STATISTICAL ANALYSIS PLAN

A Phase 2, Uncontrolled, Three-Stage, Dose-Escalation Cohort Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity, and Clinical Activity of OMS721 in Adults with Thrombotic Microangiopathies

Sponsored by:

Omeros Corporation

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Confidentiality Statement

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Definition
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
AUC	area-under-the-curve
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
FAS	Full Analysis Set
GVHD	graft-versus-host disease
Hgb	hemoglobin
HSCT	hematopoietic stem cell transplant
HSCT-TMA	HSCT-associated thrombotic microangiopathy
IV	intravenous
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
MAGIC	Mount Sinai Acute GVHD International Consortium
MASP-2	mannan-binding lectin-associated serine protease 2
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PAS	Per-protocol Analysis Set
PD	pharmacodynamic
PK	pharmacokinetic
RBC	red blood cell
RRT	renal replacement therapy
SAP	statistical analysis plan
SAE	serious adverse event
SOC	System Organ Class
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal

Within this Statistical Analysis Plan (SAP), narsoplimab is referred to as OMS721.

1. STUDY DESCRIPTION

1.1. Study Objectives

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

The co-primary objectives of this study are to:

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

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

- Duration of response
- 100-day survival
- Overall survival (OS)
- Renal function in patients who had renal dysfunction at baseline
- Platelet count change from baseline
- Lactate dehydrogenase change from baseline
- Haptoglobin change from baseline
- Hemoglobin (Hgb) change from baseline
- Creatinine change from baseline in patients who had no reason other than HSCT-TMA for creatinine elevation
- Freedom from platelet transfusion in patients who received at least 1 platelet transfusion within 2 weeks of the first OMS721 dose
- Freedom from red blood cell (RBC) transfusion in patients who received at least 1 RBC transfusion within 2 weeks of the first OMS721 dose
- The PK of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)

- The PD of multiple-dose administration of OMS721(this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)
- The immunogenicity of multiple-dose administration of OMS721 (this will be assessed in patients with HSCT-TMA as well as patients with aHUS and TTP)

The exploratory objectives of this study are to:

- Assess the effect of baseline circulating mannan-binding lectin (MBL) levels on PK and PD measures
- Assess the effect of baseline circulating mannan-binding lectin-associated serine protease 2 (MASP-2) levels on PK and PD measures
- Describe the effect of OMS721 on TMA laboratory markers in patients with aHUS and TTP

1.2. Study Design

This is a Phase 2, uncontrolled, three-stage, ascending-dose-escalation study in patients with TMA: aHUS, TTP, or HSCT- TMA. As originally designed, the primary outcomes to be measured were safety and clinical activity. The secondary outcomes to be measured were PK, PD, and immunogenicity (i.e., presence of anti-drug antibody [ADA] response). Amendment [redacted] discontinued enrollment of patients with aHUS and TTP. Amendment [redacted] provides for collection of additional data from patients with HSCT-TMA, changes the primary and secondary objectives to focus on HSCT-TMA, and defines criteria by which to determine clinical response to treatment. Amendment 11 also provides for collection of PK and PD measures for analysis within integrated population PK and PD analyses across different studies.

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

Each patient in Stage 1 received 4 weekly doses of OMS721. Prior to Amendment 10, patients in Stage 2 with aHUS received 12 weekly doses and patients with TTP or HSCT-TMA received 4 weekly doses, and Stage 3 allowed for additional treatment based upon the patient's response to therapy. As of Amendment 11 of the protocol, Stage 1 is complete.

