OMEROS

OMEROS CORPORATION

CLINICAL PROTOCOL

PROTOCOL NO. OMS721-HUS-002
Amendment 01

Investigational New Drug
OMS721

A Phase 3 Study to Evaluate the Safety and Efficacy of OMS721 for the Treatment of Atypical Hemolytic Uremic Syndrome (aHUS) in Adults and Adolescents

31 May 2017

APPROVED BY:

[redacted]

Date

1.1. Investigator Agreement

I have read Omeros Protocol No. OMS721-HUS-002 Amendment 01 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

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-HUS-002	
Title of Study: A Phase 3 Study to Evaluate the Safety and Efficacy of OMS721 for the Treatment of Atypical Hemolytic Uremic Syndrome (aHUS) in Adults and Adolescents	
Planned Number of Clinical Study Center(s): Approximately 50	**Phase of Development:** Phase 3
Expected Duration of Study: Approximately 60 months (first subject first visit to last subject last visit)	

Objectives:

The primary objective of this study is to evaluate the effect of OMS721 in subjects with aHUS on:

- Platelet count change from baseline

The secondary objectives of this study are to evaluate the effect of OMS721 in subjects with aHUS on:

- Safety and tolerability measured by adverse events (AEs), serious AEs (SAEs), vital signs, laboratory measures, electrocardiograms (ECGs), and physical examination
- The proportion of subjects who achieve complete thrombotic microangiopathy (TMA) response defined as normalization of platelet count, normalization of serum lactate dehydrogenase (LDH), and > 25% decrease in the baseline serum creatinine on at least 2 consecutive measurements over at least 4 weeks
- The duration of complete TMA response measured from the time of the first measurement of complete TMA response to the end of the complete TMA response
- The time to complete TMA response measured by the time to reach the first measurement of complete TMA response
- The proportion of subjects who achieve TMA event-free status during treatment defined as no decrease in platelet count of > 25% from baseline, no plasma exchange or plasma infusion, and no initiation of new dialysis for ≥ 12 consecutive weeks
- The time to TMA event-free status measured by the time to reach the first documented TMA event-free status from the first dose of OMS72
- The proportion of subjects who achieve an increase of > 15 ml/min/1.73 m^2 in the estimated glomerular filtration rate (eGFR) calculated by either the Modification of Diet in Renal Disease Study (MDRD) Equation for subjects aged ≥ 18 years and the Schwartz equation for subjects < 18 years

- The time to eGFR increase of > 15 ml/min/1.73 m^2 measured by the time to reach the first measurement increase in eGFR of > 15 ml/min/1.73 m^2 from the first dose of OMS721
- The proportion of subjects who achieve hematological normalization defined as normalization of platelet count and normalization of serum LDH on at least 2 consecutive measurements over at least 4 weeks
- The time to hematological normalization measured by the time to reach the first measurement of hematological normalization from the first dose of OMS721
- The proportion of subjects who achieve TMA remission defined as platelet count ≥ 150,000/μL on at least 2 consecutive measures over at least 2 weeks
- Quality of life as measured by EQ-5D-5L
- Serum creatinine change from baseline
- Serum LDH change from baseline
- Serum haptoglobin change from baseline
- Rate of TMA interventions defined as the number of dialysis events, plasma infusion events and plasma exchange events per subject per day
- Determine the pharmacokinetics (PK) of OMS721
- Determine the pharmacodynamics (PD) of OMS721
- Determine the immunogenicity of OMS721 [Proportion of subjects who develop anti-drug antibody (ADA)]

Methodology:

In this study, OMS721 is to be used in conjunction with standard of care treatments. Standard of care treatments are not to be delayed or withheld from subjects entering this study. These treatments, including immunizations, should be administered according to local standard of care. Subjects who have failed a treatment, e.g., subjects with plasma therapy-resistant aHUS, do not require continued treatment with the failed therapy.

This uncontrolled, open-label study will evaluate the effect of OMS721 in subjects with aHUS. The primary outcome to be measured is platelet count change from baseline. The secondary outcomes to be measured are other efficacy measures, safety, PK, PD, and immunogenicity (i.e., presence of anti-drug antibody [ADA] response).

Subjects with plasma therapy-resistant aHUS and plasma therapy-responsive aHUS will be eligible. Prior clinical experience indicates that most (≥ 70%) subjects will be plasma therapy-resistant. The efficacy endpoints, including the primary efficacy endpoint, may not be relevant for plasma therapy-responsive subjects because these subjects may enter the study with normal markers of aHUS activity due to successful treatment with plasma therapy. Therefore, efficacy analyses will be performed separately in the plasma therapy-resistant and plasma therapy-responsive subjects. The principal efficacy analyses will be the analyses in the plasma therapy-resistant cohort and efficacy analyses of the plasma therapy-responsive cohort will be supportive. Safety analyses will be conducted in all subjects.

Safety will be monitored on a regular basis throughout the study by the Data Monitoring Committee (DMC) (Section 10.4). An interim analysis is planned when approximately 40 patients in the full analysis set (Section 13.2.4.2) have been followed for at least 26 weeks. The purpose of the interim analysis is to provide an extensive safety and efficacy data review in addition to the regular safety monitoring. The study will not be stopped for efficacy based on the interim data and, therefore, no multiplicity adjustment is required. The DMC and the Sponsor will review the interim data and make recommendations according to the DMC charter (see also Section 10.4).

This study has four periods: Screening, Treatment Induction, Treatment Maintenance, and Follow-up.

Screening Period

The Screening Period for subjects with plasma therapy-resistant aHUS and plasma therapy-responsive aHUS will be different. The Screening Period for subjects who are plasma therapy-resistant will last no more than 5 days. The Screening Period for subjects who are plasma therapy-responsive will last 14 – 28 days.

Plasma Therapy-Resistant Cohort

Subjects are considered plasma therapy-resistant if they have thrombocytopenia at screening despite previously receiving at least 4 treatments of plasma therapy (plasma infusion or plasma exchange) in 7 days without resolution of the thrombocytopenia. The week of plasma therapy may occur any time prior to screening. Preferably, the plasma therapy will occur in the week prior to screening, however, subjects who previously received 4 plasma therapy treatments in a 7-day period without resolution of the thrombocytopenia are not required to repeat plasma therapy provided the plasma therapy can be documented through the investigative site medical records or communication from referring physicians.

Subjects who remain thrombocytopenic despite plasma therapy as described above will enter screening. The screening visit is Visit 1. At screening, four sets of laboratory samples will be collected: the first two sets will include one set for analysis in the local laboratory to determine eligibility and the other set for analysis in the central laboratory to be used for efficacy and safety evaluations. Local laboratory measures will include at least platelet count, hemoglobin, LDH, creatinine, haptoglobin, schistocyte count, alanine transaminase (ALT), and aspartate transaminase (AST) to determine eligibility. The third and fourth sets of laboratory samples are platelet count only and will be drawn between 1 and 4 hours following the first and second sets: one set will be analyzed by the local laboratory to determine eligibility and the other set will be sent for analysis at the central laboratory. Eligibility will be determined by local laboratory measures. The platelet count used for eligibility will be the mean of the two screening platelet counts measured at the local laboratory.

Because some plasma therapy-resistant subjects may have severe or unstable aHUS when enrolled and certain laboratory tests can require several days for reporting, Investigators may initiate treatment with OMS721 prior to receiving the screening central laboratory results for the Shiga toxin assay, the human immunodeficiency virus (HIV) assay, and the ADAMTS13 assay. If a subject receives treatment prior to investigative site receipt of any of the Shiga toxin assay, the HIV assay, and the ADAMTS13 assay and any of those assays is subsequently found to be positive, the subject will be immediately discontinued from the study. This

possibility that a subject may be withdrawn from OMS721 treatment following its initiation will be explained in the informed consent document.

Plasma Therapy-Responsive Cohort

Subjects are considered plasma therapy-responsive if they have a documented history of requiring plasma therapy to prevent aHUS exacerbation including decrease in platelet count and increase in LDH when the frequency of plasma therapy has been decreased (including discontinuation of plasma therapy). Subjects must have received plasma therapy at least once every 2 weeks at an unchanged frequency for at least eight weeks before first dose of OMS721. These historical data must be documented through investigative site medical records or communication from referring physicians.

The screening visit is Visit 1. At screening, four sets of laboratory samples will be collected: the first two sets will include one set for analysis in the local laboratory to determine eligibility and the other set for analysis in the central laboratory to be used for efficacy and safety evaluations. Local laboratory measures will include at least platelet count, LDH, creatinine, haptoglobin, ALT, AST, and schistocyte count to determine eligibility. The third and fourth sets of laboratory samples are platelet count only and will be drawn between 1 and 4 hours following the first and second sets: one set will be analyzed by the local laboratory to determine eligibility and the other set will be sent for analysis at the central laboratory. Eligibility will be determined by local laboratory measures. The platelet count used for eligibility will be the mean of the two screening platelet counts measured at the local laboratory.

Plasma therapy will be documented over at least 14 days before initiating OMS721 treatment.

<u>Treatment Induction Period (Day 1 to Day 4)</u>

The Treatment Induction Period will generally differ between the plasma therapy-resistant and plasma therapy-responsive subjects because plasma therapy-responsive subjects will continue to receive plasma therapy through this period with supplemental OMS721 doses while plasma therapy-resistant subjects may not. The supplemental OMS721 doses will allow subjects to attain steady-state OMS721 plasma concentrations.

After completing the Screening Period, eligible subjects will enter the Treatment Induction Period. The first treatment visit is Visit 2. Prior to the first OMS721 treatment subjects will have two platelet count samples collected. The second platelet count sample will be collected between 1 and 4 hours following the first platelet count sample. These samples will be sent to the central laboratory and the mean value will be used as the baseline platelet count for analyses. Visit 1 and Visit 2 may be combined for plasma therapy-resistant subjects. If Visit 1 and Visit 2 are combined, laboratory measures collected for Visit 1 will serve as the laboratory measures for Visit 2 as well.

During the Treatment Induction Period, subjects will receive OMS721 370 mg IV administered on Days 1 and 4. Beginning on the day of the first dose, subjects will also begin treatment with 150 mg SC once daily. The first SC injection will be prepared and administered by study site personnel to demonstrate proper technique. The next three SC doses will be prepared and administered by the subject or subject's caregiver to ensure that proper dose preparation and injection technique are being employed. Additional SC injections may be administered at the site at the discretion of site personnel if needed for instructional purposes.

If a subject receives plasma therapy on Day 2 or Day 3 during the Treatment Induction Period, the subject will receive supplemental OMS721 185 mg IV as provided in Section 9.1.3.1. If the subject receives plasma therapy on Day 1 or Day 4 of the Treatment Induction Period, the regularly scheduled OMS721 IV dose will be administered within one (1) hour after plasma exchange or within one (1) hour before plasma infusion.

Treatment Maintenance Period

After completion of the IV dosing during the Treatment Induction Period, subjects will enter the Treatment Maintenance Period. During this period, subjects will continue to receive OMS721 150 mg SC once daily. This dosing regimen will continue throughout the treatment period. Subjects or subject caregivers will do dipstick urine tests at least 3 times weekly. If the presence of blood is detected, the Investigator will be contacted immediately for potential evaluation of aHUS exacerbation.

For plasma therapy-responsive subjects, at the time of the last IV dose of the Treatment Induction Period, the frequency of plasma therapy will be decreased by one plasma therapy treatment per week (discontinued for subjects receiving plasma therapy with a frequency of ≤ once weekly) until plasma therapy is discontinued.

If a subject receives plasma therapy during the Treatment Maintenance Period, the subject will receive supplemental OMS721 185 mg IV as provided in Section 9.1.3.1. The procedures to be performed during the supplemental doses are provided in Section 10.1.8.

Rescue Therapy

At the discretion of the Investigator, OMS721 370 mg IV administered once every 3 days and/or plasma therapy may be reinitiated for any subjects who experience a TMA relapse. OMS721 SC injections should continue throughout this period. If a subject requires Rescue Therapy during the Treatment Maintenance Period, the Investigator may contact the Sponsor and, if agreed, increase the daily SC dose of OMS721 to not more than 300 mg SC daily to account for potential PK variability of SC administration. Also, if a subject receives plasma therapy during this period, the subject will receive supplemental OMS721 185 mg IV as provided in Section 9.1.3.1. If the subject receives plasma therapy on Rescue Therapy Day 1, the regularly scheduled OMS721 IV dose will be administered within one (1) hour after completion of plasma exchange or within one (1) hour before plasma infusion.

The total time of the Treatment Induction and Treatment Maintenance Periods is two years.

Follow-up Period

After completion of the Treatment Maintenance Period or early discontinuation of study treatment, subjects will undergo two Follow-up visits. Subjects who complete the Treatment Maintenance Period may be eligible to continue treatment under a future protocol amendment or under expanded access (compassionate use).

During the study, subjects will have 38 scheduled visits. If a subject relapses, there will be additional treatment visits. The length of time for individual subject participation will be approximately 111-114 weeks. The total time of the study from first subject first visit to last subject last visit is anticipated to be approximately 60 months.

