduscopic examination will be performed to exclude malignant hypertension. Rectal or genital examinations are not required, unless medically indicated.
6. A 12-lead ECG will be taken (after at least 5 minutes of rest in the supine position).
7. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis.

8. Serum pregnancy test will be performed in women of childbearing potential.
9. Serology tests will be performed for HIV antibodies.
10. Stool will be tested for Shiga toxin if STEC-HUS has not been previously excluded.
11. Direct Coombs test will be performed if not previously obtained.
12. Complement genetic testing will be performed in patients with primary aHUS if not previously obtained.
13. ADAMTS13 activity testing will be performed if not previously obtained.

10.1.1.2. Stage 1 Baseline Platelet Counts

Eligible patients will have the platelet count performed on at least 2 separate days in the week prior to the first OMS721 dose (Day 1) to establish the baseline (averaged with the pre-dose value on Day 1). In patients who are receiving plasma therapy, the platelet counts should be obtained prior to such therapy.

10.1.1.3. Stage 1 Method of Assigning Patients to Treatment Cohorts

Eligible patients will be assigned to the current dose cohort in the first stage of the study.

10.1.1.4. Stage 1 Treatment – Week 1 (Visit 2, Day 1)

This visit is for the first dose of OMS721 administration. The study drug should be requested from the site pharmacy and prepared no earlier than 3.5 hours prior to the start of administration.

Prior to dosing with study drug, the following procedures will be performed:

1. Review of AEs, presence of TMA symptoms, concomitant medications, and therapies.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position).
3. ECG will be taken (after at least 5 minutes of rest in the supine position).
4. Laboratory tests will be performed, including:
    - Hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis.
    - Serum or urine pregnancy test will be performed in women of childbearing potential. If the test result is positive, then the patient will be excluded from the study.
    - Blood samples for future research related to TMA will be taken. The samples will enable DNA, RNA, proteins, and cells to be extracted for analyses.
    - Serum PK sample will be taken.
    - Serum PD sample will be taken.
    - Serum ADA sample will be taken.

OMS721 will be administered by IV infusion over approximately 30 minutes.

After start of dosing with study drug, the following procedures will be performed:

1. AEs will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: 15 minutes after start of dosing, 30 minutes after start of dosing (after end of dosing), 1 hour after start of dosing (30 minutes after end of dosing), 2.5 hours after start of dosing (2 hours after end of dosing).
3. ECG will be taken (after at least 5 minutes of rest in the supine position) immediately before the 5 minute PK sample.
4. Serum PK samples will be taken at the following time points after end of dosing: 5 minutes, 2 hours, 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4).
5. Serum PD sample will be taken 2 hours after end of dosing.
6. The patient may be discharged after completion of the 2 hours after end-of-dosing procedures and arrangements made for the patient to undergo collection of PK samples on Day 2, Day 3, and Day 4.

10.1.1.5. Stage 1 Treatment – Week 2 (Visit 3, Day 8 ± 1)

This is the second dose of OMS721 administration. The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: prior to dosing and at 15 minutes, 30 minutes, 1 hour, and 2.5 hours after start of dosing.
3. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis (prior to OMS721 administration).
4. Blood sample for future research related to TMA will be taken (prior to OMS721 administration).
5. OMS721 will be administered by IV infusion over approximately 30 minutes.
6. Serum PK samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing.
7. Serum PD samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing.
8. Serum ADA sample will be taken prior to dosing.
9. AEs during and after the IV infusion will be recorded.

10.1.1.6. Stage 1 Treatment – Week 3 (Visit 4, Day 15 ± 1)

This is the third dose of OMS721 administration. The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.

2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: prior to dosing and at 15 minutes, 30 minutes, 1 hour, and 2.5 hours after start of dosing.
3. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis (prior to OMS721 administration).
4. Blood sample for future research related to TMA will be taken (prior to OMS721 administration).
5. OMS721 will be administered by IV infusion over approximately 30 minutes.
6. Serum PK samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing.
7. Serum PD samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing.
8. Serum ADA sample will be taken prior to dosing.
9. AEs during and after the IV infusion will be recorded.

10.1.1.7. Stage 1 Treatment – Week 4 (Visit 5, Day 22 ± 1)

This is the fourth and last dose of OMS721 administration. The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: prior to dosing and at 15 minutes, 30 minutes, 1 hour, and 2.5 hours after start of dosing.
3. ECG will be taken (after at least 5 minutes of rest in the supine position) prior to dosing.
4. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis (prior to OMS721 administration).
5. Blood sample for future research related to TMA will be taken (prior to OMS721 administration).
6. OMS721 will be administered by IV infusion over approximately 30 minutes.
7. ECG will be taken (after at least 5 minutes of rest in the supine position) immediately before the 5 minute PK sample.
8. Serum PK samples will be taken prior to dosing and at the following time points after end of dosing: 5 minutes, 2 hours, 24 hours (Day 23), 48 hours (Day 24), 72 hours (Day 25).
9. Serum PD samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing.
10. Serum ADA sample will be taken prior to dosing.
11. AEs during and after the IV infusion will be recorded.

12. Arrangements should be made for the patient to undergo collection of PK samples on the 3 days following Visit 4 (Day 23, Day 24, and Day 25 if Visit 4 occurs on Day 22).

10.1.1.8. Stage 1 Follow-Up (Visit 6, Day 29 ± 1)

The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position).
3. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, and urinalysis.
4. Blood sample for future research related to TMA will be taken.
5. Serum PK sample will be taken.
6. Serum PD sample will be taken.
7. Serum ADA sample will be taken.

10.1.1.9. Stage 1 Follow-Up (Visit 7, Day 36 ± 2)

The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position).
3. Clinical laboratory tests will be performed for hematology, chemistry, LDH, and haptoglobin.
4. Blood sample for future research related to TMA will be taken.
5. Serum PK sample will be taken.
6. Serum PD sample will be taken.
7. Serum ADA sample will be taken.

10.1.1.10. Stage 1 Follow-Up (Visit 8, Day 50 ± 3)

The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Clinical laboratory tests will be performed for hematology, chemistry, LDH, and haptoglobin.
3. Blood sample for future research related to TMA will be taken.
4. Serum PK sample will be taken.

5. Serum PD sample will be taken.
6. Serum ADA sample will be taken.

10.1.1.11. Stage 1 Follow-Up End of Study (Visit 9, Day 78 ± 7)

The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Clinical laboratory tests will be performed for hematology, chemistry, LDH, and haptoglobin.
3. Serum or urine pregnancy test will be performed in women of childbearing potential.
4. Blood sample for future research related to TMA will be taken.
5. Serum PK sample will be taken.
6. Serum PD sample will be taken.
7. Serum ADA sample will be taken.

The patient will complete the study at this visit.

10.1.2. Stage 2 and Stage 3

The study visits in Stage 2 and Stage 3 are described as Treatment (T) visits and Follow-up (F) visits. All patients will undergo the same procedures at the Screening, Treatment, and Follow-up visits. The number of Treatment and Follow-up visits will vary between stages and cohorts. As of Amendment 11, enrollment in the study has been completed.

10.1.2.1. Stage 2 Screening Visit (Visit 1, Up to Day –28)

Screening evaluations will occur within 28 days prior to dosing (Day 1). Before any of the screening evaluations are performed for the specific purpose of this study, the patient must provide informed consent for this study in compliance with regulations and governing ethics committee requirements. The procedures listed below will be performed and documented to determine patient eligibility prior to treatment assignment.

1. A medical history, including directed questioning regarding prior mycobacterial infection or significant fungal infection, will be taken and demographics will be recorded.
2. The history of TMA will be recorded, including the following information:
    - Type of TMA (aHUS, TTP, or HSCT-TMA). As of Amendment 10 of this protocol, enrollment of aHUS and TTP patients is closed.
    - Date of diagnosis (for HSCT-TMA, interval from time of transplantation)
    - History of previous episodes of TMA (record dates for prior episodes)
    - Family history of TMA
    - History of kidney transplantation for TMA-induced renal failure

- Symptoms related to current episode of TMA
- Diagnostic evaluations for TMA, e.g., Shiga toxin testing, complement genetic testing, ADAMTS13, Coombs test
- Description of the type and frequency of plasma therapy during current episode
- Description of frequency of dialysis during current episode
- Immune suppressive medications to treat current episode
- If taking calcineurin inhibitors chronically, changes, if any, to the dose and regimen during current episode

3. Use of prior and concomitant medications will be obtained.
4. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position).
5. A complete physical examination will be performed, including height and weight. If diastolic BP is > 120 mm Hg, then a funduscopic examination will be performed to exclude malignant hypertension. Rectal or genital examinations are not required, unless medically indicated.
6. A 12-lead ECG will be taken (after at least 5 minutes of rest in the supine position).
7. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis.
8. Serum pregnancy test will be performed in women of childbearing potential.
9. Serology tests will be performed for HIV antibodies.
10. Stool will be tested for Shiga toxin if STEC-HUS has not been previously excluded.
11. Direct Coombs test will be performed if not previously obtained.
12. Complement genetic testing will be performed in patients with primary aHUS if not previously obtained.
13. ADAMTS13 activity testing will be performed if not previously obtained.

10.1.2.2. Stage 2 Baseline Platelet Counts

Eligible patients will have the platelet count performed on at least 2 separate days in the week prior to the first OMS721 dose (Day 1) to establish the baseline (averaged with the pre-dose value on Day 1). In patients who are receiving plasma therapy, the platelet counts should be obtained prior to such therapy.

10.1.2.3. Stage 2 and Stage 3 Method of Assigning Patients to Treatment Cohorts

Eligible patients will be assigned to the selected dose and relevant disease cohort in the second stage of the study. Patients eligible to continue in Stage 3 will remain at the same dose and in the same disease cohort as assigned in Stage 2.

10.1.2.4. Stage 2 Treatment – Week 1 (Visit T-1, Day 1)

This visit is for the first dose of OMS721 administration. The study drug should be requested from the site pharmacy and prepared no earlier than 3.5 hours prior to the start of administration.