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

Table 1: OMS721-TMA-001 Treatment Stages and Cohorts

Cohort and (Stage)	Number of Patients			OMS721 Dose
	aHUS	TTP	HSCT-TMA	
1 (Stage 1)	3	0	0	0.675 mg/kg weekly x 4
2 (Stage 1)	2	1	0	2.0 mg/kg weekly x 4
3 (Stage 1)	2	0	2	4.0 mg/kg weekly x 4
4 (aHUS only) (Stage 2 and 3)	14	0	0	4.0 mg/kg weekly x 12 for each Stage
	4	0	0	400 mg weekly x 12
5 (TTP or HSCT-TMA) (Stage 2 and 3)	0	4	22	4.0 mg/kg weekly x 4 for each Stage
5 (TTP or HSCT-TMA) (Stage 2 and 3)	0	0	4	370 mg weekly x 4 for each Stage

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

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

These additional data are outlined in Protocol Amendment [redacted] These data will include supplemental data on patient demographics and baseline conditions, donor characteristics, the transplant procedure, concomitant medications, TMA-related laboratory measures, transfusions, transplant complications, and outcomes. Details of these data are provided in Appendix 1 of the protocol amendment. These data will be derived from medical records from the time of transplant conditioning through the last available patient contact with the site or 2 years (104 weeks) after the first OMS721 dose, whichever is earlier. These data were requested by regulatory authorities because patients who have undergone HSCT typically have complicated post-transplant courses and these additional data will allow for better understanding of OMS721 response and outcomes. As of Amendment 11, enrollment in the study has been completed, and the additional data will be collected until a predetermined data cutoff date for those patients who have not reached 2 years after first OMS721 dose.

1.3. Determination of Sample Size

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

In stage 2, the sample size for each cohort (aHUS, and HSCT-TMA/TTP) is determined by comparison to the total sample size of uncontrolled Phase 2 studies that provided sufficient data for approval of eculizumab for the treatment of aHUS [Legendre 2013]. This sample size is considered adequate in these orphan diseases to identify treatment effects in uncontrolled studies.

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

2. STATISTICAL METHODS

2.1. Study Endpoints

The co-primary endpoints are:

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

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

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

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

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

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

  and

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

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

        or
      - Discontinuation of renal replacement therapy (RRT),

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

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

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

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

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

  or
  - Freedom from transfusion (no transfusions for at least 4 weeks from the last transfusion except for patients who died within 4 weeks of the last transfusion, only evaluated in patients who received transfusions within the 2 weeks prior to or on the first OMS721 dose date).

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

- Duration of response defined as the number of days from the first response date to the first relapse date
- 100-day survival, from the date of TMA diagnosis
- Overall survival, from the date of TMA diagnosis
- Freedom from platelet transfusion defined as no platelet transfusions for at least 4 weeks following the last platelet transfusion except for patients who died within 4 weeks of the last platelet transfusion (only evaluated in patients who had platelet transfusions in the 2 weeks prior to or on the first OMS721 dose date)
- Freedom from RBC transfusion defined as no RBC transfusions for at least 4 weeks following the last RBC transfusion except for patients who died within 4 weeks of the last RBC transfusion (only evaluated in patients who had RBC transfusions in the 2 weeks prior to or on the first OMS721 dose date)
- Change from baseline in platelet count (post-baseline platelet counts without platelet transfusions 2 days before and on the day of the platelet count collection will be used) over time using central laboratory values
- Change from baseline in LDH over time using central laboratory values
- Change from baseline in haptoglobin over time using central laboratory values
- Change from baseline in Hgb (post-baseline Hgb without RBC and whole blood transfusions 6 days before and on the day of the Hgb collection will be used) over time using central laboratory values
- Change from baseline in creatinine over time using central laboratory values

2.2. Analysis Populations

Efficacy analyses will be performed for the Full Analysis Set (FAS) population and the Per-protocol Patient Set (PAS) population. The FAS population will include all HSCT-TMA patients

who received any amount of study drug. The PAS population will include all HSCT-TMA patients who received at least 4 weeks of study treatment (treatment period is greater than or equal to 28 days).

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

The Enrolled population is defined as all patients who completed the informed consent.

2.3. Protocol Deviations/Violations

Protocol deviations and violations will be summarized outside of this statistical analysis plan.

2.4. Study Day and Treatment Period

Study day is defined as

- Event Date – First Dose Date + 1 if the event date is on or after the first dose date
- Event Date – First Dose Date if the event date is before the first dose date

Study Day 1 is defined as the first dose date.