Number of Subjects (Planned): Approximately 80

Diagnostic Criteria and Main Criteria for Inclusion:

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

1. Competent to provide informed consent or, if a minor, have at least one parent or legal guardian to provide informed consent with written assent from the subject.
2. If an adult, 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. If a minor, at least one parent or legal guardian must provide informed consent and the subject must provide assent 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. Willing and able to comply with study procedures.
4. Are age ≥12 at screening (Visit 1).
5. Have a primary aHUS, diagnosed clinically, and have ADAMTS13 activity > 5% in plasma. Patients are eligible with or without a documented complement mutation or 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 four plasma therapy treatments in a 7-day period prior to screening
        - Evidence of microangiopathic hemolysis (at least one of: (1) presence of schistocytes, (2) serum LDH > 1.5 times upper limit of normal (ULN), and (3) haptoglobin < LLN)
        - Serum creatinine > ULN
    - Plasma therapy-responsive aHUS patients must have all of the following:
        - Have a documented history of requiring plasma therapy to prevent aHUS exacerbation defined as all of the following:
            - decrease in platelet count > 25% when plasma therapy frequency has been decreased (including discontinuation of plasma therapy)
            - LDH > 1.5 times ULN when plasma therapy frequency has been decreased (including discontinuation of plasma therapy)
        - Have received plasma therapy at least once every 2 weeks at an unchanged frequency for at least 8 weeks before first dose of OMS721
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.
7. Do not have access to eculizumab treatment, have not derived therapeutic benefit from eculizumab treatment, or have not been able to tolerate eculizumab treatment.

Exclusion Criteria:

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

1. Have STEC-HUS.
2. Have a positive direct Coombs test.
3. Have a history of hematopoietic stem cell transplant.
4. Have HUS from an identified drug.
5. History of vitamin B12 deficiency-related HUS.
6. History of Systemic Lupus Erythematosus.
7. History of antiphospholipid syndrome.
8. Active cancer or history of cancer (except non-melanoma skin cancers) within 5 years of screening.
9. Have been on hemodialysis or peritoneal dialysis for ≥ 12 weeks.
10. Have an active systemic bacterial or fungal infection requiring systemic antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed).
11. Baseline resting heart rate < 45 beats per minute or > 115 beats per minute.
12. Baseline QTcF > 470 milliseconds.
13. Have malignant hypertension (diastolic blood pressure [BP] > 120 mm Hg with bilateral hemorrhages or “cotton-wool” exudates on funduscopic examination).
14. Have a poor prognosis with a life expectancy of less than three months in the opinion of the Investigator.
15. Are pregnant or lactating.
16. Have received treatment with an investigational drug or device within four weeks of the screening visit.
17. Have abnormal liver function tests defined as ALT or AST > five times ULN.
18. Have HIV infection.
19. History of cirrhosis of the liver.
20. Are an employee of Omeros, an Investigator, a study staff member, or their immediate family member.
21. Have a known hypersensitivity to any constituent of the product.
22. Presence of any condition that the Investigator believes would put the subject at risk or confound the interpretation of the data.
23. Have previously completed treatment in an OMS721study.
24. Have received intravenous immunoglobulin (IVIG) treatment within 8 weeks of screening visit.
25. Have received rituximab within 24 weeks of screening visit.

Investigational Product, Dosage, and Mode of Administration

[redacted] OMS721 Drug Product, [redacted]
OMS721 Drug Product, [redacted]

- IV dosing at 370 mg [redacted]
- SC dosing at 150 mg [redacted]

Duration of Treatment:

104 weeks

Reference Therapy, Dosage, and Mode of Administration:

Not applicable

Study Endpoints:

Primary Endpoint

- Platelet count change from baseline to week 26

Secondary Endpoints

- Safety as assessed by AEs, SAEs, vital signs, ECGs, physical examinations, and laboratory measures
- Complete TMA response defined as normalization of platelet count, normalization of serum LDH, and > 25% decrease in serum creatinine on at least 2 consecutive measures over at least 4 weeks
- Duration of complete TMA response measured from the time of the first measurement of complete TMA response to the last consecutive measurement of complete TMA response
- Time to complete TMA response measured by the time to reach the first measurement of complete TMA response
- TMA event-free status during treatment defined as no decrease in platelet count of > 25% from baseline, no plasma exchange or plasma infusion, and no initiation of new dialysis for at least 12 consecutive weeks
- Time to TMA event-free status measured by the time to reach the first documented TMA event-free status from the first dose of OMS721
- Increase of > 15 ml/min/1.73 m^2 in the estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease Study (MDRD) Equation for subjects aged ≥ 18 years and the Schwartz equation for subjects < 18 years
- Time to eGFR increase of > 15 ml/min/1.73 m^2 measured by the time to reach the first measurement increase in eGFR of > 15 ml/min/1.73 m^2 from the first dose of OMS721

- Hematological normalization defined as normalization of platelet count and normalization of serum LDH on at least 2 consecutive measurements over at least 4 weeks
- Time to hematological normalization measured by the time to reach the first measurement of hematological normalization from the first dose of OMS721
- TMA remission defined as platelet count ≥ 150,000/μL on at least 2 consecutive measures over at least 2 weeks
- Quality of life as measured by EQ-5D-5L
- Serum creatinine change from baseline
- Serum LDH change from baseline
- Serum haptoglobin change from baseline
- Rate of TMA interventions defined as the number of dialysis events, plasma infusion events and plasma exchange events per subject per day over the treatment period
- PK of OMS721
- PD of OMS721
- ADA

Statistical Methods:

Determination of Sample Size

The sample size is based on the plasma therapy-resistant cohort. Assuming that the true mean platelet count change from baseline is $78x10^{-9}$/L with a standard deviation of $64x10^{-9}$/L (Legendre, et al., 2013), a sample size of 56 plasma therapy-resistant subjects will provide 90% power to test a null mean platelet count change from baseline of $45x10^{-9}$/L at two-sided significance level of 5% using t-test. It is assumed that 70% of the eligible subjects will be plasma therapy-resistant. Therefore, the total sample size is 80 subjects who meet the full analysis set criteria.

Analysis Populations

The full analysis set (FAS) will include all subjects who receive any amount of study treatment and have at least one post-baseline platelet count. The primary efficacy analyses will be based on the FAS.

The safety analysis set will include all subjects who receive any amount of study treatment. The safety analyses will be based on the safety analysis set.

Efficacy Analyses

The plasma therapy-resistant cohort will be the primary subject cohort for the evaluation of efficacy of OMS721. All efficacy analyses will be performed separately for the plasma therapy-resistant cohort and the plasma therapy-responsive cohort. Primary efficacy analyses will be based on the FAS. Supportive efficacy analyses will be based on the safety analysis set.

The primary efficacy endpoint (platelet count change from baseline) will be summarized descriptively by visit and cohort during the treatment period (induction and maintenance). A

repeated measures model with time and baseline platelet count as fixed effects, and subject as random effect will be used to evaluate the primary endpoint by cohort. A generalized estimating equation (GEE) method will be applied to estimate the least-squares mean change from baseline with 95% confidence interval at each scheduled time point.

Secondary efficacy endpoints will be summarized with descriptive statistics by cohort. Unless otherwise specified, 95% confidence interval for mean using t-distribution for continuous endpoints, 95% confidence interval for median time-to-event endpoints using Kaplan-Meier method, and exact 95% confidence interval for binary endpoints will be provided as appropriate.

Pharmacokinetic Analyses

Serum concentration will be summarized by cohort and visit. Pharmacokinetic parameters will be calculated and summarized by cohort.

Anti-Drug Antibody Response

The proportion of subjects with detected antibody responses will be summarized by cohort and visit. The antibody titer and neutralizing activity will be determined for ADA positive samples.

Pharmacodynamic Analyses

The PD effect will be assayed *ex vivo* by quantifying lectin pathway activity and summarized by cohort and visit.

Pharmacokinetic/Pharmacodynamic Relationship

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

Safety Analyses

Safety analyses will be based on the safety analysis set. Safety endpoints will be descriptively summarized by cohort. Adverse events will be coded according to preferred term and system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary.

3. TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES

TABLE OF CONTENTS

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
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under time-concentration curve
BIW	Twice weekly
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CL	Clearance
C_{max}	Maximum concentration
CRF	Case report form
DNA	Deoxyribonucleic acid
DMC	Data monitoring committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HPF	High-power field
HSCT	Hematopoietic stem cell transplant
HUS	Hemolytic uremic syndrome
IC_{50}	Inhibitory concentration 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalised ratio
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous immunoglobulin
Kg	Kilogram
λz	Elimination rate constant
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
µL	Microliter
mAb	Monoclonal antibody
MASP	Mannan-binding lectin-associated serine protease

Abbreviation or Specialist Term	Explanation
MBL	Mannan-binding lectin
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
mM	Millimolar
mm Hg	Millimeter of mercury
Ng	Nanogram
nM	Nanomolar
NOAEL	No observed adverse effect level
PD	Pharmacodynamic
PK	Pharmacokinetic
pM	Picomolar
PT	Prothrombin time
QD	Once Daily
QW	Once weekly
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
STEC	Shiga toxin-producing E. coli
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TMA	Thrombotic microangiopathies
T_{max}	Time to maximum concentration
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
V_z	Volume of distribution

5. INTRODUCTION

5.1. Background

5.1.1. Description of OMS721

Omeros Corporation (Omeros, Sponsor) is developing OMS721, a human 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.

There are three ways under which the complement system can be activated in response to distinct initiating events: the classical, lectin, and alternative pathways. The classical pathway is triggered by immune complexes, as part of the adaptive immune response, and mediates important immune effector functions. Lectin pathway activation is initiated by MBL or other types of lectin recognition molecules, including ficolins and collectins, complexed with MASP-2 [Yongqing 2012]. OMS721 blocks the activity of MASP-2, inhibiting the lectin pathway of complement without affecting the lytic arm of the classical pathway, thereby leaving antigen-antibody complexing and the adaptive immune response intact. In contrast, C5 inhibition (e.g., eculizumab) blocks the classical pathway's lytic arm. Functioning primarily as an amplification loop, the alternative pathway is continuously activated at a low level and is kept in check by a series of regulatory proteins.

OMS721 is a fully human IgG4 mAb directed against MASP-2. OMS721 avidly binds to recombinant MASP-[redacted]

5.1.2. Indication – Atypical Hemolytic Uremic Syndrome

Based on mechanism of action and results of clinical studies, OMS721 is in development for the treatment of aHUS, one form of TMA. Thrombotic microangiopathies are a diverse group of diseases and may present as a primary condition or in association with other diseases. 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. Vascular injury is common to all TMAs [George 2014]. The disorders that are associated with TMA are characterized by systemic or intrarenal aggregation of platelets, thrombocytopenia, and mechanical injury to erythrocytes.

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 aHUS, HSCT-TMA, thrombotic thrombocytopenic purpura (TTP), cancer chemotherapy-associated TMA, and calcineurin inhibitor-associated TMA.

Atypical HUS is a rare, life-threatening disease that, if left untreated, results in end-stage renal disease in 50% of patients within one year of diagnosis [Loirat 2011]. Approximately 67% of these patients are children. Dysregulation of the complement system lies at the heart of aHUS pathogenesis, and genetic abnormalities in complement genes have been identified in approximately 50% 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.

Untreated, aHUS commonly causes end-stage renal disease or death. Atypical HUS is treated with plasma therapy (plasma exchange or plasma infusion) or eculizumab, an anti-complement factor 5 (C5) mAb. Plasma exchange or plasma infusion can replace defective complement regulatory proteins. This treatment is not effective in all patients. Eculizumab is approved for treatment of aHUS, but is not available in many countries due to its cost (approximately US$600,000/year) [George 2014]or lack of local regulatory approval. Additionally, some aHUS patients have not experienced resolution of aHUS signs and symptoms or have not tolerated eculizumab treatment. Therefore, additional treatment options for patients with aHUS are needed.

During maintenance treatment, eculizumab is dosed intravenously every two weeks [Alexion 2015, Alexion 2016]. The eculizumab dosing regimen is based on achieving a high level (≥ 90%) of complement inhibition at trough plasma concentrations. This dosing regimen provides continuous complement inhibition without lapses in inhibition, which may allow complement

damage to continue [FDA 2011]. Increasing the eculizumab dose or dosing frequency may be required during times of acute inflammation, such as concurrent infection. One type of TMA, HSCT-associated TMA, may require dosing more frequently than every 2-3 days to achieve a treatment effect [Jodele 2016]. Eculizumab has allowed withdrawal of hemodialysis in patients who required dialysis prior to treatment. Often this occurs within weeks, but may require several months [Fakhouri 2016, Legendre 2013]. The TMA relapse rate in patients following discontinuation of eculizumab treatment has been reported to be higher than in patients remaining on eculizumab (19.9/100 patient-years vs. 7.3/100 patient-years) [Menne 2015]. Regulatory agencies caution that patients may relapse following discontinuation of eculizumab treatment [Alexion 2015, Alexion 2016]. Current treatment protocols suggest life-long treatment with eculizumab [Kavanagh 2013].

5.1.3. Scientific Rationale

The lectin pathway acts as an innate immune sensor of tissue injury and has a dominant role in activating complement in settings of endothelial cell stress or injury [Collard 1999]. Because endothelial injury is a universal aspect of TMA, including aHUS, the lectin pathway likely plays a role in initiating and perpetuating complement activation in aHUS. Therefore, inhibition of the lectin pathway may address aspects of complement-mediated cellular injury in TMA. In addition, the complement cascade interacts with the coagulation cascade. In particular, MASP-2 activates prothrombin in a similar manner to factor Xa, generating active thrombin [Krarup 2007], and activates Factor XII, which activates the intrinsic pathway of coagulation [Kozarcanin 2016]; [Omeros-Nilsson data 2016]. Therefore, inhibition of MASP-2 may provide anticoagulant activity as part of its beneficial effect on TMA.