Prior to dosing with study drug, the following procedures will be performed:

1. Review of AEs, presence of TMA symptoms, concomitant medications, and therapies.
2. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position).
3. ECG will be taken (after at least 5 minutes of rest in the supine position).
4. Laboratory tests will be performed, including:
    - Hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis.
    - Serum or urine pregnancy test will be performed in women of childbearing potential. If the test result is positive, then the patient will be excluded from the study.
    - Blood samples for future research related to TMA will be taken. The samples will enable DNA, RNA, proteins, and cells to be extracted for analyses.
    - Serum PK sample will be taken.
    - Serum PD sample will be taken.
    - Serum ADA sample will be taken.

OMS721 will be administered by IV infusion over approximately 30 minutes.

After start of dosing with study drug, the following procedures will be performed:

1. AEs will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: 15 minutes after start of dosing, 30 minutes after start of dosing (after end of dosing), 1 hour after start of dosing (30 minutes after end of dosing), 2.5 hours after start of dosing (2 hours after end of dosing).
3. ECG will be taken (after at least 5 minutes of rest in the supine position) immediately before the 5-minute PK sample.
4. Serum PK samples will be taken at the following time points after end of dosing: 5 minutes, 2 hours, 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4).
5. Serum PD sample will be taken 2 hours after end of dosing.
6. The patient may be discharged after completion of the 2 hours after end-of-dosing procedures and arrangements made for the patient to undergo collection of PK samples on Day 2, Day 3, and Day 4.

10.1.2.5. Stage 2 and Stage 3 Treatment – Visit T-N (where N is > 1 [the week of treatment after the week of the first dose])

The following procedures will be performed on the subsequent doses of OMS721:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: prior to dosing and at 15 minutes, 30 minutes, 1 hour, and 2.5 hours after start of dosing.
3. Clinical laboratory tests will be performed for hematology, chemistry, LDH, haptoglobin, coagulation, and urinalysis (prior to OMS721 administration).
4. Blood sample for future research related to TMA will be taken (prior to OMS721 administration).
5. Serum PK samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing. At the last treatment visit, additional PK samples will also be taken at the following timepoints: 24 hours, 48 hours, and 72 hours after the end of the last dose.
6. Serum PD samples will be taken at the following time points: prior to dosing and at 2 hours after end of dosing.
7. OMS721 will be administered by IV infusion over approximately 30 minutes.
8. AEs during and after the IV infusion will be recorded.

10.1.2.6. Stage 2 or Stage 3 Follow-Up – Visit F-N (where N is the number of the follow-up visit)

The following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Clinical laboratory tests will be performed for hematology, chemistry, LDH, and haptoglobin.
3. Blood sample for future research related to TMA will be taken.
4. Serum PK sample will be taken.
5. Serum PD sample will be taken.
6. Serum ADA sample will be taken.
7. Serum or urine pregnancy test will be performed in women of childbearing potential at the last Follow-Up visit only.

10.1.3. Early Termination

All patients will be encouraged to complete all evaluations. However, patients who prematurely discontinue the study will have the assessments for the last Follow-up visit, if possible.

10.1.4. Unscheduled Visits - Supplemental OMS721 Administration for Patients Receiving Plasma Therapy or Adverse Events

If a patient has a cardiovascular AE, e.g., chest pain, palpitations, presyncope or syncope, hypo- or hypertension, an ECG should be taken and a serum PK sample taken immediately after the ECG.

Patients who are receiving plasma therapy (plasma exchange or plasma infusion) will be treated with supplemental doses of OMS721 as provided in Section 9.1.3.1.

If the patient is receiving plasma exchange or plasma infusion on the day of study drug administration, then the study drug should be given within 3 hours after completion of plasma therapy.

If plasma exchange is performed at any time prior to the next scheduled dose, then a supplemental dose (50% of assigned dose) should be administered within 1 hour after completion of each plasma exchange up to 4 supplemental doses per week. The total weekly dose should not exceed 300% of the assigned dose.

If plasma infusion is performed at any time prior to the next scheduled dose, then a supplemental dose (50% of assigned dose) should be administered before each plasma infusion up to 4 supplemental doses per week. The total weekly dose should not exceed 300% of the assigned dose.

On the day of supplemental OMS721 administration, the following procedures will be performed:

1. AEs, presence of TMA symptoms, concomitant medications, and therapies will be recorded.
2. Pre-dose vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position).
3. Pre-dose serum PK sample will be taken.
4. OMS721 will be administered by IV infusion over approximately 30 minutes.
5. Vital signs will be taken, including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest in the supine position) at the following time points: 15 minutes after start of dosing, 30 minutes after start of dosing (after end of dosing), 1 hour after start of dosing (30 minutes after end of dosing), 2.5 hours after start of dosing (2 hours after end of dosing).
6. Serum PK samples will be taken at 5 minutes after end of dosing.

10.1.5. Timing of Study Procedures

10.1.5.1. Stage 1

Procedures with a specified time frame will be considered per protocol if they are performed within the following windows: vital signs on dosing days ± 5 minutes in the first hour of start of dosing and ± 10 minutes thereafter; PK and PD draws on the day of dosing ± 5 minute; PK draws on Day 2, Day 3, Day 4, Day 23, Day 24, and Day 250 ± 2 hours. If multiple procedures

are specified at one time point, they should be performed in the following order: blood draw and then vital signs, with the blood draw at the exact specified time.

10.1.5.2. Stage 2 and Stage 3

Procedures with a specified time frame will be considered per protocol if they are performed within the following windows: vital signs on dosing days ±5 minutes in the first hour of start of dosing and ± 10 minutes thereafter; PK and PD draws on the day of dosing ± 5 minute; PK draws at the 24-, 48-, and 72-hour timepoints following the first and last dose ± 2 hours. If multiple procedures are specified at one time point, they should be performed in the following order: blood draw and then vital signs, with the blood draw at the exact specified time.

10.1.6. Timing of Study Visits

Visits outside the specified window will be considered protocol deviations. If OMS721 is not able to be administered within the visit window ± 2 days, the Investigator should contact the Sponsor Medical Monitor to discuss the course of action and disposition of the patient.

10.2. Concomitant Therapy

All concomitant medications and therapies will be recorded in the CRF.

The following guidelines will be used in relation to treatments directed to TMA, underlying conditions, and suspected infections.

10.2.1. Allowed Concomitant Therapies

10.2.1.1. Plasma Therapy

- Plasma therapy-resistant aHUS – plasma therapy during OMS721 treatment is allowed if the Investigator considers it medically indicated.
- Chronic plasma therapy-responsive aHUS – plasma therapy should be continued until there is a sign of improvement in TMA, e.g., increase in platelet count, decrease in LDH, increase in haptoglobin, increase in hemoglobin, decrease in creatinine, at which time the Investigator should consider withholding plasma therapy and monitoring TMA parameters to assess whether plasma therapy can be discontinued.
- TTP – plasma therapy is allowed if the Investigator considers it medically indicated.
- HSCT-associated TMA – plasma therapy during OMS721 treatment is discouraged because there is no evidence that it is efficacious in this setting, and it requires supplemental OMS721 dosing. It is allowed if the Investigator considers it medically indicated.

10.2.1.2. Renal Dialysis

Renal dialysis therapy should be managed according to standard of care. OMS721 is not expected to be removed by hemodialysis so no supplemental dosing is planned.

10.2.1.3. Immunosuppressive Medications

Immunosuppressive medications should be managed according to standard of care.

10.2.1.4. Erythrocyte Stimulating Agents

Erythrocyte-stimulating agents should be managed according to standard of care.

10.2.1.5. Suspected Infection

Because increased susceptibility to infections is a potential risk of inhibiting MASP-2 activity, patients should be closely monitored for symptoms or signs of infection. If the patient is suspected to have developed an infection, empiric antimicrobial therapy should be promptly initiated along with appropriate microbiological testing to identify the source of infection.

10.2.2. Prohibited Concomitant Therapies

10.2.2.1. Eculizumab

If the Investigator decides to administer eculizumab, the patient should be withdrawn from the study.

10.3. Treatment Compliance

The study drug is to be administered by study personnel. Administration dates and times must be recorded in the CRFs. If any portion of a dose of study drug is not administered, an explanation must be provided in the source document and on the CRF.

10.3.1. Definition of Departure from Protocol

The following definitions will apply to the reporting of emergency and non-emergency departures from the protocol:

Protocol Deviation: Any non-adherence to study procedures or schedules, as specified by the protocol.

10.4. Safety Monitoring

10.4.1. Dose Escalation Review

The Sponsor's Medical Monitor will monitor safety data in an ongoing manner throughout the study.

In Stage 1 of the study, after enrollment and completion of dosing for each cohort, there was a safety review to determine whether dose escalation should proceed. Data for the safety review included AEs and clinically significant abnormalities in laboratory tests. PK and PD data may be reviewed to support dose escalation review, but they are not required because the main criteria will be safety. The safety data was reviewed by a clinical study monitoring team that consisted of the Sponsor Medical Monitor, PSI Medical Monitor, and at least 2 Investigators. The dose escalation decision will be guided by using the Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) [USDHHS 2009] to grade AEs with a focus on Grade 3 or higher AEs. The number and causality of Grade 3 or higher AEs will be considered to determine if dose

escalation was appropriate. At the end of Stage 1, there was a safety and pharmacology data review to select the dose for Stage 2 and Stage 3, which were either the maximally tolerated dose or the biologically effective dose, whichever was lower.

10.4.2. Data Monitoring Committee

A DMC will meet (in-person or by telephone) and review cumulative data approximately every 6 months. The DMC will review all serious adverse events (SAEs) on an ongoing basis as they occur. After each meeting (or as needed between meetings), the chairperson of the DMC will provide in writing 1 of the following recommendations to the Sponsor: 1) continue the study as planned, 2) continue the study under an amended protocol describing the recommended amendment, 3) suspend enrollment in the study pending provision of additional information, 4) suspend treatment in the study pending provision of additional information, or 5) discontinue the study. The DMC recommendation will also include the reasons upon which the recommendation is based. The DMC recommendations will be filed in the trial master file and included as an appendix in the clinical study report.

11. ASSESSMENT OF EFFICACY

In addition to the safety assessments described in Section 12 , this study evaluates efficacy, PK, PD, immunogenicity, and exploratory measures.