Treatment period is defined as the number of days from the first dose date to the last dose date + 7. The duration of treatment is defined as last dose date + 7 – first dose date + 1.

2.5. Study Endpoint Baseline

In general, the baseline of a study endpoint is the last observation prior to the first study drug administration except for platelet count.

The baseline of a laboratory parameter will be based on the central laboratory values except for platelet count.

Platelet counts from the central laboratory are to be used in the calculation of baseline. If a central laboratory value is not available and its local laboratory value is available on the same collection date, the local laboratory value will be used. In addition, if there are at least 2 platelet count collections on the same date, the first one will be used.

Baseline platelet count is defined as the average of values obtained on different days in the week (including Day 1) prior to the first dose of OMS721. If more than 3 such values are available, then the 3 values that are most proximate to the first dose of OMS721 should be used. Table 2 is an example of a baseline platelet count calculation.

Table 2: Example of Baseline Platelet Count Calculation

Study Day	Central Lab	Local Lab	Value to be used to Determine Baseline
-5	Yes	Yes	Not used
-4	Yes	Yes	Central lab
-3	No	Yes	Local lab
-2 (1st)	No	Yes	Not used
-2 (2nd)	Yes	No	Central lab
-2 (3rd)	Yes	Yes	Not used

In addition, if at least 1 central laboratory value is used in the baseline calculation, the reference range of the central laboratory will be used to determine the toxicity grade according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). If the baseline value is calculated from local laboratory values only, then the reference range of the local laboratory will be used.

2.6. Analysis Visits and Time-points

In general, analysis visit windows will be defined approximately equally over adjacent scheduled visits (Table 3).

Table 3: Analysis Visits for Data Collected at Scheduled Visits

Scheduled Visit	Target Day [Week]	Visit Window (Study Days)
Screening	-28 [-4]	≤ -1
Day 1	1 [1]	1
Week 1	1 [1]	1 to 4
Week 2 to 9	(w-1)7 + 1 [w]	(w-1)7 - 2 to (w-1)7 + 4, w = 2 to 9
Week 10	64 [10]	61 to 71
Week 12	78 [12]	72 to 81
Week 13	85 [13]	82 to 130
Week 26 to 104, every 13 weeks	(w-1)7 + 1 [w]	Ceiling of (w-13+5.5)7 + 1 to Integer of (w+5.5)7 + 1, w = 26 to 104, every 13 weeks

If there are multiple values collected during a scheduled visit window and only 1 of the values is necessary for an analysis, the value that is closest to the target day will be used. If there are 2 values that are equally spaced from the target day, the latest one will be used in the analysis, unless otherwise specified. Exceptions are given below:

- For multiple platelet counts and Hgb concentrations collected on the same day, the first measure of the day will be used to avoid confusion when transfusions may have been administered during the day.

- For transfusion data, if there are at least 2 transfusions of the same type given on the same day, the first transfusion will be used in the analysis.

2.7. Handling of Missing Data

The following general methods will be used for producing the data summaries and the manner in which missing data will be documented:

- Available clinical data at each visit will be presented and the sample size displayed will reflect the patients with available data. Patient listings data will be provided as recorded on the case report form indicating partial dates and missing data.
- Generally, if data are missing or incomplete, the missing values will be indicated and incomplete values will be presented in the data listings. Analyses will be based on the observed data without imputation unless otherwise specified.

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

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

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

2.8. Statistical Assessment of the Study Objectives

2.8.1. Multiplicity Comparisons and Multiplicity

This is an uncontrolled study. No multiplicity adjustment will be performed.

2.8.2. Efficacy Analyses

2.8.2.1. Primary Efficacy Endpoint

A patient is a responder if this patient meets the responder criteria (Section 2.1) at any time post-baseline during the study. If a patient is not evaluable for a response criterion due to confounding factors, the non-evaluable response criterion will not be included in the determination of responder. Evaluability of each response criterion will be determined by a clinical review of relevant data and will be documented in the clinical study report. For example, potential confounding factors include graft failure for platelet count or transfusions, and nephrotoxic medications for renal function. Furthermore, laboratory values collected from both the local laboratories and the central laboratories will be used to determine response status.