[redacted]

5.2. Previous Experience

5.2.1. Nonclinical Experience

[redacted]

[redacted]

5.2.2. Clinical Experience

[redacted]

[redacted]

OMS721 has been safe and well tolerated in Phase 1 studies to date.

[redacted]

5.3. Potential Risk and Benefits

5.3.1. Known and Potential Risks

5.3.1.1. Human MASP-2 Deficiency

MASP-2 deficiency has been reported to occur in humans and the clinical phenotype of MASP-2 deficiency may be relevant to risk assessment of MASP-2 inhibition with OMS721. The literature contains conflicting reports as to whether subjects with MASP-2 deficiency are at risk for adverse effects.

Two case reports described individuals with MASP-2 deficiency due to a homozygous mutation (D120G) with clinical associations with autoimmunity or recurrent bacterial infections; one patient was healthy until 13 years of age and the other patient had cystic fibrosis [Olesen 2006, Stengaard-Pedersen 2003]. A genetic screen of 335 Polish children with recurrent respiratory tract infections identified one child with MASP-2 deficiency [Cedzynski 2004]. In contrast, in a genetic screen of 868 healthy Spaniards, two homozygous D120G individuals were identified; both subjects were healthy without clinical evidence of recurrent infections or autoimmune disorders and both had normal levels of circulating complement [Garcia-Laorden 2006].

The gene frequency of the D120G mutation is 2-4% in European populations, which would predict that approximately one in 625 to 2000 individuals in this population would be homozygotes with MASP-2 deficiency [Garcia-Laorden 2006, Thiel 2007]. Polymorphisms in the MASP-2 gene as well as the plasma concentration of MASP-2 are influenced by race. For example, the D120G mutation is the most common one in Caucasians but it is not found in Chinese or Africans [Thiel 2007]. Moreover, the circulating levels of MASP-2 were lowest in Africans (median 196 ng/mL), followed by Chinese (262 ng/mL), and Amerindian (290 ng/mL), and highest in Caucasian Danes (416 ng/mL) [Thiel 2007]. The initial studies were in Danes and a plasma concentration below 100 ng/mL was suggested as indicating MASP-2 deficiency since only individuals homozygous for the D120G mutation had this level. Subsequent studies in broader populations showed that this cutoff was inappropriate since 5% of Chinese and 19% of Africans tested had values below 100 ng/mL.

Several studies have examined the relationship between MASP-2 concentration and susceptibility to infections. In a Swiss study of 94 pediatric cancer patients, MASP-2 deficiency defined as serum levels below 200 ng/mL was identified in nine children [Schlapbach 2007]. Patients with low MASP-2 levels had significantly more episodes of febrile neutropenia with no identified microbial etiology and had longer duration of intravenous antibacterial therapy than those with normal MASP-2 levels. In a Polish study of 1788 neonates, cord blood serum MASP-2 concentration correlated with gestational age and birth weight and was significantly lower in premature babies and other pre-term babies compared with term babies [St Swierzko 2009]. Neonates with low MASP-2 concentrations did not have a higher incidence of perinatal infections when compared with those with normal MASP-2. Indeed, there was a trend towards higher MASP-2 concentrations among babies with infections. A study in Spain evaluated the frequency of D120G mutation in 868 healthy subjects as well as 967 adult patients with community-acquired pneumonia, 43 children with recurrent respiratory infections, and 130 patients with systemic lupus erythematosus and found that the allelic frequency of the D120G mutation was similar in all of these clinical groups [Garcia-Laorden 2006]. These Investigators conducted a follow-up study in which they evaluated the significance of MASP-2 deficiency in the susceptibility and outcome of community-acquired pneumonia in adults and found similar MASP-2 alleles and genotypes among patients and control subjects, leading to the conclusion that MASP-2 deficiency was not associated with an increased risk of community-acquired pneumonias [Garcia-Laorden 2008].

In summary, the literature does not provide a clear indication as to the risk for increased susceptibility to infections in individuals with MASP-2 deficiency. The researchers in Denmark who were the first to describe MASP-2 deficiency and have done the most work in this area stated in one article [Thiel 2007] that “One must conclude that (MASP-2) deficiency in itself does not result in disease, rather, it is a modifier, which may penetrate when also other elements are compromised.”

5.3.1.2. Animal Models of Infection

The role of MASP-2 in bacterial infection has been evaluated in animal models and the results vary depending on the model, ranging from disease worsening to no effect to protection. In a murine model of pneumococcal infection, inhibition of MASP-2 with a MASP-2 mAb prior to nasal inoculation of *Streptococcus pneumonia* resulted in increased severity of disease compared

to isotype control mAb [Ali 2012]. In this model, antibiotic treatment was effective in MASP-2 mAb-treated animals, resulting in a similar outcome to that in untreated controls. In contrast, in a murine model of pneumococcal meningitis, MASP-2-deficient mice had a better outcome compared to wild-type littermates [van de Beek D, unpublished observations]. In a murine model of *Pseudomonas aeruginosa* infection, MASP-2-deficient mice had no significant survival disadvantage compared to wild-type littermates [Kenawy 2012]. In a murine model of meningococcal infection, treatment with a MASP-2 mAb prior to bacterial challenge resulted in increased survival compared to treatment with isotype control mAb, demonstrating a protective effect [Omeros unpublished observations].

5.3.1.3. Clinical Data

5.3.1.4. Conclusions

[redacted]

6. STUDY PURPOSE AND OBJECTIVES

The purpose of this study is to evaluate the safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of OMS721 in patients with aHUS.

6.1. Primary Study Objective

The primary objective of this study is to evaluate the effect of OMS721 in subjects with aHUS on:

- Platelet count change from baseline

6.2. Secondary Study Objectives

The secondary objectives of this study are to evaluate the effect of OMS721 in subjects with aHUS on:

- Safety and tolerability measured by AEs, SAEs, vital signs, laboratory measures, ECGs, and physical examination
- The proportion of subjects who achieve complete TMA response defined as normalization of platelet count, normalization of serum LDH, and > 25% decrease in the baseline serum creatinine on at least 2 consecutive measurements over at least 4 weeks
- The duration of complete TMA response measured from the time of the first measurement of complete TMA response to the end of the complete TMA response

- The time to complete TMA response measured by the time to reach the first measurement of complete TMA response
- The proportion of subjects who achieve TMA event-free status during treatment defined as no decrease in platelet count of > 25% from baseline, no plasma exchange or plasma infusion, and no initiation of new dialysis for at least 12 consecutive weeks
- Time to TMA event-free status measured by the time to reach the first documented TMA event-free status from the first dose of OMS721
- The proportion of subjects who achieve an increase of > 15 ml/min/1.73 m^2 in the estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease Study (MDRD) Equation for subjects aged ≥ 18 years and the Schwartz equation for subjects < 18 years
- Time to eGFR increase of > 15 ml/min/1.73 m^2 measured by the time to reach the first measurement increase in eGFR of > 15 ml/min/1.73 m^2 from the first dose of OMS721
- The proportion of subjects who achieve hematological normalization defined as normalization of platelet count and normalization of serum LDH on at least 2 consecutive measurements over at least 4 weeks
- Time to hematological normalization measured by the time to reach the first measurement of hematological normalization from the first dose of OMS721
- The proportion of subjects who achieve TMA remission defined as platelet count ≥ 150,000/μL on at least 2 consecutive measures over at least 2 weeks
- Quality of life as measured by EQ-5D-5L
- Serum creatinine change from baseline
- Serum LDH change from baseline
- Serum haptoglobin change from baseline
- Rate of TMA interventions defined as the number of dialysis events, plasma infusion events and plasma exchange events per subject per day
- Determine the PK of OMS721
- Determine the PD of OMS721
- Proportion of subjects who develop ADA

7. STUDY DESIGN AND PROCEDURES

7.1. Study Design Summary

OMS721 is to be used in conjunction with standard of care treatments. Standard of care treatments, including immunizations, are not to be delayed or withheld from subjects entering this study. These treatments should be administered according to local standard of care. Subjects who have failed a treatment, e.g., subjects with plasma-therapy resistant aHUS, do not require continued treatment with the failed therapy.

This uncontrolled, open-label study will evaluate the effect of OMS721 in subjects with aHUS. The primary outcome to be measured is platelet count change from baseline. The secondary outcomes to be measured are other efficacy measures, safety, PK, PD, and immunogenicity (i.e., presence of anti-drug antibody [ADA] response).

Subjects with plasma therapy-resistant aHUS and plasma therapy-responsive aHUS will be eligible. Prior clinical experience indicates that most (≥ 70%) subjects will be plasma therapy-resistant. The efficacy endpoints, including the primary efficacy endpoint, may not be relevant for plasma therapy-responsive subjects because these subjects may enter the study with normal markers of aHUS activity due to successful treatment with plasma therapy. Therefore, efficacy analyses will be performed separately in the plasma therapy-resistant and plasma therapy-responsive subjects. The principal efficacy analyses will be the analyses in the plasma therapy-resistant cohort and efficacy analyses of the plasma therapy-responsive cohort will be supportive. Safety analyses will be conducted in all subjects.

Any subject who has received eculizumab within 3 months of screening of the first OMS721 treatment is required to have undergone at least one (1) plasma exchange between discontinuation of eculizumab and the first OMS721 treatment.

Safety will be monitored on a regular basis throughout the study by the Data Monitoring Committee (DMC) (Section 10.4). An interim analysis is planned when approximately 40 patients in the full analysis set (Section 13.2.4.2) have been followed for at least 26 weeks. The purpose of the interim analysis is to provide an extensive safety and efficacy data review in addition to the regular safety monitoring. The study will not be stopped for efficacy based on the interim data and, therefore, no multiplicity adjustment is required. The DMC and the Sponsor will review the interim data and make recommendations according to the DMC charter (see also Section 10.4).

This study has four periods: Screening, Treatment Induction, Treatment Maintenance, and Follow-up. The Schedule of Events (Section 19) provides details of the study periods.

Screening Period

The Screening Period for subjects who are plasma therapy-resistant will be different than the Screening Period for subjects who are plasma therapy-responsive. The Screening Period for subjects who are plasma therapy-resistant will last no more than 5 days. The Screening Period for subjects who are plasma therapy-responsive will last 14-28 days. The Schedule of Events for the Screening Period is provided in Section 19.1.

Plasma Therapy-Resistant Cohort

Subjects are considered plasma therapy-resistant if they have thrombocytopenia at screening despite previously receiving at least 4 treatments of plasma therapy (plasma infusion or plasma exchange) in 7 days without resolution of the thrombocytopenia. The week of plasma therapy may occur any time prior to screening. Preferably, the plasma therapy will occur in the week prior to screening; however, subjects who previously received 4 plasma therapy treatments in a 7-day period without resolution of the thrombocytopenia are not required to repeat plasma therapy provided the plasma therapy can be documented through the investigative-site medical records or communication from referring physicians.

Subjects who remain thrombocytopenic despite plasma therapy as described above will enter screening. The screening visit is Visit 1. At screening, four sets of laboratory samples will be collected: the first two sets will include one set for analysis in the local laboratory to determine eligibility and the other set for analysis in the central laboratory to be used for efficacy and safety evaluations. Local laboratory measures will include at least platelet count, hemoglobin, LDH, creatinine, haptoglobin, schistocyte count, alanine transaminase (ALT), and aspartate transaminase (AST) to determine eligibility. The third and fourth sets of laboratory samples are platelet count only and will be drawn between 1 and 4 hours following the first and second sets: one set will be analyzed by the local laboratory to determine eligibility and the other set will be sent for analysis at the central laboratory. Eligibility will be determined by local laboratory measures. The platelet count used for eligibility will be the mean of the two screening platelet counts measured at the local laboratory.

Because some plasma therapy-resistant subjects may have severe or unstable aHUS when enrolled and certain laboratory tests can require several days for reporting, Investigators may initiate treatment with OMS721 prior to receiving the screening central laboratory results for the Shiga toxin assay, the human immunodeficiency virus (HIV) assay, and the ADAMTS13 assay. If a subject receives treatment prior to investigative site receipt of any of the Shiga toxin assay, the HIV assay, and the ADAMTS13 assay and any of those assays is subsequently found to be positive, the subject will be immediately discontinued from the study. This possibility that a subject may be withdrawn from OMS721 treatment following its initiation will be explained in the informed consent document.

Plasma Therapy-Responsive Cohort

Subjects are considered plasma therapy-responsive if they have a documented history of requiring plasma therapy to prevent aHUS exacerbation, including documentation of a decrease in platelet count and an increase in LDH when the frequency of plasma therapy has been decreased (including plasma therapy discontinuation). Subjects must have received plasma therapy at least once every 2 weeks at an unchanged frequency for at least eight weeks before receiving the first dose of OMS721. These must be documented through investigative site medical records or communication from referring physicians.

The screening visit is Visit 1. At screening, four sets of laboratory samples will be collected: the first two sets will include one set for analysis in the local laboratory to determine eligibility and the other set for analysis in the central laboratory to be used for efficacy and safety evaluations. Local laboratory measures will include at least platelet count, LDH, creatinine, haptoglobin, ALT, AST, and schistocyte count to determine eligibility. The third and fourth sets of laboratory samples are platelet count only and will be drawn between 1 and 4 hours following the first and

second sets: one set will be analyzed by the local laboratory to determine eligibility and the other set will be sent for analysis at the central laboratory. Eligibility will be determined by local laboratory measures. The platelet count used for eligibility will be the mean of the two screening platelet counts measured at the local laboratory.