11.1. Primary Efficacy Measures

The primary efficacy measure is the proportion of patients who respond to OMS721 treatment defined as a patient with HSCT-TMA who demonstrates improvement in laboratory TMA markers (platelet count and LDH) and clinical benefit (either improvement in organ function or reduction in transfusion burden) as outlined in Section 7.3.1.

11.2. Secondary Efficacy Measures

The secondary efficacy measures are of duration of response, improved survival, organ function, or laboratory markers as outlined in Section 7.3.2 .

11.3. Pharmacokinetics Measures

Serial serum samples will be collected according to the Schedule of Events (Section 19) for analysis of OMS721 concentration. The samples will be analyzed by the bioanalytical laboratory of PRA in Lenexa, Kansas, using a validated assay method with a lower limit of quantitation (LLOQ) of 50 ng/mL. Sample collection and processing procedures will be provided in the study laboratory manual.

11.4. Pharmacodynamics Measures

Serial serum samples will be collected according to the Schedule of Events (Section 19) for analysis of the PD measure of inhibition of *ex vivo* lectin pathway activation. The samples will be analyzed by the bioanalytical laboratory of PRA in Assen, The Netherlands, using a validated

method. Sample collection and processing procedures will be provided in the study laboratory manual.

11.5. Immunogenicity Measures

Serial serum samples will be collected according to the Schedule of Events (Section 19) for analysis of ADA. The samples will be analyzed by the bioanalytical laboratory of PRA in Assen, The Netherlands, using a validated assay method. Sample collection and processing procedures will be provided in the study laboratory manual.

11.6. Exploratory Measures

Serial blood samples will be collected according to the Schedule of Events (Section 19) for future research (for patients who provide consent for this purpose), which may include analyses of DNA, RNA, protein, or cells. The proteins that are planned to be measured include MBL and MASP-2 because they are related to the mechanism of action of OMS721. Currently there are no plans for analysis of DNA, RNA, cells, or other proteins. The samples are collected in the event that emerging data from this study or published data from other research suggest that specific analyses may be informative with respect to prognosis, pharmacological response, clinical response, or toxicities.

The change from baseline in TMA laboratory markers are exploratory measures in patients with aHUS and TTP.

12. ASSESSMENT OF SAFETY

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. The Investigator is responsible for appropriate medical care of patients during the study.

Contact information for the Sponsor's Medical Monitor for this study is provided in Section 1.2.

12.1. Safety Parameters

Safety will be evaluated by assessing AEs, clinical laboratory tests, vital signs, and ECG. Only clinically significant (per Investigator opinion) changes in vital signs or laboratory tests accompanied by clinical symptoms or those that require medical intervention will be reported as AEs.

12.1.1. Laboratory Tests

For evaluation of some of the laboratory assessments, a central laboratory will be used for all of the sites. The name and address of the clinical laboratory are included in the Investigator file. The following laboratory assessments will be performed in this study:

- Chemistry tests include glucose, urea nitrogen, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, calcium, sodium, potassium, chloride, and bicarbonate.

- Hematology tests include white blood cell count with automated differential (neutrophils, segmented neutrophils, lymphocytes, monocytes, eosinophils and basophils), schistocytes per high-powered field, RBC count, Hgb, hematocrit, mean corpuscular volume, mean corpuscular Hgb, mean corpuscular hemoglobin concentration, red cell distribution width, and platelet count.
- Coagulation tests include prothrombin time, International Normalised Ratio (INR), and activated partial thromboplastin time.

Urinalysis tests include color, specific gravity, pH, glucose, protein, bilirubin, urobilinogen, blood, ketone, nitrite, leukocyte esterase and microscopic if required (RBCs, white blood cells, and bacteria).

12.1.2. Other Safety Measures

- Vital signs include systolic and diastolic BP, pulse rate, RR, and temperature.
- ECG parameters include heart rate, PR interval, QRS interval, QT interval, and QTc interval calculated by Fridericia's formula (QTcF), along with a clinical interpretation by the Investigator.

12.2. Definition of Adverse Events

12.2.1. Definition of Adverse Events

The following definitions from the International Conference on Harmonisation (ICH) Guideline E2A will apply to the reporting of AEs and adverse drug reactions:

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Adverse Drug Reaction: All noxious and unintended responses to a medicinal product related to any dose.

The phrase, "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the Investigator's Brochure.

Serious Adverse Event: Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongs existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Serious adverse events also include important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.2.2. Definitions of Severity

Adverse events will be graded using the CTCAE v.4.0 [USDHHS 2009].

Note that "seriousness" and "severity" are distinct concepts. "Serious" is a term applied to an AE that meets specific requirements (refer to Section 12.2.1). "Severity" refers to the AE intensity classification.

12.2.3. Relationship to Study Drug

The Investigator will determine the assessment of the causal relationship of the AE to the study drug.

The relationship of AEs to study drug is categorized as probable, possible, unlikely, or not related. An alternative etiology must be provided for all AEs for which the relationship to study drug is considered "possible," "unlikely," or "not related."

Definitions of each of these terms are below:

Probable: The AE has a timely relationship to administration of the study drug and there is no apparent, potential alternate etiology.

Possible: The AE has a timely relationship to administration of the study drug and there is an apparent, potential alternate etiology.

Unlikely: The AE is likely related to an etiology other than administration of study drug.

Not Related: The AE is related to an etiology other than the study drug.

An AE with causal relationship not initially determined will require follow-up to assign causality.

12.2.4. Assessment of the Clinical Outcome of Adverse Events

The Investigator (a study physician) will determine the clinical outcome of the AE as follows:

Recovered Completely: Patient has fully recovered from the event with no residual effects observable.

Recovered with Sequelae: Effects of the event are stabilized and constant. The likelihood of these effects changing (improving or worsening) is low.

Not Yet Recovered: Effects of the event are still present and changing. The event is not considered recovered completely or recovered with sequelae.

Unknown; Lost to Follow-up: Not known, not observed, not recorded, or refused to provide information.

Died: The event may or may not be the primary cause of death (may or may not be the immediate cause of death).

12.3. Reporting Adverse Events

12.3.1. Adverse Event Reporting

Adverse events will be collected from the time informed consent is obtained until the last Follow-up visit.

All AEs will be documented in the source records and will be recorded in the CRFs as appropriate. All AEs, whether observed by the Investigator or reported by the patient, and whether or not thought to be related to the study drug, will be recorded on the appropriate CRF. In describing AEs on the CRF, standard, medically accepted terminology will be used.

The description of each AE will identify the date of onset, duration, severity (see Section 12.2.2 for Definitions of Severity), any action taken (including any diagnostic procedures or laboratory tests performed and all treatments that were administered), the outcome of the event, and relationship to the study drug.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not recorded as an AE. However, if the medical condition increases in frequency or severity during or following administration of the study drug, it will be recorded as an AE on the appropriate CRF.

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Adverse events may be reported by the patient, discovered by the Investigator and Investigator's staff, or detected through physical examination, laboratory test, or other means.

Adverse events include:

- Any unfavorable and unintended sign, medical diagnosis, or symptom that occurs between the time of the first administration of study drug and the study duration required by the protocol.
- Any new undesirable medical experience or an unfavorable and unintended change of an existing condition that occurs between the time of the first administration of study drug and the study duration required by the protocol, whether or not considered related to study drug.
- Abnormal laboratory findings considered by the Investigator to be clinically significant, i.e., those that are unusual for the population being studied or individual patient.

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis into a single event term. For example, cough, rhinitis, and sneezing might be grouped together as *upper respiratory tract infection*.

In cases where the Investigator notices an unanticipated benefit to the patient, study site personnel should enter *unanticipated benefit* with the actual event term (for example, the complete actual term may be *unanticipated benefit-sleeping longer*).

12.3.2. Serious Adverse Event Reporting

All SAEs will be:

- recorded on the appropriate SAE case report form
- followed through resolution or at a stable condition by a study physician
- reviewed by a study physician.

The investigative site is required to report any SAE directly to the Sponsor's pharmacovigilance designee on the Serious Adverse Event form within 24 hours of becoming aware of the event, whether or not the SAE is deemed drug-related (see Section 1.2 for contact information).

The study physician will complete an Expedited or Serious Adverse Event Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated to study drug, will be recorded on the Expedited or Serious Adverse Event Form and faxed/electronically communicated within 24 hours of site awareness.

Other supporting documentation of the event may be requested by the pharmacovigilance staff and should be provided as soon as possible.

A distinction is drawn between serious and severe events. A severe event is a major experience of its type. A severe event does not necessarily need to be serious. For example, nausea that persists for several hours may be considered severe nausea, but not a serious adverse experience. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be considered a SAE.

Death is an outcome of an event and not an event per se (sudden death or death of unexplainable causes can be reported, but follow-up will be required until cause of death is determined).

12.3.3. Reporting of Serious Adverse Events to Regulatory Agencies

The Sponsor or its designee will submit the SAEs requiring expedited reporting to regulatory agencies. The ethics committee will be notified of SAEs in accordance with federal, national, and local laws and regulations.

12.3.4. Pregnancy and Overdose Reporting

Cases of pregnancy must be reported for tracking purposes. If a patient becomes pregnant during the study, the Sponsor's Pharmacovigilance designee must be notified by fax or email within 24 hours of site awareness and the patient discontinued from study drug. Additional instructions for reporting of the pregnancy and outcome will be provided by the Sponsor at the time of notification. Pregnancies of partners of male patients will also be followed provided the patient's partner provides informed consent for follow-up of the pregnancy.

Occurrences of overdose should be reported to the Sponsor for tracking purposes. Overdose is defined as any dosing above the protocol-defined dosing instructions. Additional instructions for reporting overdose information will be provided by the Sponsor at the time of notification.

12.4. Type and Duration of the Follow-Up of Patients After Adverse Events

All reportable AEs will be followed until satisfactory resolution or until the Investigator deems the event to be chronic or the participant to be stable.

If an SAE persists at the last visit or the time of early termination after study treatment, it will be marked as "ongoing" and "not yet recovered" in the CRF. It will be followed by the Investigator until such time that it is deemed to be resolved or at a stable condition. Follow-up data for such SAEs will be collected in the source documents and reported appropriately.