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

populations. If the lower bound of the exact 95% CI is greater than 15%, there is sufficient evidence to demonstrate efficacy of narsoplimab in the target patient population. Each criteria of the response will be listed for each patient.

Sensitivity analyses will include:

1. Subgroup analyses for the following subgroups will be performed for the FAS population:
   - Age (< 65, ≥ 65 years)
   - Gender (Male or Female)
   - Graft-versus-host disease (GVHD) (Yes or No)
   - Significant infection (Yes or No)
   - Graft failure or non-engraftment (Yes or No)
   - Female-to-male transplant (Yes or No)
   - Multiple organ TMA involvement (Yes or No)
   - Mismatched donor (Yes or No)
   - Baseline platelet counts (< 20,000 or ≥ 20,000 platelets/μL)
   - Renal dysfunction at baseline (Creatinine > ULN or spot urine protein ≥ 2+ or > 30 mg/dL; Yes or No)
   - Any transfusions within the 2 weeks prior to or on the first OMS721 dose date (Yes or No)
2. A completer analysis will be performed using the patients with non-missing responses only. Exact 95% CI for the completer response rate will be provided for the FAS population by dose.
3. Two alternative definitions of response will be analyzed:
   a. The first alternative response is defined as achieving an improvement in TMA markers and an improvement in renal function as defined in Section 2.1. The number and percent of the patients achieving the first alternative response will be summarized with exact 95% CI by dose for the FAS population.
   b. The second alternative response is defined as the same as the primary endpoint by excluding the neurological function as defined in Section 2.1. The number and percent of the patients achieving the second alternative response will be summarized with exact 95% CI by dose for the FAS population.

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

2.8.2.2. Secondary Efficacy Endpoints

2.8.2.2.1. 100-day Survival

The 100-day survival status will be determined as a binary variable. A patient achieves a 100-day survival if the overall survival from the date of HSCT-TMA diagnosis of the patient is greater

than or equal to 100 days. If the 100-day survival status of a patient is unknown (i.e., censored before 100 days), this patient will be considered to have died prior to 100 days. The 100-day survival rate will be estimated with exact 95% CI by dose for the FAS population.

In addition, cumulative incidence at 100 days for each of the pre-specified cause of death (GVHD, graft failure, infections, progression of underlying disease, HSCT-TMA and other) will be estimated by a competing risks analysis (Section 2.8.2.2.2).

2.8.2.2.2. Overall Survival

Overall survival will be calculated from the date of HSCT-TMA diagnosis. For the patients who are alive, their overall survival will be censored at the last known date of alive in the database. The method for handling a partially missing date of death is presented in Section 2.7.

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

In addition, a competing risks analysis for overall survival will be performed. The cumulative incidence function of each pre-specified causes of death (GVHD, graft failure, infections, progression of underlying disease, HSCT-TMA, and others) will be estimated by nonparametric maximum likelihood method. The estimated cumulative incidence functions and their 95% CI will be displayed graphically.

2.8.2.2.3. Duration of Response

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

2.8.2.2.4. Other Secondary Endpoints

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

For each of the continuous secondary efficacy endpoints, 2 analyses will be performed by dose for the FAS population:

1. A time-weighted average analysis will be performed. The time-weighted average of the change from baseline is defined as the area-under-the-curve (AUC) of the change from baseline divided by the observation time over the study period. The AUC of the change from baseline is calculated by the trapezoidal rule using all observed change from baseline data. Summary statistics and 95% CI for the mean time-weighted average will be provided. One-sample t-test will also be performed.

2. A repeated measures model with the baseline value of the endpoint and time as fixed effects will be used to estimate the mean change from baseline over time. Time will be defined as a categorical variable in weeks according to the scheduled visits (Section 2.6). A generalized estimating equation approach with an autoregression (AR(1)) working correlation structure will initially be used to estimate the model parameters. If estimation of this model fails due to any reason, alternative model specifications (e.g., linear, quadratic, or log-scale time trends) will be considered by examination of the data. The least squares mean change from baseline will be estimated with 95% CI for each time point.