Plasma therapy will be documented over at least 14 days before initiating OMS721 treatment.

Treatment Induction Period

Plasma therapy-resistant and plasma therapy-responsive subjects will undergo different procedures during the Treatment Induction Period. Plasma therapy-responsive subjects will continue to receive plasma therapy through the Treatment Induction Period with supplemental OMS721 doses administered contemporaneously with plasma therapy to allow subjects to attain steady-state OMS721 plasma concentrations. The Schedule of Events for the Treatment Induction is provided in Section 19.3.

After completing the Screening Period eligible subjects will enter the Treatment Induction Period. The first treatment visit is Visit 2. Prior to the first OMS721 treatment, subjects will have two platelet count samples collected. The second platelet count sample will be collected between 1 and 4 hours following the first platelet count sample. These samples will be sent to the central laboratory and the mean value will be used as the baseline platelet count for analyses. Visit 1 and Visit 2 may be combined for plasma therapy-resistant subjects. If Visit 1 and Visit 2 are combined, laboratory measures collected for Visit 1 will serve as the pre-treatment laboratory measures for Visit 2, as well. The Schedule of Events for Combined Visit 1 and Visit 2, is provided in Section 19.2.

During the Treatment Induction Period, subjects will receive OMS721 370 mg IV on Days 1 and 4. Beginning on the day of the first dose (Day 1) subjects will also begin treatment with OMS721 150 mg SC once daily. The first SC injection will be prepared and administered by study site personnel to demonstrate proper technique. The next three SC doses will be prepared and administered by the subject or subject's caregiver to ensure that proper dose preparation and injection technique are being employed. Additional SC injections may be administered at the site at the discretion of site personnel if needed for instructional purposes.

If a subject receives plasma therapy during the Treatment Induction Period the subject will receive supplemental OMS721 185 mg IV as provided in Section 9.1.3.1. If the subject receives plasma therapy on Day 1 or Day 4 of the Treatment Induction Period, the regularly scheduled OMS721 dose will be administered within one (1) hour after plasma exchange or within one (1) hour before plasma infusion.

Treatment Maintenance Period

After completion of the IV dosing during the Treatment Induction Period, subjects will enter the Treatment Maintenance Period. During this period, subjects will continue to receive OMS721 150 mg SC once daily. This dosing regimen will continue throughout the treatment period. Subjects or subject caregivers will do urine dipstick tests at least 3 times weekly. If the presence of blood is detected the Investigator will be contacted immediately for potential evaluation of aHUS exacerbation. The Schedule of Events for the Treatment Maintenance Period is provided in Section 19.4.

For plasma therapy-responsive subjects, at the time of the last IV dose of the Treatment Induction Period the frequency of plasma therapy will be decreased by one plasma therapy treatment per week (discontinued for subjects receiving plasma therapy with a frequency of ≤ once weekly) until plasma therapy is discontinued.

Rescue Therapy

At the discretion of the Investigator, OMS721 370 mg IV administered once every 3 days and/or plasma therapy may be reinitiated for any plasma therapy-responsive subjects or plasma therapy-resistant subjects who experience a TMA relapse. OMS721 SC injections should continue through this period. If a subject requires Rescue Therapy during the Treatment Maintenance Period, the Investigator may contact the Sponsor and, if agreed, increase the daily SC dose of OMS721 to not more than 300 mg SC daily to account for potential PK variability of SC administration. Also, if a subject receives plasma therapy during the Treatment Maintenance Period, the subject will receive supplemental OMS721 as provided in Section 9.1.3.1.

The IV Rescue Therapy may continue as long as deemed necessary by the Investigator. During the period of IV Rescue Therapy subjects will continue to receive once daily OMS721 SC treatment. When the Investigator deems the subject no longer needs Rescue Therapy the IV OMS721 treatment may be discontinued. The SC OMS721 treatment will continue. Each instance of IV treatment during OMS721 Rescue Therapy that does not occur on a scheduled visit will be considered a Rescue Therapy visit. When a subject receives Rescue Therapy, the subject will continue to attend regularly scheduled visits. When Rescue Therapy visits do not coincide with regularly scheduled visits, the investigative site will record adverse events, concomitant medications and other treatments, perform a symptom-directed physical examination, if appropriate, and collect blood samples for central laboratory evaluation of hematology, chemistry, and PK assessments. The Schedule of Events for Rescue Therapy is provided in Section 19.5.

The total time of the Treatment Induction and Treatment Maintenance Periods is two years.

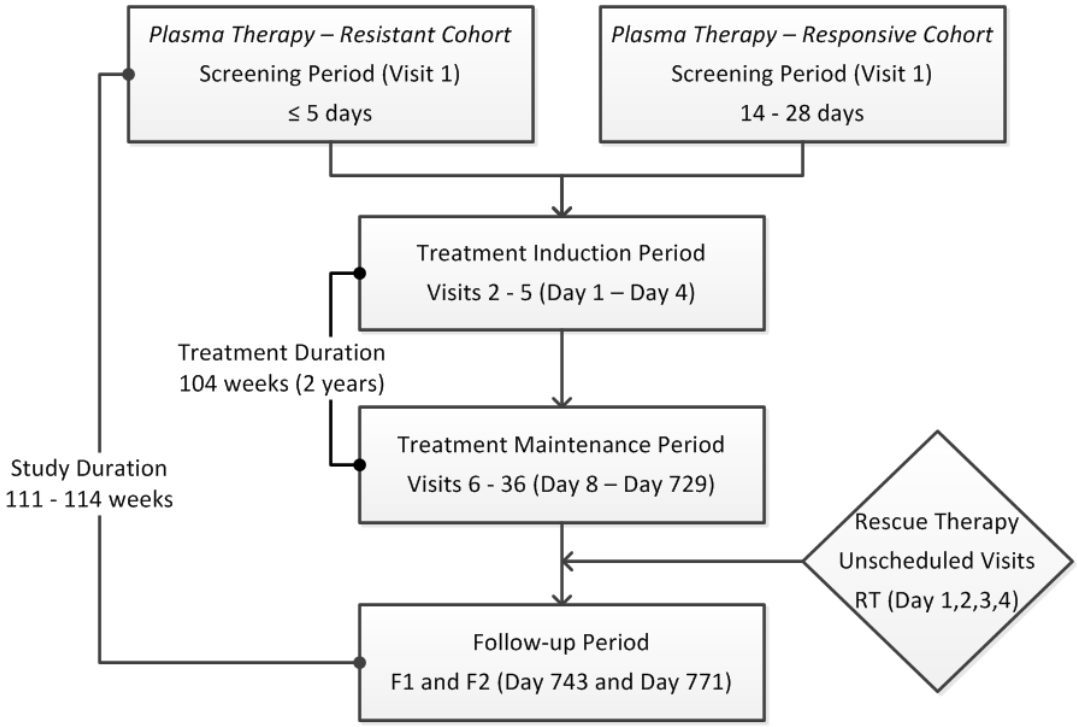
Follow-up Period

After completion of the Treatment Maintenance Period or early discontinuation, subjects will undergo two (2) Follow-up visits. Subjects who complete the Treatment Maintenance Period may be eligible to continue treatment under a future protocol amendment or under expanded access (compassionate use).

During the study, subjects will have 38 scheduled visits. If a subject relapses, there will be additional treatment visits.

A diagram of the study is provided in Figure 2.

Figure 2: Study Design Schematic



The length of time for individual subject participation will be approximately 111-114 weeks. The total time of the study from first subject first visit to last subject last visit is anticipated to be approximately 60 months.

Approximately 80 subjects will be enrolled in this study.

7.2. Study Rationale

Improvements in TMA markers have been observed in subjects with aHUS and HSCT-TMA. OMS721 has been well tolerated by TMA subjects, by subjects in a Phase 2 study of glomerulonephropathies, and by healthy volunteers in Phase 1 studies. Results from nonclinical toxicity studies of OMS721 and prior clinical experience indicate that there is an adequate safety profile to conduct this study at the proposed doses in subjects with aHUS. A chronic toxicology study supports chronic dosing. Toxicology studies also support dosing in subjects aged 12 and older.

7.2.1. Rationale for Selection of Doses

Pharmacodynamic data in TMA subjects suggest that OMS721 concentrations greater than 5,000 ng/mL may be required to assure high levels of lectin pathway inhibition (>90% inhibition). Pharmacokinetic variability has also been observed. In view of the severe risk in some patients posed by aHUS relapse (e.g., acute renal failure or stroke), targeting a trough plasma concentration greater than 5,000 ng/mL is appropriate to mitigate the risk of aHUS relapse.

Pharmacokinetic modeling and data from healthy volunteers in Study OMS721-NHV-002 indicate that repeating a fixed 150 mg SC dose once daily should provide continuous inhibition

of the lectin pathway in most, if not all, subjects. Similar to eculizumab dosing, this dosing regimen is based on achieving trough plasma concentrations that will provide high levels of complement inhibition without breaks. Also, fixed dosing and the use of the adult dosing schedule in adolescents are appropriate based on the weight-, Body Mass Index (BMI)-, and Body Surface Area (BSA)-independent clearance of OMS721. Intravenous loading doses will be used to provide immediate therapeutic plasma concentrations at the initiation of treatment, with plasma therapy, and for rescue if needed.

7.3. Study Endpoints

7.3.1. Primary Endpoint

- Platelet count change from baseline to week 26

7.3.2. Secondary Endpoints

- Safety as assessed by AEs, SAEs, vital signs, ECGs, physical examinations, and laboratory measures
- Complete TMA response defined as normalization of platelet count, normalization of serum LDH, and > 25% decrease in serum creatinine on at least 2 consecutive measures over at least 4-weeks
- Duration of complete TMA response measured from the time of the first measurement of complete TMA response to the last consecutive measurement of complete TMA response
- Time to complete TMA response measured by the time to reach the first measurement of complete TMA response
- TMA event-free status during treatment defined as no decrease in platelet count of > 25% from baseline, no plasma exchange or plasma infusion, and no initiation of new dialysis for at least 12 consecutive weeks
- Time to TMA event-free status measured by the time to reach the first documented TMA event-free status from the first dose of OMS721
- Increase of > 15 ml/min/1.73 m^2 in eGFR calculated by the MDRD Equation for subjects aged ≥ 18 years and the Schwartz equation for subjects < 18 years
- Time to eGFR increase of > 15 ml/min/1.73 m^2 measured by the time to reach the first measurement increase in eGFR of > 15 ml/min/1.73 m^2 from the first dose of OMS721
- Hematological normalization defined as normalization of platelet count and normalization of serum LDH on at least 2 consecutive measurements over at least 4 weeks
- Time to hematological normalization measured by the time to reach the first measurement of hematological normalization from the first dose of OMS721
- TMA remission defined as platelet count ≥ 150,000/μL on at least 2 consecutive measures over at least 2 weeks
- Quality of life as measured by EQ-5D-5L

- Serum creatinine change from baseline
- Serum LDH change from baseline
- Serum haptoglobin change from baseline
- Rate of TMA interventions defined as the number of dialysis events, plasma infusion events and plasma exchange events per subject per day over the treatment period
- PK of OMS721
- PD of OMS721
- ADA

7.4. Study Extension

Subjects completing the treatment period may be eligible for extended treatment through either a protocol amendment to extend treatment or expanded access (compassionate use).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Competent to provide informed consent or, if a minor, have at least one parent or legal guardian to provide informed consent with written assent from the subject.
2. If an adult, 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. If a minor, at least one parent or legal guardian must provide informed consent and the subject must provide assent 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. Willing and able to comply with study procedures.
4. Are age ≥12 at screening (Visit 1).
5. Have a primary aHUS, diagnosed clinically, and have ADAMTS13 activity > 5% in plasma. Patients are eligible with or without a documented complement mutation or anti-CFH antibody. Patients are categorized according to their response to plasma therapy (plasma exchange or plasma infusion):
    a. Plasma therapy-resistant aHUS patients must have all of the following:
        i. Screening platelet count < 150,000/μL despite at least 4 plasma therapy treatments in a 7-day prior to screening
        ii. Evidence of microangiopathic hemolysis (at least one of: (1) presence of schistocytes, (2) serum LDH > 1.5 times upper limit of normal (ULN), and (3) haptoglobin < LLN)
        iii. Serum creatinine > ULN

b. Plasma therapy-responsive aHUS patients must have all of the following:

i. Have a documented history of requiring plasma therapy to prevent aHUS exacerbation defined as all of the following:

1. decrease in platelet count > 25% when plasma therapy frequency has been decreased (including discontinuation of plasma therapy)
2. LDH > 1.5 times ULN when plasma therapy frequency has been decreased (including discontinuation of plasma therapy)

ii. Have received plasma therapy at least once every 2 weeks at an unchanged frequency for at least 8 weeks before first dose of OMS721

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.
7. Do not have access to eculizumab treatment, have not derived therapeutic benefit from eculizumab treatment, or have not been able to tolerate eculizumab treatment.