12.5. Appropriateness of Measurements

12.5.1. Efficacy Measures

The primary efficacy measure evaluates the proportion of patients who respond to OMS721 treatment. The response criteria include laboratory measures of TMA activity and clinical status. These measures provide an assessment of underlying TMA activity as well as potential clinical benefit experienced by patients. Secondary efficacy measures provide population-level support for patient-level responses observed.

12.5.2. Pharmacokinetic Measures

Drug concentrations are standard PK measures.

12.5.3. Pharmacodynamic Measures

Inhibition of *ex vivo* lectin pathway activation is a relevant PD measure as this is the biological target of OMS721.

12.5.4. Immunogenicity Measures

Anti-drug antibody response is a standard immunogenicity measure for a therapeutic protein.

12.5.5. Exploratory Measures

Mannan-binding lectin and MASP-2 concentrations are being measured to assess whether OMS721 administration alters them. Laboratory TMA measures in patients with aHUS and TTP are appropriate exploratory evaluations in these populations.

12.5.6. Safety Measures

The collection of AEs, clinical laboratory tests, vital signs, and ECGs are standard safety measures.

13. STATISTICS

13.1. Determination of Sample Size

In Stage 1 of the study, 3 patients per dose escalation cohort is a common scheme and is considered to be sufficient in combination with data from the Phase 1 study to allow selection of a dose for Stage 2.

In Stage 2, the sample size for each cohort (aHUS and HSCT-TMA/TTP) is 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 [Legendre 2013]. This sample size is considered adequate in these orphan diseases to identify treatment effects in uncontrolled studies.

It is expected that approximately 28 HSCT-TMA patients enrolled before Protocol Amendment 11 will be included to support a regulatory approval. The width of the exact 95% confidence interval (CI) for the response rate based on 28 HSCT-TMA patients ranges from 12.3% to 38.7%. If the observed response rate is 50%, the exact 95% CI is 30.6% to 69.4%.

Because this is an exploratory study, the sample size may be adjusted based on emerging data. If the sample size differs markedly from the planned enrollment, the protocol will be amended to accommodate the change.

13.2. Statistical and Analytical Plans

The statistical and analytical plans presented below are an overview of key analysis methods. Details of the analysis will be specified in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to interim database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

13.2.1. General Considerations

All data summaries will be descriptive in nature. Summary statistics for continuous variables will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be provided. When required for the statistical analysis of a particular variable, the baseline value will be the last recorded value prior to the administration of the first dose of study treatment. There are 2 exceptions. The baseline platelet count is defined as the average of the 2 predose values. The baseline creatinine is defined as the maximum creatinine value between the diagnosis of TMA and 4 weeks after the first dose of OMS721.

Statistical analyses will be focused on the HSCT-TMA patients and will be summarized by OMS721 dose (4.0 mg/kg, 370 mg, and both doses combined). Atypical hemolytic uremic syndrome and TTP patients will be summarized separately by OMS721 dose.

13.2.1.1. Handling of Missing Data

Non-responder imputation will be used to handle missing data for the binary efficacy endpoints. Time-weighted average analysis and repeated measures models will be used to analyze the continuous secondary efficacy endpoints over time.

13.2.1.2. Analysis Populations

Efficacy analyses will be performed for the Full Analysis Set (FAS) population and the Per-protocol Patient Set (PAS) population. The FAS population will include all HSCT-TMA patients who received any amount of study drug. The PAS population will include all HSCT-TMA patients who received at least 4 weeks of study treatment (treatment period is ≥ 28 days).

Safety analyses will be based on the Safety Analysis Set population, which includes all patients (aHUS, TTP, and HSCT-TMA) who received any amount of study drug.

13.2.2. Patient Disposition

An accounting of study patients by disposition will be tabulated by disease and dose. Patients who discontinued study drug prematurely or withdrew from the study will be summarized and listed, with reason for early termination/withdrawal.

13.2.3. Patient Characteristics

Demographic, other baseline characteristics, concomitant medications, and therapies (plasma therapy or renal dialysis) will be summarized descriptively by disease and dose.

13.2.4. Treatment Compliance

Because all dosing will be under direct supervision of study personnel, treatment compliance will not be analyzed. Dosing information, including supplemental dosing in conjunction with plasma therapy, will be listed.

13.2.5. Efficacy Analyses

13.2.5.1. Analysis of Primary Efficacy Endpoint

A patient is a responder if this patient meets the responder criteria (Section 7.3) at any time post baseline during the study. 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 and will be documented in the clinical study report. For example, potential confounding factors include graft failure for platelet count or transfusions and nephrotoxic medications for renal function. Furthermore, laboratory values collected from both the local laboratories and the central laboratories will be used to determine response status.

Analysis of the primary efficacy endpoint will use a non-responder imputation to impute missing or incomplete data to evaluate response. The number and percent of responders will be summarized with exact 95% CI (Clopper-Pearson) by dose and total for the FAS and PAS populations. If the lower bound of the exact 95% CI is greater than 15%, there is sufficient

evidence to demonstrate efficacy of OMS721 in the target patient population. Each criteria of the response will be listed for each patient.

Sensitivity analyses will include:

- Subgroup analyses for the FAS population
- A completer analysis will be performed using the patients with non-missing responses only. Exact 95% CI for the completer response rate will be provided for the FAS population by dose.
- Two alternative definitions of response will be analyzed:
  - The first alternative response is defined as achieving an improvement in TMA markers and an improvement in renal function as defined in Section 7.3. The number and percent of the patients achieving the first alternative response will be summarized with exact 95% CI by dose for the FAS population.
  - The second alternative response is defined as the same as the primary endpoint by excluding the neurological function defined in Section 7.3. The number and percent of patients achieving the second alternative response will be summarized with exact 95% CI by dose for the FAS population.

In addition, individual patient plots of platelet count and LDH over time will be provided.

13.2.5.2. Analysis of Secondary Efficacy Endpoints

The 100-day survival status will be determined as a binary variable. A patient achieves a 100-day survival if the overall survival from the date of HSCT-TMA diagnosis of the patient is ≥ 100 days. If the 100-day survival status of a patient is unknown (i.e., censored before 100 days), this patient will be considered to have died prior to 100 days. The 100-day survival rate will be estimated with exact 95% CI by dose for the FAS population.

Overall survival will be calculated from the date of TMA diagnosis. Overall survival will be analyzed using Kaplan-Meier method by dose for the FAS population. Median overall survival and its 95% CI will be estimated by dose.

The duration of response will be estimated for the FAS population. Duration of response is defined as the number of days from the first response date to the first relapse date (first relapse date – first response date + 1). The first response date is the first date that platelet count and LDH response is achieved. Relapse is defined as having a platelet count greater than 50% decrease from the maximum platelet count and an LDH greater than 1.5 times the ULN. Relapse will be evaluated using the platelet count and the LDH collected within 1 week. Duration of response will be censored at the last platelet or LDH collection date if relapse does not occur during the study. Kaplan-Meier analysis of the duration of response will be performed for the patients who achieve a response by dose for the FAS population. Median duration of response will be presented with 95% CI.

Binary secondary efficacy endpoints will be summarized with exact 95% CI by dose for the FAS population. Non-responder imputation will be used to handle missing data.

In addition, efficacy laboratory values of platelet count, LDH, creatinine, hemoglobin, and haptoglobin will be plotted over time for the HSCT-TMA patients.

13.2.6. Pharmacokinetic Analyses

Plasma concentrations of OMS721 and PD measures will be provided in listings. These data will be used in integrated population PK/PD analyses across studies. A PK/PD analysis plan will document the analyses.

13.2.7. Pharmacodynamic Analyses

The number and percent of patients with ADA will be summarized by disease, dose, Drug Product formulation, and time. Potential effects of ADA on PK and PD will be evaluated in integrated population PK/PD analyses which will be documented in the PK/PD analysis plan.

13.2.8. Exploratory Analyses

The concentration of MBL and MASP-2 will be summarized with descriptive statistics by disease, dose time, and Drug Product formulation, if appropriate. Thrombotic microangiopathy markers will be summarized by disease for aHUS and TTP.

13.2.9. Safety Analyses

13.2.9.1. Extent of Exposure

Study drug administration and duration of treatment will be summarized by disease and dose.

13.2.9.2. Adverse Events

Adverse events collected during the study and significant AEs will be combined for analysis. They will be labeled as AEs for simplicity. Significant AEs are the AEs that occurred outside the protocol-specified reporting period and will be collected for the HSCT-TMA patients only. For reporting purposes, AEs will be divided into 2 categories:

- Those that occurred prior to the start of study treatment (pre-treatment events) and
- Those that occur or worsen in intensity after the start of study treatment (treatment-emergent adverse events).

Summary of AEs will include the non-serious AEs during the AE evaluation period and all reported serious AEs. The AE evaluation period is defined from the time of informed consent to 37 days after the last study drug administration.

All AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). An AE is considered treatment-related if the relationship to study drug is either probable or possible as assessed by the Investigator.

Patient incidence of the following AEs will be provided:

- Pre-treatment AEs by MedDRA System Organ Class (SOC), preferred term, dose, and disease
- Treatment-emergent AEs by MedDRA SOC, preferred term, dose, and disease

- Treatment-emergent AEs by MedDRA preferred term, dose, and disease
- Treatment-related AEs by MedDRA SOC, preferred term, dose, and disease
- Treatment-emergent AEs by MedDRA preferred term, maximum severity, dose, and disease
- AEs leading to study discontinuation by MedDRA SOC, preferred term, dose, and disease
- Treatment-emergent serious AEs (SAEs) by MedDRA SOC, preferred term, dose, and disease
- Treatment-related SAEs by MedDRA SOC, preferred term, dose, and disease
- AEs leading to death by MedDRA SOC, preferred term, dose, and disease

In addition, the following analyses will be performed:

- Treatment-emergent AEs and treatment-emergent SAEs during the AE evaluation period will be summarized separately for patients with and without ADA postdose.
- Treatment-emergent AEs that started or worsen in intensity after the AE evaluation period will be summarized with patient incidence by SOC, preferred term, disease group, and dose level.
- Pre-treatment and treatment-emergent significant infections will be summarized by infection type, which will be determined before database lock and will be documented in the CSR.