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

2.8.2.2.5. Additional Analysis of Secondary Efficacy Endpoints

The analyses of the secondary efficacy endpoints specified in the previous sections (Section 2.8.2.2.1, 2.8.2.2.2, and Section 2.8.2.2.4) will be performed separately for the responders and non-responders for the FAS population.

2.8.2.2.6. Plasma Therapy

Plasma therapy will be analyzed as follows:

- The number and percent of patients who do not receive any plasma therapy (plasma exchange or plasma infusion) during study will be summarized separately for patients who have or have not used plasma therapy before Day 1 by dose and disease for the safety analysis population.
- The number of plasma infusions received, and the number of plasma exchanges received post baseline will be summarized by dose and disease for the safety analysis population.

[redacted]

2.8.4. Safety Analyses

All safety analyses will be descriptive in nature Section 3.4.

2.8.5. Timing of Planned Analyses

The coronavirus associated lockdown situation in various countries has created uncertainty in the ability to collect all follow-up data and resolve all queries on a few patients enrolled in the study. When adequate data on the primary and secondary endpoints is available, the database will be

locked for interim analyses and creation of an interim CSR to enable regulatory submission for drug approval. Efforts will continue to collect additional follow-up data and resolve any outstanding queries.

3. STATISTICAL SUMMARIES

3.1. General Conventions

All data summaries will be descriptive in nature. Summary statistics for continuous variables will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be provided. All confidence intervals will be constructed at the two-sided 95% confidence level.

Efficacy analyses will be focused on the HSCT-TMA patients. Atypical hemolytic uremic syndrome and TTP patients will be summarized separately by OMS721 dose.

All statistical analyses will be performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC).

3.2. Patient Disposition and Treatment

3.2.1. Patient Disposition

The number of patients treated, completing the study, and terminated from the study early will be summarized by dose and disease for the safety analysis population. The reason for early termination from the study will be summarized. A list of patients failing any eligibility criteria will be provided.

In addition, the eligibility criteria for the TMA diagnosis in HSCT-TMA patients will be summarized.

3.2.2. Study Treatment Compliance and Extent of Exposure

3.2.2.1. Study Treatment Compliance

No specific analyses for treatment compliance are planned for this study. A listing of any patients not completing treatment for any reason will be provided.

3.2.2.2. Extent of Exposure

Scheduled drug administrations will be summarized with the total dose volume (mL) received, the total intended dose volume (mL), the number of doses received and the duration of treatment will be summarized by dose and disease. Intended dose volume for doses in mg/kg at each dose administration is calculated as:

Intended dose in mg/kg × [minimum of Weight (kg) and 100] ÷ 100.

As of OMS721-TMA-001 Protocol Amendment [redacted], the intended dose is 370 mg weekly and the drug concentration is 185 mg/mL. Therefore, the intended dose volume for each dose administration is 370/185 = 2 mL.

Relative dose intensity (%), defined as the total dose volume received as a percentage of the total intended dose volume will be summarized by dose and disease. The number of patients whose duration of treatment is ≥ 1 week, ≥ 4 weeks and ≥ 8 weeks may also be summarized.

The number of doses received for the supplemental OMS721 treatments due to plasma therapy will be summarized by dose and disease.

Listing of dosing information will also be provided.

3.2.3. Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be listed and summarized by dose and disease for the safety population. Baseline characteristics include

- Weight (kg)
- Body mass index (BMI)
- Baseline platelet count
- Baseline platelet count (< 20,000 or ≥ 20,000 platelets/μL, HSCT-TMA only)
- Baseline LDH
- Baseline Hgb
- Baseline creatinine
- Baseline haptoglobin

3.2.4. Thrombotic Microangiopathy History

TMA history will be summarized with descriptive statistics by dose and disease for the safety population:

- Time (months or years) from TMA diagnosis to Day 1
- Time from HSCT to TMA diagnosis (HSCT-TMA only)
- Total number of previous episodes of TMA
- Time (days or months) from the onset of the current TMA episode to Day 1
- Shiga-toxin producing *E. Coli* test for current TMA episode (positive or negative for a-HUS patients only)
- Direct coombs test for current TMA episode (positive or negative)
- Most recent ADAMTS13 test result prior to dosing (historical data is allowed)
- Any transfusions within the 2 weeks prior to or on the first OMS721 dose date (Yes or No, HSCT-TMA only)
- Other risk factors for the HSCT-TMA patients will be identified after review of their historical data.