8.2. Subject Exclusion Criteria

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

1. Have STEC-HUS.
2. Have a positive direct Coombs test.
3. Have a history of hematopoietic stem cell transplant.
4. Have HUS from an identified drug.
5. History of vitamin B12 deficiency-related HUS.
6. History of systemic lupus erythematosus.
7. History of antiphospholipid syndrome.
8. Active cancer or history of cancer (except non-melanoma skin cancers) within 5 years of screening.
9. Have been on hemodialysis or peritoneal dialysis for ≥ 12 weeks.
10. Have an active systemic bacterial or fungal infection requiring systemic antimicrobial therapy (prophylactic antimicrobial therapy administered as standard of care is allowed).
11. Baseline resting heart rate < 45 beats per minute or > 115 beats per minute.
12. Baseline QTcF > 470 milliseconds.
13. Have malignant hypertension (diastolic blood pressure [BP] > 120 mm Hg with bilateral hemorrhages or “cotton-wool” exudates on funduscopic examination).

14. Have a poor prognosis with a life expectancy of less than 3 months in the opinion of the Investigator.
15. Are pregnant or lactating.
16. Have received treatment with an investigational drug or device within four weeks of the screening visit.
17. Have abnormal liver function tests defined as ALT or AST > 5 times ULN.
18. Have HIV infection.
19. History of cirrhosis of the liver.
20. Are an employee of Omeros, an Investigator, a study staff member, or their immediate family member.
21. Have a known hypersensitivity to any constituent of the product.
22. Presence of any condition that the Investigator believes would put the subject at risk or confound the interpretation of the data.
23. Have previously completed treatment in an OMS721study.
24. Have received intravenous immunoglobulin (IVIG) treatment within 8 weeks of screening visit.
25. Have received rituximab within 24 weeks of screening visit.

8.3. Subject Withdrawal Criteria

8.3.1. Early Discontinuation of Study Drug Administration

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

- Diagnostic evaluations demonstrate subject does not have primary aHUS.
- The subject becomes pregnant. Study drug must be discontinued immediately and the pregnancy reported to the Sponsor.
- The subject or subject's legal guardian wishes to discontinue study drug treatment for any reason.
- The subject experiences a medical emergency that necessitates discontinuing study drug treatment.
- The subject receives a prohibited concomitant therapy.
- The Investigator, Sponsor, or subject's primary care physician decides to discontinue treatment for medical reasons or due to the subject's noncompliance with the protocol.

The reason for termination of study drug before study completion must be recorded in the subject's case report form (CRF). The subject should complete all scheduled study Follow-Up visits provided that written consent to do so has not been withdrawn. Subjects who discontinue study drug prematurely will not be replaced.

8.3.2. Subject Withdrawal from the Study

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

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

The reason for withdrawal must be recorded in the subject's CRF. The subject should complete the evaluations scheduled for the last Follow-up visit, provided written consent to do so has not been withdrawn. Subjects 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 discontinued from the study protocol, the Sponsor and the ethics committee will be notified and provided with the reasons for subject discontinuation from this study protocol.

9. STUDY DRUG AND TREATMENT OF SUBJECTS

OMS721 is manufactured under current Good Manufacturing Practices (cGMP) for investigational use. OMS721 is a human IgG4 mAb directed against MASP-2. [redacted]

9.1. OMS721 Drug Product

[redacted]

9.1.1. Packaging and Labeling of Drug Product

[redacted]

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 [redacted]
- 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. 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.

[redacted]

9.1.3.1. Supplemental Drug Administration for Subjects Receiving Plasma Therapy

Treatment Induction Period

If the subject receives plasma therapy on Day 1 or Day 4 of the Treatment Induction Period, the regularly scheduled OMS721 dose will be administered within one (1) hour after completion of plasma exchange or within one (1) hour before plasma infusion. [redacted]

Treatment Maintenance Period

If plasma exchange is performed at any time during the Treatment Maintenance Period, [redacted]

If plasma infusion is performed at any time during the Treatment Maintenance Period, [redacted]

The total number of IV supplemental doses cannot exceed 4 supplemental doses per week.

Rescue Therapy

If the subject receives plasma therapy on Rescue Therapy Day 1, the regularly scheduled OMS721 IV dose will be administered within one (1) hour after completion of plasma exchange or within one (1) hour before plasma infusion. [redacted]

9.1.4. Storage and Handling of Drug Product

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

[redacted]

9.2. Study Drug Accountability

In compliance with U.S. Food and Drug Administration (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. 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.

The Investigator (or designee) and/or Pharmacist designee is responsible for reconciling and documenting (in the study drug accountability logs) the number of vials dispensed to the subject, the number of vials used by the subject and the number of used and unused vials returned by the subject during the days study drug is self-administered at home. Any study drug issues must be

resolved and documented appropriately. Any used or unused study drug can only be destroyed or returned to Omeros after being reviewed by the responsible Omeros Study Monitor. However, if the institution's policy does not allow any used study drug to be stored, the site may destroy any returned/used study drug on site in accordance with the institution's applicable SOP, local laws and regulations. Omeros may request a copy of or request to review the SOP.

9.3. 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 is summarized in Section 19.

10.1. Study Schedule

The study visits are described as Screening, Treatment Induction, Treatment Maintenance, and Follow-Up (F) visits.

10.1.1. Screening Visit (Visit 1)

The Screening Period for plasma therapy-resistant subjects will be no more than 5 days and, for plasma therapy-responsive subjects, it will be 14-28 days.

Before any study-specific procedures are performed, informed consent (and assent, if applicable) will be obtained in compliance with regulations and governing ethics committee requirements. The procedures listed below will be performed and documented to determine subject eligibility prior to treatment.

1. A medical history will be taken and demographics will be recorded.
2. The history of aHUS will be recorded, including the following information:
    - Date of diagnosis
    - History of previous episodes of aHUS
    - Family history of aHUS
    - History of kidney transplantation for aHUS
    - Signs and symptoms related to current episode of aHUS
    - Diagnostic evaluations, e.g., Shiga toxin testing, complement genetic testing, ADAMTS13, Coombs test
    - Description of the type and frequency of plasma therapy during current episode and, for plasma therapy-responsive subjects only, the effect on platelet count and LDH when plasma therapy has been decreased
    - Description of frequency of dialysis during current episode
    - Description of any other therapies for aHUS

3. Use of concomitant medications will be obtained, including any prior eculizumab use.
4. Vital signs will be taken including BP, pulse rate, respiratory rate (RR) and temperature (after at least five 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 five minutes of rest in the supine position).
7. Four sets of laboratory samples will be collected:
    a. Clinical laboratory tests will be performed by the site's local laboratory to be used to determine subject's eligibility: hematology (including at least platelet count, hemoglobin, and schistocyte count), chemistry (including at least LDH, ALT, AST, and creatinine), haptoglobin, Direct Coombs test, and serum pregnancy test in women of child-bearing potential.
    b. Clinical laboratory tests will be performed by the central laboratory to be used for safety and efficacy evaluations: hematology, chemistry, haptoglobin, coagulation, Direct Coombs test, STEC, ADAMTS13 activity, HIV serology and urinalysis.

    Between 1 and 4 hours after the laboratory samples above (7a and 7b) are drawn:

    c. Platelet Count Sample collected and sent to the central laboratory for analysis.
    d. Platelet Count Sample collected to be analyzed by the site's local laboratory.

    The average of the 2 platelet count samples performed by the local laboratory will be used for eligibility.
8. Blood collected for complement genetic testing at a central laboratory.
9. Blood and urine samples for future research related to aHUS will be taken.
10. The QoL questionnaire (EQ-5D-5L) will be administered.
11. Health Economic Data Review.

Any subjects who have received eculizumab within 3 months of screening of the first OMS721 treatment is required to have undergone at least 1 plasma exchange between discontinuation of eculizumab and the first OMS721 treatment.

10.1.2. Baseline Platelet Counts

Eligible subjects will have 2 platelet count samples collected prior to the first OMS721 dose (Day 1/Visit 2). Two platelet count samples are collected 1 to 4 hours apart and the average of the two samples will serve as the baseline platelet count for analyses.

In subjects who are receiving plasma therapy, the platelet counts should be obtained prior to such therapy.

10.1.3. Treatment Induction Period (Visits 2-5)

After completing the Screening Period, eligible subjects will enter the Treatment Induction Period. During the Treatment Induction Period, all subjects will receive OMS721 by IV administration at Visits 2 and 5. Subjects will also receive OMS721 by SC administration on a daily basis starting at Visit 2. At Visits 2 and 5 the OMS721 SC injection will be administered within 15 minutes after the start of the IV infusion. During this period, the Investigator or designee will train the subject or subject's caregiver on the proper technique of administering study drug subcutaneously.

Plasma therapy-responsive subjects will continue to receive plasma therapy during this period with supplemental OMS721 doses administered with plasma therapy. Refer to Section 9.1.3.1 for details on supplemental dose and Section 10.1.8 for procedures required prior to and after the administration of supplemental dose.

For plasma therapy-resistant subjects, Visit 1 (Screening) and Visit 2 (Day 1) may be combined. The procedures are detailed in Section 19.2.

10.1.3.1. Visit 2 (Day 1)

This treatment visit is the first dose of OMS721 administration.

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

1. Review of AEs, symptom-directed physical examination, and concomitant medications and therapies.
2. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least five minutes of rest in the supine position).
3. ECG will be taken (after at least five minutes of rest in the supine position).
4. Laboratory tests will be performed: hematology, chemistry, haptoglobin, and urinalysis.
5. A second platelet count will be collected 1-4 hours after the earlier blood draw for the hematology laboratory tests.
6. Serum or urine pregnancy test will be performed in women of childbearing potential. If the test result is positive then the subject will be excluded from the study.
7. Serum PK, PD and ADA samples will be collected.
8. Blood samples and urine samples for future research will be collected.
9. The QoL questionnaire (EQ-5D-5L) will be administered.
10. Health Economic Data Review.

OMS721 will be administered by IV infusion over 30 minutes and by subcutaneous injection within 15 minutes after start of IV infusion. Investigative site personnel will prepare and administer this first SC injection to train the subject or subject's caregiver on the proper techniques for dose preparation and injection.

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

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least five minutes of rest in the supine position) at the following time points: 15 minutes after start of IV dosing, 30 minutes after start of IV dosing (or after end of IV dosing), one hour after start of IV dosing (30 minutes after end of IV dosing).
2. ECG will be performed (after at least 5 minutes of rest in the supine position) one hour after end of IV dosing.
3. Serum PK samples will be drawn at the following time points after end of IV dosing: 5 minutes, 1 hour, 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4).
4. Serum PD sample will be drawn one hour after end of IV dosing.
5. AEs will be recorded throughout the visit.

10.1.3.2. Visits 3-5 (Days 2-4)

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

1. AEs, symptom-directed physical examination, and concomitant medications and therapies will be recorded.
2. Vital signs will be collected.
3. Hematology, chemistry, and haptoglobin laboratory tests will be performed prior to OMS721 administration at Visit 5 (Day 4).
4. Blood and urine samples for future research will be collected at Visit 5 (Day 4).
5. Serum PK and PD samples are drawn pre-dose at Visits 3-5 (Days 2-4). The collection of the PK samples at visits 3-5 is based on the end of the first dose (24, 48 and 72 hours post the end of the first dose).
6. The QoL questionnaire will be administered at Visit 4 (Day 3).
7. Health Economic Data Review.

OMS721 SC injection is administered daily during the Treatment Induction Period. At Visit 5 (Day 4), OMS721 will be administered by IV infusion over 30 minutes followed by SC injection of OMS721 within 15 minutes of the start of the IV infusion. During Visit 3 (Day 2), Visit 4 (Day 3), and Visit 5 (Day 4) investigative site personnel will observe and ensure that the subject is trained on the proper way to prepare and administer OMS721 SC. If deemed necessary, the site may continue to instruct and observe SC injections by subject or subject's caregiver after Visit 5 (Day 4). During Visit 5 (Day 4), investigative site personnel will train the subject or subject's caregiver on the use of the urine dipsticks.

After start of study drug administration, the following procedures will be performed at specified time points:

1. Vital signs will be collected at 15 minutes, 30 minutes, and 1 hour following the start of dosing.

2. Serum PK and PD samples will be collected one hour post end of IV dosing at Visit 5 (Day 4).
3. AEs during and after the study drug administration will be recorded at every visit.
4. At the end of Visit 5 (Day 4), the Investigator and/or Pharmacist or designee will dispense the appropriate number of study drug and ancillary supplies needed for self-administration of OMS721.
5. Subjects will be instructed to perform urine dipstick tests at least 3 times weekly and to contact the investigative site immediately if a test is positive for blood.

10.1.4. Treatment Maintenance Period

During the Treatment Maintenance Period, study drug will be administered SC on a daily basis. This is self-administered (by the subject or by the subject's caregiver) at home or at the clinic. Subjects will test urine by dipstick at 3 times weekly and will contact the investigative site if a test is positive for blood. There will be 31 clinic visits during the Treatment Maintenance Period:

- Initially, weekly visits: Visit 6 (Day 8), Visit 7 (Day 15), Visit 8 (Day 22), & Visit 9 (Day 29).
- Every 2 weeks: Visit 10 (Day 43), Visit 11 (Day 57) and Visit 12 (Day 71).
- Monthly thereafter from Visit 13 (Day 99) through Visit 36 (Day 729).