13.2.9.3. Clinical Laboratory Results

Statistical analysis of clinical laboratory tests will be based on the results from central laboratories only. Results from central and local laboratories will be listed.

Summary statistics for the actual values and the change from baseline will be tabulated for laboratory results by dose, disease, and scheduled visit. Patients with laboratory values outside of the normal reference range at any post baseline assessment will be summarized by dose and disease. Shift tables comparing the baseline National Cancer Institute (NCI) CTCAE grade to the worst post baseline grade will be provided by dose and disease.

13.2.9.4. Vital Signs

Summary statistics for actual values and change from baseline will be tabulated for vital signs by dose, disease, and scheduled visit.

13.2.9.5. Electrocardiogram

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at each time point as well as the change from baseline will be summarized with descriptive statistics by dose and disease. These parameters will be determined electronically by the ECG machine at the clinical site. QTcF will be calculated using Fridericia's formula.

The overall ECG assessment will be reported as “Normal,” or “Abnormal – not clinically significant” or “Abnormal – clinically significant” with respect to relevant abnormalities by the Investigator. Shifts from the baseline ECG assessment to the worst post baseline ECG assessment will be tabulated by dose and disease. A listing of specific ECG abnormalities will be provided.

13.2.10. Interim Analyses

The coronavirus associated lockdown situation in various countries has created uncertainty in the ability to collect all follow-up data and resolve all queries on a few patients enrolled in the study. When adequate data on the primary and secondary endpoints is available, the database will be locked for interim analyses and creation of an interim CSR to enable regulatory submission for drug approval. Efforts will continue to collect additional follow-up data and resolve any outstanding queries.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will maintain appropriate medical and research records for this trial in accordance with ethics committee, regulatory, and ICH requirements for the protection of confidentiality of patients. The Investigator and his/her study center(s) will permit authorized representatives of the Sponsor, the governing ethics committee, competent authority, FDA, EMA, and/or other regulatory agencies to examine clinical records for the purposes of assisting with data entry, monitoring the study, including verifying the accuracy and completeness of data, evaluating study safety, assessing protocol and regulatory adherence and quality assurance reviews, audits, and inspections.

14.1. Study Monitoring

The Investigator and his/her study center(s) agree to allow the Sponsor or its representative to have direct access to all study-related source data/documents (as noted above) during monitoring visits. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, as well as assuring that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator.

14.2. Audits and Inspections

The study center will allow representatives of the Sponsor to periodically audit, at mutually convenient times, during and after the study all CRFs and corresponding source documents for each patient. CRFs will be reviewed by the Sponsor or its representative for adherence to protocol, completeness, and acceptability. Portions of the patient's medical and hospital records pertinent to the study will be reviewed at the study center to assure accuracy. It is important that the Investigator and/or other staff are available at these visits.

Additionally, during the course of this study or after it has been completed, representatives of FDA or other regulatory agency and the Investigator's ethics committee may inspect the study and review all study documents and reports, including CRFs, each patient's medical records, and other source documents. The Investigator agrees to make all study records, reports, and correspondence available to representatives of a regulatory agency or ethics committee. It is important that the Investigator and/or other staff are available at these visits. If contacted by a regulatory agency for an inspection, please call the Sponsor's study monitor immediately. Contact information for the Sponsor's study monitor is included in the Investigator file.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Following standard operating procedures, monitors will verify that the clinical trial is conducted and that data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

The investigational site should have standard operating procedures for quality management and will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

Data management will implement quality-control procedures beginning with the data entry system and generate data-quality checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. The site will be obligated to resolve the clarification of data in a timely manner.

15.1. Monitoring

Standards for GCP, as outlined by the ICH and FDA, will be applied to all study-based procedures.

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Provide start-up training and continuing training (if applicable) to the Investigator and study personnel on the protocol, the completion of the CRFs, and study procedures.
- Make periodic monitoring visits to the investigational site.
- Be available for consultation and stay in contact with the investigational site personnel by mail, telephone, electronic mail, and/or fax.
- Monitor the patient data recorded in the CRF against source documents at the investigational site.
- Review and evaluate CRF data and use standard criteria to detect potential errors in data collection and forward them to the Investigator for resolution.

15.2. Auditing

The study may be audited periodically by the Sponsor or its representatives at any time.

16. ETHICS

16.1. Ethics Review

Each participating institution must provide for the review and approval of this protocol, the associated informed consent documents, and any patient-directed materials by a properly constituted, IEC, or IRB. Any amendments to the protocol, consent, or patient-directed materials must also be approved prior to implementation. The Investigator will provide the Sponsor or its designee with documentation of the IRB or IEC approval of the protocol, informed consent document, and patient-directed materials before the study may begin at the investigative site(s).

In addition, the Investigator will submit for review to the investigative site's IRB/IEC:

- Clinical Investigator's Brochure and updates
- Required safety and SAE reports
- Deviations from the protocol and applicable FDA regulations (as required by the IRB/IEC)
- Any additional submissions (e.g., continuing review reports or new information) required by the site's IRB/IEC

The IRB/IEC will provide initial and continuing review. The continuing review will be performed at least once per year.

The Investigator must provide the Sponsor or its designee all IRB/IEC related submission decisions, approvals, and/or acknowledgement of receipts, as appropriate.

16.2. Ethical Conduct of the Study

16.2.1. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the Declaration of Helsinki, GCP, and all other applicable national, state, and local laws, rules, and regulations.

After reading the protocol, the Investigator will sign the Investigator Agreement and return it to the Sponsor or its designee.

16.2.2. Investigator Information

The contact information and qualifications of the Investigators and name and address of the research facilities are included in the Investigator file.

16.2.3. Protocol Amendments and Study Termination

Any Investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the Sponsor prior to seeking approval from the IRB/IEC and prior to implementing. The Investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the Sponsor and to the local IRB/IEC in accordance with IRB/IEC policies.

The Sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

16.2.4. Participant Confidentiality

All reports and communications relating to patients in the study will identify each patient only by the patient's initials and/or patient number.

16.2.5. Clinical Trial Agreement

Payments by the Sponsor to Investigators and institutions conducting the trial, requirements for Investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the Clinical Trial Agreement.

16.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Any procedures specifically for the study cannot be started until the informed consent form is signed by the patient and the person conducting the consent. Discussion of risks and possible benefits of this therapy will be provided to the patients. Consent forms describing in detail the Study Agent(s)/Intervention(s) study procedures and risks are given to the patient, and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB/IEC-approved, and the patient will be asked to read and review the document. Upon reviewing the document, the Investigator or appropriate designee will explain the research study to the patient and answer any questions that may arise. The patients should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

In addition, patients will provide written permission for use and disclosure of protected health information collected in connection with participation in this study through an authorization that satisfies the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (see 45 CFR 164.508). The authorization will be provided to patients in accordance with IRB procedures. The authorization may either be combined with the informed consent or provided as a separate document.

When a patient who may be enrolled in the trial only with the consent of the patient's legally acceptable representative (e.g., minors or participants with severe dementia), the patient should be informed about the trial to the extent compatible with the patient's understanding. If capable,

the patient should assent and sign and personally date the written consent form. A separate IRB/IEC-approved assent form, describing (in simplified terms) the details of the Study Agent(s)/ Intervention(s), study procedures, and risks may be used. Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative.

Data or records provided to Omeros will be coded, redacted, and de-identified to protect patient anonymity. All personal identifying data from this study will be treated in accordance with national and local data protection laws.

16.4. Investigator Reports

During the conduct of the study and at its completion, the Investigator will report to the IRB/IEC as required by the applicable IRB/IEC requirement and regulations. In addition, the Investigator will report to the Sponsor in accordance with regulation 21 CFR 312.64.

17. DATA HANDLING AND RECORDKEEPING

17.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the Investigator's site staff to ensure that the documents are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the Investigator.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

17.2. Data Capture Methods

Case Report Forms are used to transmit the information collected in the performance of this study to the Sponsor and FDA. The original CRFs will be retained by the Sponsor, and the Investigator will retain copies of the CRFs with the other records for this study.

The Investigator and study personnel will ensure that proper data for the clinical study are collected and accurately documented in the appropriate sections of the CRFs. The Investigator will review each CRF for completeness and accuracy and sign and date the forms where indicated. In addition, it will be the Investigator's responsibility to provide signatures where requested indicating concurrence with data in the CRF.

Case Report Forms will be reviewed by monitors from the Sponsor or its representative for adherence to protocol, completeness, and acceptability. Portions of the patient's medical and hospital records pertinent to the study will be reviewed at the study center to assure accuracy.

17.3. Source Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory, and institutional requirements, for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Food and Drug Administration regulations require that the Investigator prepares and maintains adequate and accurate records for each patient treated with study drug.

17.4. Retention of Records

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary.

Case Report Forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory agencies. The original CRFs will be retained by the Sponsor, and the Investigator will retain copies of the CRFs with the other records for this study.

Food and Drug Administration regulations require that the Investigator prepares and maintains adequate and accurate records for each patient treated with study drug. Source documents, such as hospital, clinic or office charts, laboratory reports, ECGs, operative reports, anesthesia records, consultation reports, history and physical examination reports, study worksheets, and the signed informed consent, will be included in the Investigator's files with the patient's study records.