3.2.5. Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy History

HSCT history will be summarized with descriptive statistics by dose for the safety population:

- Underlying disease
- Donor source (related or unrelated)
- Time from HSCT to Day 1
- Graft-versus-host disease (Yes or No)
- Significant infection (Yes or No)
- Refractory primary disease or primary disease relapse (Yes or No)
- Graft failure or non-engraftment (Yes or No)
- Female-to-male transplant (Yes or No)
- Multiple organ TMA involvement (Yes or No)
- Mismatched donor (Yes or No)
- Neurological findings at baseline (Yes or No)
- Renal dysfunction at baseline (Creatinine > ULN, or spot urine protein ≥ 2+ or > 30 mg/dL; Yes or No)

3.2.6. Prior and Concomitant Medications

Concomitant medications will be coded with World Health Organization Drug Dictionary. Prior (medications with end dates prior to the first dose date) and concomitant medications will be listed.

Conservative treatments and their durations prior to the first dose of OMS721 will be listed for the HSCT-TMA patients in the safety population.

3.2.7. Medical and Surgical History

A listing of reported medical and surgical history will be provided.

3.3. Analysis of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Endpoints

See Section 2.8.3.

3.4. Analysis of Safety Endpoints

3.4.1. Clinical Adverse Events

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

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

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

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

Patient incidence of the following AEs will be provided:

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

In addition, the following analyses will be performed:

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

Listings of all AEs collected will be provided.

3.4.2. Clinical Laboratory Tests

Statistical analysis of clinical laboratory tests, except for those as secondary endpoints (platelet count, LDH, creatinine, hemoglobin and haptoglobin) will be based on the results from central laboratories only. Results from central and local laboratories will be listed.

Summary statistics for the actual values and the change from baseline will be tabulated for laboratory results by dose, disease, and scheduled visit. Patients with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized by dose and disease. Shift tables comparing the baseline NCI CTCAE grade to the worst post-baseline grade will be provided by dose and disease. These laboratory summary tables will exclude the laboratory tests that are the efficacy endpoints (Section 2.1).

Laboratory results may be presented graphically over the study scheduled visits, e.g., using box plots.

3.4.3. Vital Signs

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

3.4.4. Electrocardiogram

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at each time point as well as the change from baseline will be summarized with descriptive statistics by dose and disease. These parameters will be determined electronically by the ECG machine at the clinical site. QTc interval will be calculated using Fridericia's formula and will be categorized into the following groups: ≤ 450, > 450 – 480, > 480 – 500 and > 500 ms. Categorized QTc intervals will be summarized with frequency and percentage by time point, dose, and disease. Shift tables comparing the baseline categorized QTc interval to the maximum post-baseline categorized QTc interval will be provided by dose and disease. In addition, increase of > 30 ms and > 60 ms from baseline in QTc interval will be summarized with frequency and percentage by study time point, dose, and disease.

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

4. PROTOCOL AND STATISTICAL ANALYSIS PLAN AMENDMENTS AND DEVIATIONS FROM THE PROTOCOL

SAP v1.1 incorporates changes made in Protocol Amendment [redacted] These changes include the sample size of Stage 2 and the addition of Stage 3. The sample size determination was also clarified in SAP v1.1 and the statistical analyses remained the same. In addition, the dose of 4 mg/kg weekly for Stage 2 was selected based on the safety review of Stage 1 data.

SAP v2.0 incorporates changes made in Protocol Amendment [redacted] The majority of the changes are due to the addition of the study endpoints and additional data collection for the HSCT-TMA patients.

REFERENCES

Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013;368(23):2169-81.