For plasma therapy-responsive subjects, at the time of the last IV dose in the Treatment Induction Period (Visit 5, Day 4):

- The frequency of plasma therapy will be decreased by one treatment/week until plasma therapy is discontinued.
- If the frequency of plasma therapy is less than or equal to once weekly, plasma therapy is discontinued.

If a subject undergoes plasma therapy during the Treatment Maintenance Period, the subject will receive supplemental doses as detailed in Sections 9.1.3.1 and 10.1.8.

10.1.4.1. Study Procedures at Visits 6-36

The following procedures will be performed during the subject's clinic visits (Visits 6-36) unless otherwise indicated:

1. Adverse events, symptom-directed physical examination, and concomitant medications and therapies will be recorded.
2. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least five minutes of rest in the supine position).
3. Clinical laboratory tests will be performed for hematology, chemistry, and haptoglobin.
4. Clinical laboratory samples will be collected for coagulation, urinalysis, pregnancy test in women of child-bearing potential, blood for research, and urine for research at Visit 6 (Day 8), Visit 7 (Day 15), Visit 9 (Day 29), Visit 11 (Day 57), Visit 13 (Day 99), Visit 15

(Day 155), Visit 18 (Day 239), Visit 21 (Day 323), Visit 24 (Day 407), Visit 27 (Day 491), Visit 30 (Day 575), Visit 33 (Day 659), and Visit 36 (Day 729).

5. PK and PD samples will be collected at Visit 6 (Day 8), Visit 7 (Day 15), Visit 9 (Day 29), Visit 10 (Day 43), Visit 12 (Day 71), Visit 14 (Day 127), Visit 16 (Day 183), Visit 18 (Day 239), Visit 20 (Day 295), Visit 22 (Day 351), Visit 24 (Day 407), Visit 26 (Day 463), Visit 28 (Day 519), Visit 30 (Day 575), Visit 32 (Day 631), Visit 34 (Day 687), and Visit 36 (Day 729).
6. ADA Samples will be collected at Visit 9 (Day 29), Visit 11 (Day 57), Visit 14 (Day 127), Visit 16 (Day 183), Visit 18 (Day 239), Visit 20 (Day 295), Visit 22 (Day 351), Visit 24 (Day 407), Visit 26 (Day 463), Visit 28 (Day 519), Visit 30 (Day 575), Visit 32 (Day 631), Visit 34 (Day 687), and Visit 36 (Day 729).
7. ECGs will be performed (after at least 5 minutes rest in the supine position) at Visit 10 (Day 43), Visit 16 (Day 183), Visit 22 (Day 351), Visit 29 (Day 547), and Visit 36 (Day 729).
8. At each clinic visit (except Visit 36, Day 729), the Investigator or designee will dispense the study drug and ancillary supplies including urine dipsticks. Subject or subject's caregiver will be instructed to always bring the OMS721 vials (used only) at the next clinic visit and to perform urine dipstick tests three times weekly at home. If test is positive for blood, subject should be instructed to contact the investigative site immediately.
9. At each clinic visit, the Investigator or designee will retrieve and reconcile the used and/or unused study drug vials returned by the subject and document any study drug discrepancies or disposition in the study drug accountability logs.
10. The QoL questionnaire (EQ-5D-5L) will be administered at Visit 6 (Day 8), Visit 8 (Day 22), Visit 12 (Day 71), Visit 16 (Day 183), Visit 20 (Day 295), Visit 24 (Day 407), Visit 28 (Day 519), Visit 32 (Day 631), and Visit 36 (Day 729).
11. Health Economic Data Review.
12. The subject will be responsible for maintaining a daily patient diary that records if the appropriate study drug was self administered. Subjects will bring the diary into each clinic visit for review by the clinic staff.
13. Height will be collected for adolescents under 18 years at visits 16, 22, 28, and 34 for calculation of the eGFR.

Investigator or designee will follow-up with subjects by telephone between clinic visits during the Treatment Maintenance Period to assess adverse events and subject's compliance to study treatment and urine dipstick tests. Refer to the Schedule of Events (Section 19.4).

10.1.5. Follow-up Visits 1 and 2 (F1 & F2)

All subjects will have two Follow-up visits: Follow-up visit #1 (F1) occurs 14 days post the last dose while Follow-up visit #2 (F2) is scheduled 42 days after the last dose.

The following procedures will be performed at the two Follow-up visits unless indicated otherwise:

1. Adverse events, symptom-directed physical examination, and concomitant medications and therapies will be recorded.
2. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least five minutes of rest in the supine position).
3. Clinical laboratory tests will be performed for hematology, chemistry, and haptoglobin.
4. Clinical laboratory tests will be performed for coagulation and urinalysis only at the last Follow-up visit (F2).
5. Serum PK, PD, and ADA samples will be collected only at the last Follow-up visit (F2).
6. Blood and urine samples for future research will be collected only at the last Follow-up visit (F2).
7. Serum or urine pregnancy test will be performed in women of childbearing potential only at the last Follow-up visit (F2).
8. ECG will be performed (after at least 5 minutes of rest in the supine position) at the last Follow-up visit (F2).
9. The QoL questionnaire (EQ-5D-5L) will be administered at the last Follow-up visit (F2).
10. Health Economic Data Review at all Follow-up visits.
11. At Follow-up visit #1, the Investigator or designee will retrieve and reconcile the used and/or unused study drug vials returned by the subject and document any study drug discrepancies or disposition in the study drug accountability logs.

10.1.6. aHUS Relapse and Rescue Therapy

Subjects with aHUS may experience a delayed clinical improvement or relapse or worsening of their disease during the study. At the discretion of the Investigator, OMS721 370 mg IV administered once every 3 days and/or plasma therapy may be reinitiated for any subjects who experience a TMA relapse. OMS721 SC injections should continue through this period. If a subject requires Rescue Therapy during the Treatment Maintenance Period the Investigator may contact the Sponsor and, if agreed, increase the daily SC dose of OMS721 to not more than 300 mg SC daily to account for potential PK variability of SC administration. Also, if a subject receives plasma therapy during the Treatment Maintenance Period, the subject will receive supplemental OMS721 185 mg IV as provided in Section 9.1.3.1.

Visits at which subjects receive IV OMS721 Rescue Therapy will typically be unscheduled. The first day of Rescue Therapy will be denoted as Day RT1. Subsequent days of Rescue Therapy or Rescue Therapy follow-up will be denoted by consecutive RT (n) designations.

Data from these visits will be recorded in the CRF. Following each dose of IV OMS721 Rescue Therapy, subjects will have at least 3 consecutive days of follow-up. If a subject is continuing to receive IV OMS721 Rescue Therapy the third follow-up day will be the day the subject receives the next IV OMS721 dose. In this case, the subject will undergo all of the procedures described

for RT1 with subsequent Follow-up visits. After the subject receives the last dose of IV OMS721 Rescue Therapy, the third follow-up day will be the last day of Rescue Therapy follow-up. The subject will then resume the regularly scheduled visits. The following procedures will be performed when a subject receives IV OMS721 rescue treatment:

1. On the day of IV OMS721 Rescue Therapy, (RT1) the subject will have assessments of adverse events and concomitant medications, a symptom-directed physical examination, assessment of adverse vital signs (vitals taken at pre-dose, 15, 30, 60 minutes post start of IV), clinical laboratory tests for hematology, chemistry, haptoglobin, and urinalysis, blood and urine research sample collection, PK (pre-dose, post end of IV at 5min, 1hr, 24hr, 48hr, and 72hr), PD and ADA laboratory sample collection, IV OMS721 Rescue Therapy administration, and standard daily SC OMS721 administration (Section Section 19.5).
2. On the first and second days following IV OMS721 Rescue Therapy administration (RT2 and RT3), the subject will have assessments of adverse events and concomitant medications, a symptom-directed physical examination, assessment of adverse vital signs, PK laboratory sample collection, and standard daily SC OMS721 administration.
3. On the third day following IV OMS721 Rescue Therapy administration (RT4), the subject will have either (1) the same procedures as RT2 and RT3 if the subject will not have additional doses of IV OMS721 Rescue Therapy or (2) the same procedures as RT1 if the subject will have additional doses of IV OMS721 Rescue Therapy.

10.1.7. Early Termination

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

10.1.8. Unscheduled Visits - Supplemental OMS721 Administration for Subjects Receiving Plasma Therapy

Subjects 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.

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

1. AEs, presence of aHUS signs and 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 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 IV dosing, 30 minutes after start of IV dosing (after end of dosing), and one hour after start of IV dosing (30 minutes after end of dosing.
6. Serum PK samples will be taken at 5 minutes after end of dosing.

10.1.9. Timing of Study Procedures

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 IV day of dosing ±5 minute; PK draws when specified at the 24, 48, and 72 hour timepoints following IV dosing will be ±2 hours. If multiple procedures are specified at one time point they should be performed in the following order: blood draw, ECG, and then vital signs, with the blood draw at the exact specified time.

10.1.10. Timing of Study Visits

During the treatment maintenance and Follow-up Periods, the allowable visit window is +/- 2 days. 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 subject.

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 aHUS, 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 discouraged, but allowed if the Investigator considers it medically indicated.
- Chronic plasma therapy-responsive aHUS – plasma therapy should be continued through the Treatment Induction Period and decreased in the Treatment Maintenance Period as described in Section 7.1.

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 for renal dialysis.

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

Since increased susceptibility to infections is a potential risk of inhibiting MASP-2 activity, subjects should be closely monitored for symptoms or signs of infection. If the subject 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

Administration of eculizumab is prohibited during the study. If the Investigator decides to administer eculizumab, the subject should be withdrawn from the study.

10.3. Treatment Compliance

Intravenous doses of the study drug are 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.

When subjects are receiving SC OMS721, treatment compliance will be determined by study drug reconciliation and patient interviews before dispensing drug supplies for the next visit interval.

10.3.1. Definition of Departure from Protocol

A protocol deviation is defined as any non-adherence to study procedures or schedules, as specified by the protocol.

10.4. Safety Monitoring

The Sponsor's Medical Monitor will monitor safety data in an ongoing manner throughout the study. An independent Data Monitoring Committee (DMC) will meet (in-person or telephonically) and review cumulative data every four months and after approximately 40 patients in the full analysis set (Section 13.2.4.2) have been followed for at least 26 weeks. The DMC will review all serious adverse events on an ongoing basis as they occur. Following each meeting (or as needed between meetings), the chairperson of the DMC will provide in writing one 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

This study evaluates efficacy, PK, PD, immunogenicity, and exploratory measures.

11.1. Primary Efficacy Measure

- Platelet count change from baseline

11.2. Secondary Efficacy Measures

The secondary efficacy measures include:

- Complete TMA response defined as normalization of platelet count, normalization of serum LDH, and > 25% decrease in serum creatinine on at least 2 consecutive measures over at least 4-weeks.

- Duration of complete TMA response measured from the time of the first measurement of complete TMA response to the last consecutive measurement of complete TMA response.
- Time to complete TMA response measured by the time to reach the first measurement of complete TMA response.
- TMA event-free status during treatment defined as no decrease in platelet count of > 25% from baseline, no plasma exchange or plasma infusion, and no initiation of new dialysis for at least 12 consecutive weeks.
- Time to TMA event-free status measured by the time to reach the first documented TMA event-free status from the first dose of OMS721
- Increase of > 15 ml/min/1.73 m^2 in eGFR calculated by the MDRD Equation for subjects aged ≥ 18 years and the Schwartz equation for subjects < 18 years.
- Time to eGFR increase of > 15 ml/min/1.73 m^2 measured by the time to reach the first measurement increase in eGFR of > 15 ml/min/1.73 m^2 from the first dose of OMS721
- Hematological normalization defined as normalization of platelet count and normalization of serum LDH on at least 2 consecutive measurements over at least 4 weeks.
- Time to hematological normalization measured by the time to reach the first measurement of hematological normalization from the first dose of OMS721
- TMA remission defined as platelet count ≥ 150,000/µL on at least 2 consecutive measures over at least 2 weeks.
- Quality of life as measured by EQ-5D-5L.
- Serum creatinine change from baseline.
- Serum LDH change from baseline.
- Serum haptoglobin change from baseline.
- Rate of TMA interventions defined as the number of dialysis events, plasma infusion events and plasma exchange events per subject per day.

11.3. Pharmacokinetic Measures

Serial serum samples will be collected according to the Schedule of Events (Section 19) for analysis of OMS721 concentration. [redacted]

11.4. Pharmacodynamic 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. [redacted]

11.5. Immunogenicity Measures

Serial serum samples will be collected according to the Schedule of Events (Section 19) for analysis of ADA. [redacted]

11.6. Exploratory Measures

[redacted]

11.7. Quality of Life Assessments

Patient quality of life (QoL) will be assessed using the EQ-5D-5L instrument (EuroQol Research Foundation, Rotterdam, The Netherlands). This questionnaire-based tool is widely validated, available in multiple languages, and is used to quantify preference-based health states based on patient health ratings on the day that they are administered the questionnaire.

Questionnaires will be administered to each patient according to the Schedule of Events (Sections 19.1, 19.2, 19.3, and 19.4).

11.8. Health Economic Data Review

Health economic data related to treatment and outcomes of aHUS will be collected. These data will include dialysis treatment, plasma therapy treatment, and other aspects of health care utilization.