Records containing patient medical information must be handled in accordance with the requirements of the HIPAA Privacy Rule (US) or applicable privacy regulations in the relevant countries and consistent with the terms of the patient authorization contained in the informed consent document for the study (the authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the authorization. Furthermore, CRFs and other documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of patient identities.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

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19. APPENDICES

19.1. Study Schedule of Events – Stage 1

Period	**SCR**	**Treatment**										**Follow-Up**			
Visit	1	2				3	4	5				6	7	8	9
Day	Up to –28	1	2	3	4	8	15	22	23	24	25	29	36	50	78
Informed Consent, Medical History, and Physical Examination	X														
Vital Signs	X	X[4]				X[4]	X[4]	X[4]				X	X		
ECG	X	X[5]						X[5]							
Chemistry and Hematology	X	X[6]				X[6]	X[6]	X[6]				X	X	X	X
Platelet Count	X[1]	X[6, 11]				X[6, 11]	X[6, 11]	X[6, 11]				X[11]	X[11]	X[11]	X[11]
LDH and Haptoglobin	X	X[6]				X[6]	X[6]	X[6]				X	X	X	X
Coagulation	X	X[6]				X[6]	X[6]	X[6]							
HIV Serology	X														
Urinalysis	X	X[6]				X[6]	X[6]	X[6]				X			
Pregnancy Test	X[12]	X[6]													X
Complement Genetics	X[2]														
ADAMTS13, STEC, and Coombs Test	X[3]														
Research Sampling		X[6,7]				X[10]	X[10]	X[10]				X[10]	X[10]	X[10]	X[10]
Study Drug Administration		X				X	X	X							
PK Sampling – serum		X[8]	X[8]	X[8]	X[8]	X[9]	X[9]	X[8]	X[8]	X[8]	X[8]	X	X	X	X
PD Sampling – serum		X[9]				X[9]	X[9]	X[9]				X	X	X	X
ADA Sampling		X[6]				X[6]	X[6]	X[6]				X	X	X	X
Adverse Events		X				X	X	X				X	X	X	X
ConMeds and Therapy	X	X				X	X	X				X	X	X	X

Abbreviations: ADA = anti-drug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; ConMeds = concomitant medications; ECG = electrocardiogram; h = hour; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; min = minutes; PD = pharmacodynamics; PK = pharmacokinetics; SCR = screening; STEC = Shiga toxin-producing E. coli.

[1] at least 2 values on separate days obtained in the week prior to Day 1 to establish baseline.

[2] aHUS population only, if not performed previously.

[3] if not previously performed for Coombs and ADAMTS13, if not previously excluded for STEC.

[4] predose; post start of dosing: 15 min, 30 min, 1 h, 2.5 h.

[5] predose; post dose obtained immediately before the 5-minute PK sample.

[6] pre dose.
[7] DNA, RNA, protein, cells.
[8] predose; post end of dosing: 5 min, 2 h, 24 h, 48 h, 72 h.
[9] predose; post end of dosing: 2 h.
[10] protein, cells.
[11] included as part of hematology.
[12] Serum pregnancy test is required at screening; serum or urine pregnancy test for all other time points.

19.2. aHUS Cohort, Stages 2 and 3 Study Scheduled Events

	Sta2e 2: aHUS Coho1·t														
Petiod	**SCR**	**Treatment**										**Follow-Up**			
Visit	1	T-1				T-N	T-12					F-1	F-2	F-3	F-4
Days	Upto -28	I	2	3	4	8-77	78		79	80	**81**	**85**	92	106	**120**
lnfo1med Consent, Medical History, and Phvsical Examination	X														
Vital Signs	X	x4				x4	x4								
ECG	X	x5													
Chemistry and Hematology	X	x6				x6	x6					X	X	X	X
Platelet Count	XI	X6,11				X6,1	X6,11					x11	x11	XII	x11
..,DH	X	x6				x6	x6					X	X	X	X
Haptoglobin	X	x6				x6	x6					X	X	X	X
Coagulation	X	x6				x6	x6								
HIV Serology	X														
Urinalysis	X	x6				x6	x6								
Pregnancy Test	x14	x6													X
Complement Genetics	x2														
ADAMTS13, STEC, and Coombs Test	x3														
Research Sampling		x6,1				x6,10	x6,10					xio	xio	xto	xio
Study Dmg Administrntion		X				X	X								
PK Sampling - semm		xs	xs	xs	xs	x9	x9,12		x12	x12	x12	X	X	X	X
PD Sampling - sernm		x9				x9	x9					X	X	X	X
ADA Sampling		x6				x6	x6					X	X	X	X
Adverse Events		X				X	X					X	X	X	X
ConMeds and Therapy	X	X				X	X					X	X	X	X
Stage 3 Assessment and Info1med =:'.011Sent						x!3									

Abbreviations: ADA= anti-diug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type **1** motif, member 13; aHUS = atypical hemolytic uremic syndi·ome; ConMeds = concomitant medications; ECG = electrocardiogram; h = hour; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; min = minutes; PD = pharmacodynamics; PK = pharmacokinetics; SCR = screening; STEC = Shiga toxin-producing E. coli.

[1] at least 2 values on separate days obtained in the week prior to Day 1 to establish baseline.

[2] aHUS population only, if not perfonned previously.

[3] if not previously performed for Coombs and ADAMTS13, if not previously excluded for STEC.
[4] predose; post start of dosing: 15 min, 30 min, 1 h, 2.5 h.
[5] predose; post dose obtained immediately before the 5-minute PK sample.
[6] pre dose.
[7] DNA, RNA, protein, cells.
[8] predose; post end of dosing: 5 min, 2 h, 24 h, 48 h, 72 h.
[9] predose; post end of dosing: 2 h.
[10] protein, cells.
[11] included as part of hematology.
[12] performed if this is the last day of dosing – predose, post end of dosing: 2 h, 24 h, 48 h, 72 h.
[13] The patient's treating Investigator and the Sponsor's medical monitor will determine eligibility for Stage 3 based upon the patient's response to therapy and safety and tolerability prior to the last scheduled treatment visit in Stage 2 in order to determine the appropriate PK draws following that visit.
[14] Serum pregnancy test is required at screening; serum or urine pregnancy test for all other time points.

	Stage 3: aHUS Cohort									
Period	**Treatment**						**Follow-Up**			
Visit	T-13	T-14 to T-23	T-24				F-1	F-2	F-3	F-4
Days	85	92 – 155	162	163	164	165	169	176	190	204
Informed Consent, Medical History, and Physical Examination										
Vital Signs	X[4]	X[4]	X[4]							
ECG										
Chemistry	X[6]	X[6]	X[6]				X	X	X	X
Hematology	X[6]	X[6]	X[6]				X	X	X	X
Platelet Count	X[6, 11]	X[6, 11]	X[6, 11]				X[11]	X[11]	X[11]	X[11]
LDH	X[6]	X[6]	X[6]				X	X	X	X
Haptoglobin	X[6]	X[6]	X[6]				X	X	X	X
Coagulation	X[6]	X[6]	X[6]							
HIV Serology										
Urinalysis	X[6]	X[6]	X[6]							
Pregnancy Test										X
Complement Genetics										
ADAMTS13, STEC, and Coombs Test										
Research Sampling	X[6, 10]	X[6, 10]	X[6, 10]				X[10]	X[10]	X[10]	X[10]

	Stage 3: aHUS Cohort									
Period	**Treatment**						**Follow-Up**			
Visit	T-13	T-14 to T-23	T-24				F-1	F-2	F-3	F-4
Days	85	92 – 155	162	163	164	165	169	176	190	204
Study Drug Administration	X	X	X							
PK Sampling – serum	X[9]	X[9]	X[8]	X[8]	X[8]	X[8]	X	X	X	X
PD Sampling – serum	X[9]	X[9]	X[9]				X	X	X	X
ADA Sampling	X[6]	X[6]	X[6]				X	X	X	X
Adverse Events	X	X	X				X	X	X	X
ConMeds and Therapy	X	X	X				X	X	X	X

Abbreviations: ADA = anti-drug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; ConMeds = concomitant medications; ECG = electrocardiogram; h = hour; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; min = minutes; PD = pharmacodynamics; PK = pharmacokinetics; STEC = Shiga toxin-producing E. coli.

[1] at least 2 values on separate days obtained in the week prior to Day 1 to establish baseline.
[2] aHUS population only, if not performed previously.
[3] if not previously performed for Coombs and ADAMTS13, if not previously excluded for STEC.
[4] predose; post start of dosing: 15 min, 30 min, 1 h, 2.5 h.
[5] predose; post dose obtained immediately before the 5-minute PK sample.
[6] pre dose.
[7] DNA, RNA, protein, cells.
[8] predose; post end of dosing: 5 min, 2 h, 24 h, 48 h, 72 h.
[9] predose; post end of dosing: 2 h.
[10] protein, cells.
[11] included as part of hematology.

19.3. TTP/HSCT-TMA Cohort: Stages 2 and 3 Study Schedule of Events

		Stage 2: TTP/HSCT-TMA													
Period	**SCR**	**Treatment**										**Follow-Up**			
Visit	1	T-1				T-2	T-3	T-4				F-1	F-2	F-3	F-4
Days	Up to -28	1	2	3	4	8	15	22		23	24	25	29	36	50	92
Info1med Consent, Medical History, and Physical Examination	X															
Vital Si!ms	X	X4				X4	X4	X4								
ECG	X	XS														
Chemistiy	X	X6				X6	X6	X6					X	X	X	X
Hematology	X	X6				X6	X6	X6					X	X	X	X
Platelet Count	X1	X6,1				X6,1	1X6,	X6,11					X11	X11	X11	X11
LDH	X	X6				X6	X6	X6					X	X	X	X
Haptoglobin	X	X6				X6	X6	X6					X	X	X	X
Coagulation	X	X6				X6	X6	X6								
HIV Seroloev	X															
Urinalysis	X	X6				X6	X6	X6								
Pre!mancy Test	X14	X6														X
Complement Genetics																
ADAMTS13, STEC, and Coombs Test	X3															
Research Sampling		x6,1				X10	X10	X10					xio	xio	xio	xrn
Study Dmg Administration		X				X	X	X								
PK Sampling - serum		XS	XS	XS	XS	X9	X9	X9,12		X12	X12	X12	X	X	X	X
PD Sampling - serum		X9				X9	X9	X9					X	X	X	X
ADA Sampling		X6				X6	X6	X6					X	X	X	X
Adverse Events		X				X	X	X					X	X	X	X
ConMeds and Theraov	X	X				X	X	X					X	X	X	X
Stage 3 Assessment and Info1med Consent							X1									

Abbreviations: ADA= anti-diug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ConMeds = concomitant medications; ECG = electrocardiogram; HIV = human immunodeficiency vims; LDH = lactate dehydrogenase; PD = pha1macodynamics; PK = phannacokinetics; SCR = screening; STEC = Shiga toxin-producing E. coli; TTP/HSCT-TMA = thrombotic thrombocytopenic purpw-a/hematopoietic stem cell transplant-thrombotic microangiopathies.