12. ASSESSMENT OF SAFETY

Investigators are responsible for monitoring the safety of subjects 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 subject. The Investigator is responsible for appropriate medical care of subjects 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, SAEs, clinical laboratory tests, vital signs, physical examination, and ECG. Only clinically significant (per Investigator opinion) changes in physical examination, vital signs, ECGs, 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 lactate dehydrogenase, haptoglobin, glucose, urea nitrogen, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, 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 HPF, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, and platelet count.
- Coagulation tests include prothrombin time (PT), International Normalised Ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis tests include color, specific gravity, pH, glucose, protein, bilirubin, urobilinogen, blood, ketone, nitrite, leukocyte esterase and microscopic if required (red blood cells, 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 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 subject 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 subject 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 subject 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 Common Terminology Criteria for Adverse Events (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 adverse event 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: Subject 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 subject, 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 adverse event 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 which were administered), the outcome of the event, and relationship to the study drug.

Any medical condition that is present at the time that the subject 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 subject 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 subject, 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 subject.

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 subject, study site personnel should enter *unanticipated benefit* with the actual event term (for example, the complete actual term would 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 serious adverse event.

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 subject 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 subject 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 subjects will also be followed provided the subject'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 Subjects 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

Measures of TMA activity include the following tests: platelet count, hemolysis (serum LDH, serum haptoglobin, hemoglobin, schistocytes), and organ dysfunction (e.g., serum). The need for continued plasma therapy or renal dialysis is medically relevant and also reflects aHUS activity. These measures are relevant for evaluation of aHUS activity and are individual endpoints or part of composite endpoints in this study. The EQ-5D-5L is a relevant and accepted measure of health-related quality of life.

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

ADA response is a standard immunogenicity measure for a therapeutic protein. Samples demonstrating the presence of ADA will undergo testing to determine if the ADA titer and if the ADA are neutralizing.

12.5.5. Safety Measures

Adverse events, SAEs, clinical laboratory tests, vital signs, physical examination, and ECG are standard safety measures.

13. STATISTICS

13.1. Determination of Sample Size

The sample size is based on the plasma therapy-resistant cohort. Assuming that the true mean platelet count change from baseline is $78x10^{-9}$/L with a standard deviation of $64x10^{-9}$/L [Legendre 2013], a sample size of 56 plasma therapy-resistant subjects will provide 90% power to test a null mean platelet count change from baseline of $45x10^{-9}$/L at two-sided significance level of 5% using t-test. It is assumed that 70% of the eligible subjects will be plasma therapy-resistant. Therefore, the total sample size is 80 subjects who meet the full analysis set criteria.

13.2. Statistical and Analytical Plans

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 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 subjects, 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. The exception is the baseline platelet count, which is defined as the average of the two pre-dose values. All confidence intervals will be constructed at the 95% confidence level.

13.2.2. Adjustments for Covariates

It is possible that some potential baseline subject and disease characteristics may impact the interpretation of the efficacy results. Subgroup analyses and regression analyses may be performed to adjust for the potential covariate effects. These analyses will be considered exploratory and, if performed, will be discussed in the clinical study report.

13.2.3. Multicenter Study

This is a multicenter study. Descriptive statistics of the primary efficacy endpoint will be provided for each site to evaluate potential site differences.

13.2.4. Multiple Comparisons and Multiplicity

This is a single-arm study with one primary efficacy endpoint. No multiplicity adjustment is necessary.

13.2.4.1. Handling of Missing Data

Unless otherwise specified, statistical analyses will be based on observed data without imputation.

13.2.4.2. Analysis Populations

The full analysis set (FAS) will include all subjects who receive any amount of study treatment and have at least one post-baseline platelet count. The primary efficacy analyses will be based on the FAS.

The safety analysis set will include all subjects who receive any amount of study treatment. The safety analyses will be based on the safety analysis set.

13.2.5. Subject Disposition

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

13.2.6. Subject Characteristics

Demographic, other baseline characteristics, concomitant medications, and aHUS-related therapies (e.g., plasma therapy or renal dialysis) will be listed. Demographics and disease characteristics will be summarized.

13.2.7. Treatment Compliance

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

Treatment compliance with daily SC dosing will be evaluated using relative dose intensity (Section 13.2.13.1).

13.2.8. Primary and Secondary Efficacy Analyses

The plasma therapy-resistant cohort will be the primary subject cohort for the evaluation of efficacy of OMS721. All efficacy analyses will be performed separately for the plasma therapy-resistant cohort and the plasma therapy-responsive cohort. Primary efficacy analyses will be based on the FAS. Supportive efficacy analyses will be based on the safety analysis set. Definitions of the efficacy endpoints are presented in Section 7.3.

Baseline for platelet count is defined as the average of two tests obtained prior to the first dose of OMS721. If more than two tests are performed, then the two that are most proximate to the first dose of OMS721 should be used. Baseline for other endpoints is defined as the value most proximate to the first dose of OMS721.

13.2.8.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint (platelet count change from baseline) will be summarized descriptively by visit and cohort during the treatment period (induction and maintenance). A repeated measures model with time and baseline platelet count as fixed effects, and subject as random effect will be used to evaluate the primary endpoint by cohort. Time is a categorical variable for the scheduled visit. A generalized estimating equation (GEE) method will be applied to estimate the least-squares mean change from baseline with 95% confidence interval at each scheduled time point.

13.2.8.2. Analyses of Secondary Efficacy Endpoints

Summary statistics for each secondary efficacy endpoint will be provided by cohort using the FAS. Analyses of the secondary efficacy endpoints are presented as follows:

- The complete TMA response will be summarized with the number and percent of responders during the treatment period (induction and maintenance) and an exact binomial two-sided 95% confidence interval for the complete TMA response rate by cohort.
- The duration of complete TMA response will be based on the subjects who achieve a complete TMA response. If the last laboratory measurement is the last consecutive measurement of the complete TMA response, the duration will be censored at the date of the last laboratory measurement. The Kaplan-Meier method will be used to estimate the distribution. Median duration will be estimated with two-sided 95% confidence interval using the complementary log-log transformation [Collett 1994].
- The time to complete TMA response will be analyzed by the Kaplan-Meier method. Subjects who do not achieve a complete TMA response during study will have their event time censored at the last laboratory measurement. Median time to the complete TMA response will be estimated with two-sided 95% confidence interval using the complementary log-log transformation [Collett 1994]. The complete TMA response rates at 26 weeks, 1 year and 2 years will be estimated with two-sided 95% confidence interval using the Kaplan-Meier method.
- The number and percent of subjects achieving TMA event-free status will be summarized with two-sided exact binomial 95% confidence interval. Subjects whose TMA event-free status cannot be evaluated (e.g., early dropouts or death) will be considered as not achieving TMA event-free status.
- The time to TMA event-free status will be analyzed by the Kaplan-Meier method. Subjects who do not achieve a TMA event-free status during study will have their event time censored at the last visit. Median time to the TMA event-free status will be estimated with two-sided 95% confidence interval using the complementary log-log transformation [Collett 1994]. The TMA event-free status rates at 26 weeks, 1 year and 2 years will be estimated with two-sided 95% confidence interval using the Kaplan-Meier method.

- The number and percent of subjects who achieve an increase in eGFR from baseline of > 15 ml/min/1.73 m^2 will be summarized with two-sided exact binomial 95% confidence interval. Subjects whose eGFR cannot be evaluated (e.g., early dropouts or death) will be considered as not achieving the required increase in eGFR.
- The time to increase in eGFR from baseline of > 15 ml/min/1.73 m^2 will be analyzed by the Kaplan-Meier method. Subjects who do not achieve an increase in eGFR from baseline of > 15 ml/min/1.73 m^2 during study will have their event time censored at the last laboratory measurement. Median time to the increase in eGFR from baseline of > 15 ml/min/1.73 m^2 will be estimated with two-sided 95% confidence interval using the complementary log-log transformation [Collett 1994]. The increase in eGFR from baseline of > 15 ml/min/1.73 m^2 rates at 26 weeks, 1 year and 2 years will be estimated with two-sided 95% confidence interval using the Kaplan-Meier method.
- The number and percent of subjects achieving hematological normalization will be summarized with two-sided exact binomial 95% confidence interval. Subjects whose hematological normalization status cannot be evaluated (e.g., early dropouts or death) will be considered as not achieving hematological normalization.
- The time to hematogical normalization will be analyzed by the Kaplan-Meier method. Subjects who do not achieve hematogical normalization during study will have their event time censored at the last laboratory measurement. Median time to hematogical normalization will be estimated with two-sided 95% confidence interval using the complementary log-log transformation [Collett 1994]. The hematogical normalization rates at 26 weeks, 1 year and 2 years will be estimated with two-sided 95% confidence interval using the Kaplan-Meier method.
- The number and percent of subjects achieving TMA remission will be summarized with two-sided exact binomial 95% confidence interval. Subjects whose TMA remission status cannot be evaluated (e.g., early dropouts or death) will be considered as not achieving TMA remission.
- The 5 dimensions of EQ-5D-5L will be summarized with frequency and percentage by visit and cohort. The EQ-5D-5L Visual Analogue scale (EQ VAS) and its change from baseline will be summarized with descriptive statistics by visit and cohort. The t-distribution will be used to calculate the two-sided 95% confidence interval for the mean change from baseline.
- Change from baseline of key laboratory parameters (LDH and haptoglobin) will be summarized with descriptive statistics and two-sided 95% confidence interval for the mean change using t-distribution.
- The rate of TMA interventions will be summarized with descriptive statistics and two-sided 95% confidence interval for the mean rate using t-distribution.

13.2.9. Pharmacokinetic Analyses

Standard pharmacokinetic analyses will be performed and will be described in a Pharmacokinetic Analysis Plan.

13.2.10. Pharmacodynamic Analyses

The extent of *ex vivo* lectin pathway activation will be calculated relative to the subject's baseline (pre-dose) result. The lectin pathway activity of post-dose samples is expressed as % inhibition relative to baseline. The lectin pathway activity will be summarized.

13.2.11. Pharmacokinetic-Pharmacodynamic Analyses

The relationship between OMS721 concentration and lectin pathway activity will be plotted.

13.2.12. Immunogenicity Analyses

The presence of ADA and neutralizing antibodies will be summarized by cohort.

13.2.13. Safety Analyses

13.2.13.1. Extent of Exposure

The following exposure items will be summarized with descriptive statistics by route (IV and SC) and cohort using the safety analysis set:

- Cumulative doses in milligrams taken by treatment period (the Treatment Induction Period, the Treatment Maintenance Period and the entire treatment period).
- Duration of treatment in weeks by treatment period, which is defined as (the last dose date of the treatment period – the first dose date of the treatment period + 1)/7.
- The number of vials used.
- The intended number of vials.
- Absolute dose intensity (ADI), which is defined as the actual dose taken in milligrams per week by treatment period. (ADI = Cumulative doses taken in milligrams /Duration of treatment in weeks).
- Intended dose intensity (IDI), which is defined as the initial assigned dose in milligrams per week by treatment period. The IDI of the IV route during the Treatment Induction Period is 2x370 = 740 mg/week if supplemental IV doses are not given. The IDI of the SC route for the SC route during the Treatment Induction Period and the Treatment Maintenance Period is 150 x 7 = 1050 mg/week.
- Relative dose intensity (RDI), which is defined as the ADI as a percentage of the IDI by treatment period. (RDI = ADI/IDI × 100).

13.2.13.2. Adverse Events

The incidence of all reported AEs and treatment-related AEs will be tabulated by cohort. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. A treatment-emergent AE (TEAE) is defined as an event that first occurs or worsens in intensity after the administration of study drug.

An overview of AEs, which includes subject incidence of TEAEs, treatment-related AEs, AEs related to study procedures, SAEs, death, and AEs leading to discontinuation, will be presented by cohort.

The subject incidence of treatment-related AEs will be summarized by system organ class and preferred term.

AEs judged to be related to protocol procedures or study conduct by the Investigator will be listed.

13.2.13.3. Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

13.2.13.4. Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit and cohort. Subjects with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized.

Shifts from baseline laboratory values (normal/abnormal) will be tabulated.

13.2.13.5. Vital Signs

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

13.2.13.6. Electrocardiogram

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at each time recorded as well as the change from screening will be summarized with descriptive statistics by scheduled visit and cohort. 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. A shift table comparing the ECG assessment over the treatment period to baseline will be presented by cohort.

13.2.13.7. Plasma Therapy

Plasma therapy will be analyzed as follows:

- Subject incidence of no plasma therapy use during study will be summarized by cohort.
- The number of plasma infusions received and the number of plasma exchanges received post baseline will be summarized by cohort.
- The total number of units of plasma infusions received and the total volume of plasma exchanges received post baseline will be summarized by cohort.

13.2.13.8. Dialysis

Dialysis will be analyzed as follows:

- Subject incidence of no dialysis received during study will be summarized by cohort.
- The number of dialyses received post baseline will be summarized by cohort.

13.2.13.9. Rescue Therapy

Subject incidence of use of Rescue Therapy will be summarized by Rescue Therapy type and cohort. Rescue therapies used will be listed by subject.

13.2.14. Interim Analysis

One interim analysis is planned when approximately 40 patients in the FAS have been followed for at least 26 weeks. The purpose of the interim analysis is to provide an extensive safety and efficacy data review in addition to the regular safety monitoring. The study will not be stopped for efficacy based on the interim data and, therefore, no multiplicity adjustment is required.

The interim analysis will include, but not be limited to, the primary analyses of the efficacy and safety endpoints, and PK analysis. The DMC and the Sponsor will review the interim data and make recommendations according to the DMC charter.

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 subjects. 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 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 subject. CRFs will be reviewed by the Sponsor or its representative for adherence to

protocol, completeness, and acceptability. Portions of the subject'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 subject'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 subject 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, independent ethics committee (IEC) or Institutional Review Board (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 subject) must be approved by the Sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The Investigator is responsible for enrolling subjects 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 subjects in the study will identify each subject only by the subject's initials and/or subject 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

In this study, adult subjects must provide written informed consent. Subjects who are minors may only participate with written informed consent from a legal guardian and written assent from the subject.

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 subject and the person conducting the consent. Discussion of risks and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the Study Agent(s)/Intervention(s) study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB/IEC-approved and the subject 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 subject and answer any questions that may arise. The subjects should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects 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, subjects 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 Privacy Rule (see 45 CFR 164.508). The authorization will be provided to subjects in accordance with IRB procedures. The authorization may either be combined with the informed consent or provided as a separate document.

When a subject may be enrolled in the trial only with the consent of the subject's legally acceptable representative, the subject should be informed about the trial to the extent compatible with the subject's understanding. If capable, the subject 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 subject's legally acceptable representative.

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. Data will be collected using the Medidata Rave EDC system.

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 electronic casebook. The Investigator will review each electronic casebook for completeness and accuracy and apply an electronic signature for approval where indicated.

Data captured is electronically stored by the EDC vendor during the study. At the end of the trial, the sites will be provided with an electronic file of all of the CRFs and associated CRF queries for their subjects.

CRFs will be reviewed by monitors from the Sponsor or its representative for adherence to protocol, completeness, and acceptability. Portions of the subject'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. FDA regulations require that the Investigator prepares and maintains adequate and accurate records for each subject 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.

CRFs 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.

FDA regulations require that the Investigator prepares and maintains adequate and accurate records for each subject treated with study drug. Source documents such as hospital, clinic or office charts, laboratory reports, electrocardiograms, 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 subject's study records.

Records containing subject 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 subject 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 subject 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.

18. REFERENCES

Full-text references are available upon request.

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19. APPENDICES

19.1. Schedule of Events – Screening Period

Screening Visit [Visit 1]	
Informed Consent and Assent (if applicable)	X
Demographics and Medical History, including aHUS History	X
Plasma Therapy and Dialysis History	X
Concomitant Medications & Therapies	X
Comprehensive Physical Examination, including Height and Weight	X
Vital Signs	X
ECG	X
Local Laboratory Tests for Eligibility: Hematology (including at least platelet count, hemoglobin, and schistocyte count), Chemistry (including at least LDH, ALT, AST, and creatinine), Haptoglobin, Direct Coombs Test, and Serum Pregnancy Test, if applicable	X
Central Laboratory Tests for Hematology & Chemistry, Haptoglobin, Direct Coombs, STEC, ADAMTS13, HIV serology	X
Platelet Count 1-4 Hours Following the First Blood Draws (Central & Local Laboratory)	X
Coagulation Testing (Central Laboratory)	X
Complement Genetic Testing (Central Laboratory)	X
Blood Research Sampling(Central Laboratory)	X
Urine Sample for Urinalysis (Central Laboratory)	X
Urine Research Sampling (Central Laboratory)	X
Quality of Life (QoL) Assessment (EQ-5D-5L)	X
Health Economic Data	X

19.2. Schedule of Events – Screening (Visit 1) and Visit 2 (Day 1) Combined (only for Plasma Therapy-Resistant Subjects)

COMBINED Visit 1 (Screening) and Visit 2 (Day 1)	
Informed Consent and Assent (if applicable)	X
Demographics and Medical History, including aHUS History	X
Plasma Therapy and Dialysis History	X
Concomitant Medications & Therapies	X
Comprehensive Physical Examination, including Height and Weight	X
Vital Signs	X[1]
ECG	X[3]
Local Laboratory Tests for Eligibility: Hematology (including at least platelet count, hemoglobin, and schistocyte count), Chemistry (including at least LDH, ALT, AST, and creatinine), Haptoglobin, Direct Coombs Test, and Serum Pregnancy Test, if applicable	X
Central Laboratory Tests for Hematology & Chemistry, Haptoglobin, Direct Coombs, STEC, ADAMTS13, HIV serology	X
Platelet Count 1-4 Hours Following the First Blood Draws (Central & Local Laboratory)	X[5]
Coagulation Testing (Central Laboratory)	X
Complement Genetic Testing (Central Laboratory)	X
Blood Research Sampling(Central Laboratory)	X
Urine Sample for Urinalysis (Central Laboratory)	X
Urine Research Sampling (Central Laboratory)	X
Study Drug Administration-IV	X
Study Drug Administration-SC	X[7]
PK Serum Sampling (Central Laboratory)	X[8]
PD Serum Sampling (Central Laboratory)	X[3]
ADA Serum Sampling (Central Laboratory)	X
Quality of Life (QoL) Assessment (EQ-5D-5L)	X
Health Economic Data	X

19.3. Schedule of Events – Treatment Induction Period

Period:	**Treatment Induction**			
Visit:	2	3	4	5
Day:	1	2	3	4
Symptom-Directed Physical Examination	X	X	X	X
Vital Signs	X[1]	X[2]	X[2]	X[1]
ECG	X[3]			
Hematology (includes platelet count #1 on Day 1-Central Laboratory)	X[4]			X[4]
Chemistry and Haptoglobin (Central Laboratory)	X[4]			X[4]
Platelet Count #2 on Day 1 (Central Laboratory)	X[4,5]			
Pregnancy Test for women of child-bearing potential	X[6]			
Blood Research Sampling (Central Laboratory)	X[4]			X[4]
Urine Sample for Urinalysis (Central Laboratory)	X[4]			
Urine Research Sampling (Central Laboratory)	X[4]			X[4]
Study Drug Administration-IV	X			X
Study Drug Administration-SC	X[7]	X[7]	X[7]	X[7]
PK Serum Sampling (Central Laboratory)	X[8]	X[4]	X[4]	X[3]
PD Serum Sampling (Central Laboratory)	X[3]	X[4]	X[4]	X[3]
ADA Serum Sampling (Central Laboratory)	X[4]			
Instruct on the Use of Urine Dipsticks				X
Adverse Events	X	X	X	X
Concomitant Medications & Therapies	X	X	X	X
Dispense study drug and ancillary supplies to Subject for SC Injection at Home				X
Quality of Life (QoL) Assessment (EQ-5D-5L)	X[4]			
Health Economic Data	X	X	X	X

Screening (Visit 1) and Visit 2 (Day 1) Combined and Treatment Induction Period Footnotes:

[1] Pre-dose, Post start of IV dosing: 15 minutes, 30 minutes, 1 hour
[2] Pre-dose, Post SC injection: 15 minutes, 30 minutes, 1 hour
[3] Pre-dose, Post end of IV dosing: 1 hour
[4] Pre-dose and for only the PK samples at Visits 3, 4, & 5 (Days 2, 3 & 4) the time of the blood collection will be coordinated with the 24-, 48- & 72-hour PK blood samples following the Day 1 IV dose (see footnote 8) allowing a single blood sample to provide both the post-IV PK samples and the pre-SC dose PK samples
[5] This platelet count will be collected pre-dose between 1 and 4 hours after the blood collection for the hematology tests
[6] Serum or Urine Pregnancy test
[7] Subjects will receive once daily OMS721 SC administration starting at Visit 2 (Day1). SC injection of OMS721 will be administered by the investigative site personnel at Visit 2 (Day 1) to train subject or subject's caregiver on the proper way of SC injection. The SC injections at Visit 2 (Day 1) and Visit 5 (Day 4) will occur within 15 minutes of starting the IV infusion. The SC dosing on Visits 3, 4 & 5 (Days 2, 3 & 4) will be done at the clinic under the supervision of the investigative site personnel. Following the SC dose on Visit 5 (Day 4) the daily SC dose may be administered without the investigative site's instruction or observation. However, if deemed necessary, the site may continue to instruct and observe daily SC injections by subject or subject's caregiver after Day 4
[8] Pre-dose, Post end of IV dosing: 5 minutes, 1 hour, 24 hours, 48 hours, and 72 hours

19.4. Schedule of Events – Treatment Maintenance Period and Follow-up

Period:	Treatment Maintenance																
Visit:	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Day:	8	15	22	29	43	57	71	99	127	155	183	211	239	267	295	323	351
Symptom-Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG					X						X						X
Hematology (Central Laboratory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry and Haptoglobin (Central Laboratory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Testing (Central Laboratory)	X	X		X		X		X		X			X			X	
Pregnancy Test (for WOCBP only)	X	X		X		X		X		X			X			X	
Blood Research Sampling (Central Laboratory)	X	X		X		X		X		X			X			X	
Urine Sample for Urinalysis (Central Laboratory)	X	X		X		X		X		X			X			X	
Urine Research Sampling (Central Laboratory)	X	X		X		X		X		X			X			X	
Study Drug Administration-SC[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Serum Sampling (Central Laboratory)	X	X		X	X		X		X		X		X		X		X
PD Serum Sampling (Central Laboratory)	X	X		X	X		X		X		X		X		X		X
ADA Serum Sampling (Central Laboratory)				X		X			X		X		X		X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications & Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug and ancillary supplies to Subject for SC injection at home	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Reconciliation (returned vials)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (QoL) Assessment (EQ-5D-5L)	X		X				X				X				X		
Health Economic Data	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Diary[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone Follow-up								X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]

Period:	Treatment Maintenance														Follow-Up	
Visit:	23	24	25	26	27	28	29	30	31	32	33	34	35	36	F1	F2
Day:	379	407	435	463	491	519	547	575	603	631	659	687	715	729	743	771
Symptom-Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG							X							X		X
Hematology (Central Laboratory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry and Haptoglobin (Central Laboratory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (Central Laboratory)		X			X			X			X			X		X
Pregnancy Test (for WOCBP only)		X			X			X			X			X		X
Blood Research Sampling (Central Laboratory)		X			X			X			X			X		X
Urine Sample for Urinalysis (Central Laboratory)		X			X			X			X			X		X
Urine Research Sampling (Central Laboratory)		X			X			X			X			X		X
Study Drug Administration-SC[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PK Serum Sampling (Central Laboratory)		X		X		X		X		X		X		X		X
PD Serum Sampling (Central Laboratory)		X		X		X		X		X		X		X		X
ADA Serum Sampling (Central Laboratory)		X		X		X		X		X		X		X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications & Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug and ancillary supplies to Subject for SC injection at home)	X	X	X	X	X	X	X	X	X	X	X	X	X			
Study Drug Reconciliation (returned vials)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Quality of Life (QoL) Assessment (EQ-5D-5L)		X				X				X				X		X
Health Economic Data	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Diary[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Telephone Follow-up	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		

Treatment Maintenance Period and Follow-up Footnotes:

[1] SC dosing daily

[2] Occurs between monthly visits

[3] The subject will be responsible for maintaining a daily patient diary that records if the appropriate study drug was self administered. Subjects will bring the diary into each clinic visit for review by the clinic staff

[4] If the subject is aged 17 or younger, the subject height should also be recorded at visits 16, 22, 28, and 34

19.5. Rescue Therapy Schedule

Period:	**Rescue Therapy**			
Day:	RT1	RT2	RT3	RT4[1]
Symptom-Directed Physical Examination	X	X	X	X
Vital Signs	X[2]	X	X	X
Hematology (Central Laboratory)	X[3]			
Chemistry and Haptoglobin (Central Laboratory)	X[3]			
Urinalysis	X			
Blood Research Sampling (Central Laboratory)	X[3]			
Urine Research Sampling (Central Laboratory)	X[3]			
Study Drug Administration-IV	X			
Study Drug Administration-SC	X	X	X	X
PK Serum Sampling (Central Laboratory)	X[4]	X[5]	X[5]	X[5]
PD Serum Sampling (Central Laboratory)	X[6]			
ADA Serum Sampling (Central Laboratory)	X[3]			
Adverse Events	X	X	X	X
Concomitant Medications & Therapies	X	X	X	X

Rescue Therapy Schedule Footnotes:

[1] If the subject has received the last dose of IV OMS721 Rescue Therapy the procedures at this visit will be performed. If the subject is continuing IV OMS721 Rescue Therapy the procedures on this day will not be performed, but the subject will have the procedures for RT1. RT 4 occurs only when the subject completes Rescue Therapy and resumes treatment maintenance

[2] Pre-dose, Post start of IV dosing: 15 minutes, 30 minutes, 1 hour

[3] Pre-dose

[4] Pre-dose, Post end of IV dosing: 5 minutes, 1 hour, 24 hours, 48 hours, and 72 hours for the first dose of IV OMS721 Rescue Therapy only. The 24-, 48- & 72-hour timepoint collections will be coordinated to be drawn prior to the daily SC dose. Blood collections for PK will be drawn at pre-dose and 1 hour post start of dosing for all subsequent IV OMS721 doses during a single aHUS relapse. If no dose of IV OMS721 Rescue Therapy is given on this day the only PK sample collected will be the 72-hour PK blood sample coordinated with the SC dose as described in footnote 7

[5] Pre- SC dose and the time of the blood collection will be coordinated with the 24-, 48- & 72-hour PK blood samples following the Day 1 IV dose (see footnote 6) allowing a single blood sample to provide both the post-IV PK samples and the pre-SC dose PK samples

[6] Pre- IV dose and 1 hour post start of IV dose