	Stage 3: TTP/HSCT-TMA Cohort										
Period	**Treatment**							**Follow-Up**			
Visit	T-5	T-N		T-8				F-1	F-2	F-3	F-4
Days	29	36	43	50	51	52	53	57	64	78	92
Informed Consent, Medical History, and Physical Examination											
Vital Signs	X[4]	X[4]	X[4]	X[4]							
ECG											
Chemistry	X[6]	X[6]	X[6]	X[6]				X	X	X	X
Hematology	X[6]	X[6]	X[6]	X[6]				X	X	X	X
Platelet Count	X[6, 11]	X[6, 11]	X[6, 11]	X[6, 11]				X[11]	X[11]	X[11]	X[11]
LDH	X[6]	X[6]	X[6]	X[6]				X	X	X	X
Haptoglobin	X[6]	X[6]	X[6]	X[6]				X	X	X	X
Coagulation	X[6]	X[6]	X[6]	X[6]							
HIV Serology											
Urinalysis	X[6]	X[6]	X[6]	X[6]							
Pregnancy Test											X
Complement Genetics											
ADAMTS13, STEC, and Coombs Test											
Research Sampling	X[10]	X[10]	X[10]	X[10]				X[10]	X[10]	X[10]	X[10]
Study Drug Administration	X	X	X	X							
PK Sampling – serum	X[9]	X[9]	X[9]	X[8]	X[8]	X[8]	X[8]	X	X	X	X
PD Sampling – serum	X[9]	X[9]	X[9]	X[9]				X	X	X	X
ADA Sampling	X[6]	X[6]	X[6]	X[6]				X	X	X	X
Adverse Events	X	X	X	X				X	X	X	X
ConMeds and Therapy	X	X	X	X				X	X	X	X

Abbreviations: ADA = anti-drug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ConMeds = concomitant medications; ECG = electrocardiogram; h = hour; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; m = minutes; PD = pharmacodynamics; PK = pharmacokinetics; STEC = Shiga toxin-producing E. coli; TTP/HSCT-TMA = thrombotic thrombocytopenic purpura/hematopoietic stem cell transplant-thrombotic microangiopathies.

[1] at least 2 values on separate days obtained in the week prior to Day 1 to establish baseline.

[2] aHUS population only, if not performed previously.

[3] if not previously performed for Coombs and ADAMTS13, if not previously excluded for STEC.

[4] predose; post start of dosing: 15 min, 30 min, 1 h, 2.5 h.

[5] predose; post dose obtained immediately before the 5-minute PK sample.

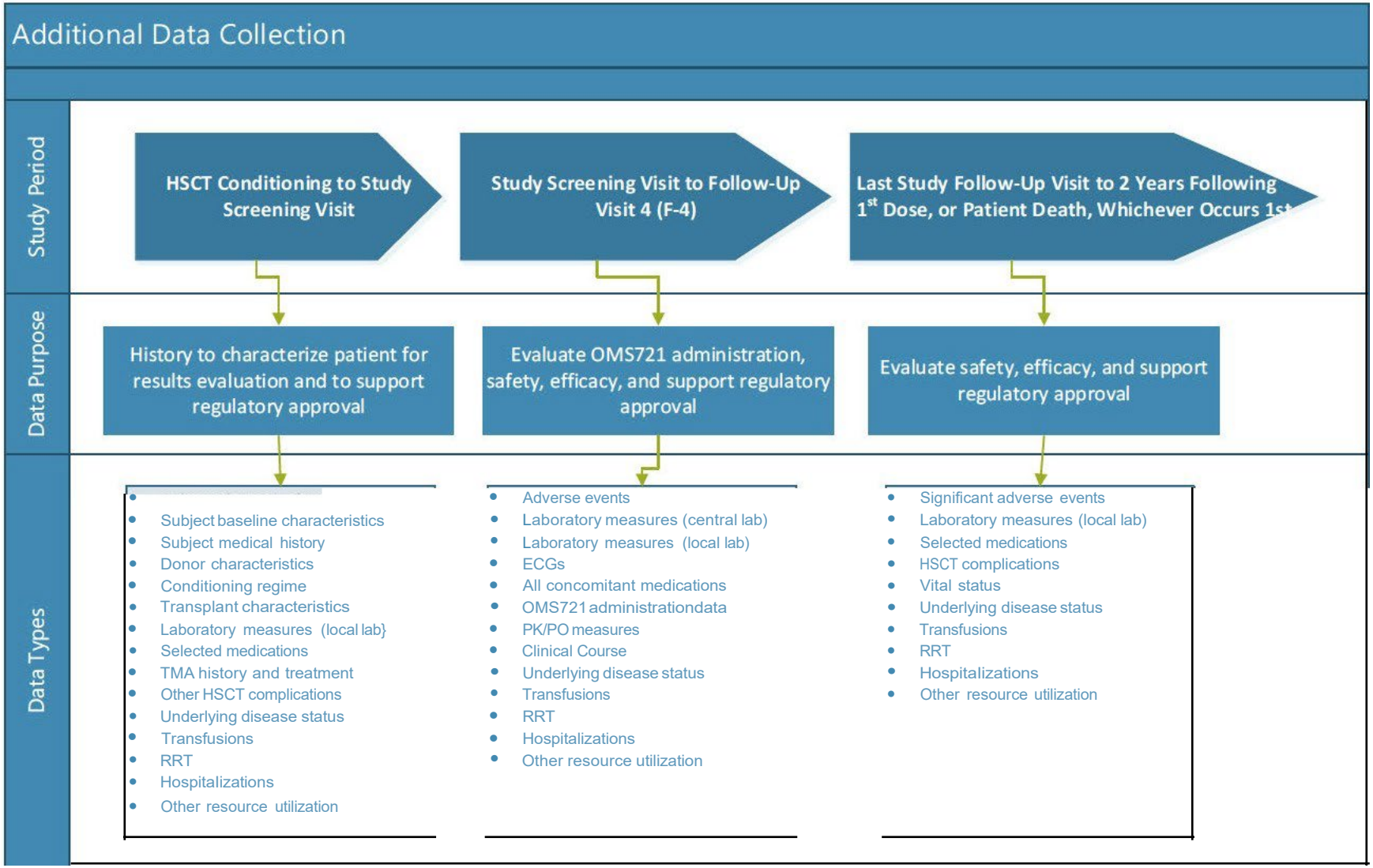
[6] pre dose.
[7] DNA, RNA, protein, cells.
[8] predose; post end of dosing: 5 min, 2 h, 24 h, 48 h, 72 h.
[9] predose; post end of dosing: 2 h.
[10] protein, cells.
[11] included as part of hematology.
[12] performed if this is the last day of dosing – predose, post end of dosing: 2 h, 24 h, 48 h, 72 h.
[13] The patient's treating Investigator and the Sponsor's medical monitor will determine eligibility for Stage 3 based upon the patient's response to therapy and safety and tolerability prior to the last scheduled treatment visit in Stage 2 in order to determine the appropriate PK draws following that visit.
[14] Serum pregnancy test is required at screening; serum or urine pregnancy test for all other time points.

19.4. Supplemental Data Collection (HSCT-TMA Patients Enrolled Under Amendment 10 or Earlier)

For patients with hematopoietic stem cell transplant-associated thrombotic microangiopathies (HSCT-TMA) enrolled under Amendment 10 or earlier versions of this protocol, additional data will be collected. These data will include supplemental data on patient demographics and baseline conditions, donor characteristics, the transplant procedure, concomitant medications, TMA-related laboratory measures, transfusions, transplant complications, and outcomes. These data will be derived 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) following the first dose of OMS721, whichever comes first.

Figure 9 below shows the periods for which additional data are to be collected and summarizes the data types. Details of the data to be collected are described in Table 2.

Figure 9: Additional Data Collection Schematic



Abbreviations: ECG= electrocardiogram; HSCT = hematopoietic stem cell transplant; PD = phannacodynamics; PK= phannacoki11etics; RRT = renal replacement therapy; TMA = thrombotic microangiopathies

Table 2: Additional Data Collection

Variables	Timing/Periodicity of Data Collection	Data Collection Rules/Definitions
Patient Baseline Data		
Blood type (ABO and Rh)	Pre-transplant, once	Pre-transplant blood type will be collected from the clinical chart and is required for interpretation of the effects of post-transplant blood transfusions.
HLA type	Pre-transplant, once	Data will be collected on at least both alleles of A, B, C, and DRB1 loci. Both alleles of the DQB1 and DPB1 loci will also be collected, if available. These data will be used to determine the degree of transplant match.
CMV antibody status	Pre-transplant, once	Values are positive, negative, and unknown.
Underlying disease	Pre-transplant, once	The disease for which the patient is receiving HSCT
Underlying disease status	Pre-transplant, once and at every assessment of status	Collect for underlying malignant diseases only. The categories are primary induction failure, complete remission, and relapse. If available, minimal residual disease will be collected. If the patient has had more than 1 complete response, each will be recorded.
Prior HSCT	Pre-transplant, once	Collect type (e.g., autologous or allogeneic), underlying disease, HLA match, donor relatedness, and cell source (bone marrow, peripheral blood stem cells, or cord blood).
Donor(s) Data		
Age	Pre-transplant, once	Required to evaluate outcomes because prognosis is better with younger donors.
Sex	Pre-transplant, once	Required to understand potential risks of female-to-male transplants.
Race	Pre-transplant, once	Collect as “American Indian or Alaska Native,” “Asian,” “Black or African American,” “Native Hawaiian or Other Pacific Islander,” “White,” or “Other” (Clinical Data Interchange Standards Consortium compliant terms).
Blood type (ABO and Rh)	Pre-transplant, once	Required for interpretation of the effects of post-transplant blood transfusions.
HLA type	Pre-transplant, once	For example, the HLA data from each donor will be required for a double cord transplant. Data will be collected on at least both alleles of A, B, C, and DRB1 loci. Both alleles of the DQB1 and DPB1 loci will also be collected, if available. These data will be used to determine the degree of transplant match.
Relatedness to patient	Pre-transplant, -once	Collect as related with relationship (parent, sibling, identical twin, or other) or unrelated. These data impact expected outcomes.
CMV antibody status	Pre-transplant, once	Values are positive, negative, and unknown. These data impact expected clinical course.
Transplant-Related Data		
Cell source	Pre-transplant, once	Collect as bone marrow, peripheral blood stem cells, or cord blood. Note the number of units if cord blood is the cell source.
Conditioning regimen	Pre-transplant, once	Collect all drugs used in conditioning with dosing regimen (dose level, frequency, and number). If radiation is used, collect radiation parameters including the total dose and whether total body irradiation or site-specific.

Variables	Timing/Periodicity of Data Collection	Data Collection Rules/Definitions
Transplant date	Transplant, once	The transplant date will be collected from the chart and used to measure survival duration. The day of transplant will be Day 0 in the survival calculation.
Neutrophil engraftment date	Post-transplant, once	This is defined as the first date on which the neutrophil count is $\geq 0.5 \times 10^9$/L for at least 3 consecutive measures on different days. This date is generally noted in the chart as the date of neutrophil engraftment. The chart-noted date will be used to define the engraftment date.
Platelet engraftment date	Post-transplant, once	Collect from clinical chart. This is defined as the first date on which the platelet count is 20×10^9/L for at least 3 consecutive measures on different days with no platelet transfusions in previous 7 days. This date is generally noted in the chart as the date of platelet engraftment. The chart-noted date will be used to define the engraftment date.
Chimerism with dates	Post-transplant, each instance	The percent chimerism will be collected with the corresponding cell type (for each cell type measured – RBC, CD34+ cells, mononuclear cells, T-cells, B-cells, granulocytes, and natural killer cells as reported).
Graft failure	Post-transplant	The diagnosis of graft failure with the date will be noted as such and may be qualified as primary or secondary. If noted in the chart, the primary or secondary nature should be noted.
GVHD prophylaxis	At time of transplant and ongoing throughout the study	Prophylaxis for GVHD will generally be provided with immunosuppressive medications. Each medication, dose, and dates of administration will be collected. Changes in the medications or decreases in dose will provide support for the requirement that patients have persistent HSCT-TMA despite modification of immunosuppression. The modification may occur prior to the chart diagnosis of HSCT-TMA because physicians react to changes in some measures (e.g., increasing LDH) while another measure (e.g., platelet count) has not become abnormal, delaying the diagnosis of HSCT-TMA.
Patient Status (with dates)		
Vital status	Last patient follow-up, once	Collect as the latest of 1) the last clinic visit or telephone contact with the patient at which the patient was alive or 2) the date of death.
Cause of death	Last patient follow-up, once	Collect for patients who have died. If no cause of death is recorded, the cause will be reported as unknown.
Date of death	Last patient follow-up, once	Collect for the patients who die.
Patient Relapse Status (with dates)		
Relapse	Each instance of relapse of the primary disease	Collect (with the date) and record as relapse. Minimal residual disease will be collected, if available.
Transplant Complications/ Interventions		
Acute GVHD	Each instance at onset	Collect with the date of diagnosis.
Chronic GVHD	At onset	Collect with the date of diagnosis.

Variables	Timing/Periodicity of Data Collection	Data Collection Rules/Definitions
VOD	At onset	Collect with the date of diagnosis.
IPS	Each instance at onset	Collect with the date of diagnosis. The presence of this syndrome will also be evidence of end-organ dysfunction. Idiopathic pneumonia syndrome will include DAH, acute interstitial pneumonitis, adult respiratory distress syndrome, peri-engraftment respiratory distress syndrome, non-cardiogenic capillary leak syndrome, and cryptogenic organizing pneumonia/bronchiolitis obliterans.
Capillary leak syndrome	At onset	Collect with the first date of diagnosis.
Posterior reversible encephalopathy syndrome	At onset	Collect with the first date of diagnosis.
Bacterial infection	Each instance at onset	Collect with the first date of diagnosis and affected organs. The organism will be collected.
Viral infection	Each instance at onset	Collect with the first date of diagnosis and affected organs. The identified virus will be collected.
Fungal infection	Each instance at onset	Collect with the first date of diagnosis and affected organs. The organism will be collected.
Parasitic infection	Each instance at onset	Collect with the first date of diagnosis and affected organs. The organism will be collected.
Suspected infection	Each instance at onset	If noted, collect with the first date of diagnosis and affected organs. If a suspected infection is later identified as caused by a specific organism, the event will be collected as an infection caused by the specific organism and not as a suspected infection.
Acute kidney injury	Each instance at onset	Collect with the date of first notation if noted in the clinical chart.
Chronic kidney disease	At onset	Collect with the date of first notation if noted in the clinical chart.
Renal replacement therapy	Each instance at onset	Defined as hemodialysis, peritoneal dialysis, and hemofiltration. Collect each instance and the date.
Stroke	At onset	Collect with the first date of diagnosis.
Confusion/Cognitive impairment	Each instance at onset	Collect with the first date of diagnosis.
Seizures	Each instance at onset	Collect with the first date of diagnosis.
Hallucinations	Each instance at onset	Collect with the first date of diagnosis.
Other central nervous system	Each instance at onset	Other neurological signs and symptoms will be collected with the first date of diagnosis from the clinical chart.
Engraftment syndrome	At onset	Collect with dates.
Hypoxia	Each instance at onset	Collect with dates.
Pulmonary arterial Hypertension	At onset	Collect with dates.
Continuous positive airway pressure	Each instance at onset	Collect with dates.

Variables	Timing/Periodicity of Data Collection	Data Collection Rules/Definitions
Mechanical ventilation/ extracorporeal membrane oxygenation	Each instance at onset	Collect with dates from the clinical chart.
Tissue biopsy	Each instance at onset	Collect with dates and findings from the clinical chart.
Transfusions (date, number of units, ABO, and Rh type)		
Red blood cell	Each instance	Collect the number of units with date. ABO and Rh group of each unit will also be collected.
Whole blood	Each instance	Collect the number of units with date. ABO and Rh group of each unit will also be collected.
Platelets	Each instance	Collect the number of units with date. ABO will be collected for each instance.
Intravenous immunoglobulin	Each instance	Collect the number of units with date.
Plasma therapy	Each instance	Plasma therapy is defined as plasma exchange or plasma infusion. Collect each instance of plasma therapy with the date.
TMA Event		
Date of diagnosis	Each instance	HSCT-TMA is required for inclusion in the study. The date of diagnosis is the first day that a diagnosis of HSCT-TMA was recorded in the clinical chart.
Date of onset	Each instance	HSCT-TMA is required for inclusion in the study.
TMA treatment	Each instance	This will be determined by review of concomitant medications and episodes of plasma therapy.
Hospital Resource Utilization		
Hospitalization time	Following TMA diagnosis	Collect all dates of hospital admission and discharge.
Intensive care unit time	Following TMA diagnosis	Collect all dates of intensive care unit admission and discharge.
Significant Adverse Events	Each instance	Collect events (with dates) requiring hospitalization or intervention with medication or procedures.
Concomitant Medications		
All immunosuppressives and changes	Each instance at onset	Collect the dates of initiation and discontinuation with each dose per administration. Collect changes in the dose per administration and frequency with dates.
All anti-infectives and changes	Each instance at onset	Collect the dates of initiation and discontinuation.
All cytotoxics	Each instance at onset	Collect the dates of initiation and discontinuation.
All targeted therapies	Each instance at onset	Collect the dates of initiation and discontinuation.
All growth factors	Each instance at onset	Collect the dates of initiation and discontinuation.

Variables	Timing/Periodicity of Data Collection	Data Collection Rules/Definitions
Eculizumab	Each instance at onset	Collect the dates of initiation and discontinuation.
Defibrotide	Each instance at onset	Collect the dates of initiation and discontinuation.
Investigational agents	Each instance at onset	Collect the dates of initiation and discontinuation.
Total parenteral nutrition	Each instance at onset	Collect the dates of initiation and discontinuation.
Ursodeoxycholic acid	Each instance at onset	Collect the dates of initiation and discontinuation.
Heparin	Each instance at onset only for VOD prophylaxis	Collect the dates of initiation and discontinuation.
Laboratory Measures		
Platelet count	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Hemoglobin	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
White blood cell	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Absolute neutrophil count	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Lactate dehydrogenase	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Haptoglobin	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Creatinine	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Bilirubin	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Aspartate aminotransferase	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Alanine aminotransferase	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Alkaline phosphatase	See laboratory measure schedule[1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Coombs	Each instance	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.

Variables	Timing/Periodicity of Data Collection	Data Collection Rules/Definitions
Schistocytes	See laboratory measure schedule [1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.
Others abnormal	See laboratory measure schedule [1]	Collect from the clinical chart. Overlapping data will also be available from the central laboratory on some dates.

Abbreviations: CMV = cytomegalovirus; DAH = diffuse alveolar hemorrhage; GVHD = graft-versus-host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; IPS = idiopathic pneumonia syndrome; LDH = lactate dehydrogenase; RBC = red blood cell; TMA = thrombotic microangiopathy; VOD = veno-occlusive disease.

[1] Laboratory measure schedule: Laboratory measures will be collected according to the schedule as outlined below.

19.5. Laboratory Measure Schedule

As available, local laboratory measures of platelet count, Hgb, white blood cell count, absolute neutrophil count, LDH, haptoglobin, creatinine, bilirubin, AST, ALT, alkaline phosphatase, and schistocytes will be collected according to the following schedule:

Pre-TMA period:

- Once immediately prior to conditioning
- On Day –1 or 0 prior to transplant (the measure closest to the transplant). (Day 0 is the day of transplant)
- On Days +2, +4, +6, +8, +10, +14, +21, +28 following transplant and weekly thereafter until 28 days prior to the diagnosis of TMA

TMA period:

- Daily from 28 days prior to the diagnosis of TMA to the later of 12 weeks following the diagnosis of TMA or 4 weeks following resolution of TMA

Post-TMA period:

- Once weekly following the TMA period for 4 weeks, then once every 2 weeks for 4 weeks, and then once monthly ± 3 days until up to 2 years following the first dose of OMS721

Platelet count should be recorded immediately before and after each platelet transfusion.

Hemoglobin levels should be recorded immediately before and after each RBC transfusion.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hgb = hemoglobin; LDH = lactate dehydrogenase; RBC = red blood cell; TMA = TMA = thrombotic microangiopathy.