STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: **ALXN1210-TMA-315**

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RAVULIZUMAB IN ADULT PARTICIPANTS WHO HAVE THROMBOTIC MICROANGIOPATHY ASSOCIATED WITH A TRIGGER

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1. APPROVAL SIGNATURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or acronym	Explanation
ADA	antidrug antibody
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
BSC	best supportive care
C5	complement component 5
CI	confidence interval
CIF	cumulative incidence function
CKD	chronic kidney disease
CKD-Epi	CKD-Epidemiology Collaboration
COVID-19	coronavirus disease 2019
EC	exclusion criteria
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
IC	inclusion criteria
ITT	intent-to-treat
IV	intravenous(ly)
KDQOL-36	Kidney Disease Quality of Life instrument™–36 items
LDH	lactate dehydrogenase
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NRI	nonresponder imputation
PA2	Protocol Amendment 2
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	Per-Protocol Set
q8w	every 8 weeks
QTc	corrected QT
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAS®	Statistical Analysis Software®
SAP	statistical analysis plan
SD	standard deviation
SF-12	Short-Form Health Survey 12 Item
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SSc-TMA	systemic sclerosis-associated thrombotic microangiopathy
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
TEAE	treatment-emergent adverse event

Abbreviation or acronym	Explanation
TESAE	treatment-emergent serious adverse event
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
TTO	time trade-off
VAS	visual analogue scale
WHO	World Health Organization

4. DESCRIPTION OF THE PROTOCOL

This was a Phase 3, randomized, double-blind, placebo-controlled study of ravulizumab in addition to best supportive care (BSC) in adult participants (≥ 18 years of age) with thrombotic microangiopathy (TMA) following a defined trigger. All participants had severe acute kidney injury and a diagnosis of TMA based on protocol-defined criteria (ie, thrombocytopenia, microangiopathic hemolytic anemia, and elevated lactate dehydrogenase [LDH]), which was associated with at least 1 trigger, such as autoimmune, infection, solid organ transplant, drugs, or malignant hypertension, occurring ≤ 14 days prior to randomization.

The study consisted of an up to 2-week Screening Period, a 26-week randomized Treatment Period, and a 26-week Post-treatment Follow-up Period. Thus, the total treatment duration was 26 weeks, and the total study duration was up to 54 weeks.

Participants were screened for eligibility for up to 2 weeks during the Screening Period. Approximately 100 adult participants were planned to be randomized in a 1:1 ratio to receive either ravulizumab or placebo. Randomization was stratified by baseline dialysis status and by primary trigger type.

During the 26-week Treatment Period, all participants received a weight-based loading dose of ravulizumab or placebo on Day 1, followed by weight-based maintenance doses of ravulizumab or placebo on Day 15 and then once every 8 weeks (q8w) thereafter. All participants received BSC throughout the study.

During the 26-week Post-treatment Follow-up Period, participants continued to receive BSC at the discretion of the Investigator and will be monitored for safety, TMA response, and clinical events of interest.

The end of the study was defined as the last participant's last visit in the Post-treatment Follow-up Period.

Enrollment in the study was closed, and the decision to terminate the study when the last participant in treatment has completed the 26-week Treatment Period was made on 24 Oct 2022.

Disclosure Statement: This was a parallel group treatment study with 2 arms that was participant, Investigator, and outcomes assessor blinded.

Number of Participants: It was planned that approximately 100 participants would be enrolled in the study. A total of 16 participants were enrolled in the study.

Intervention Groups and Duration:

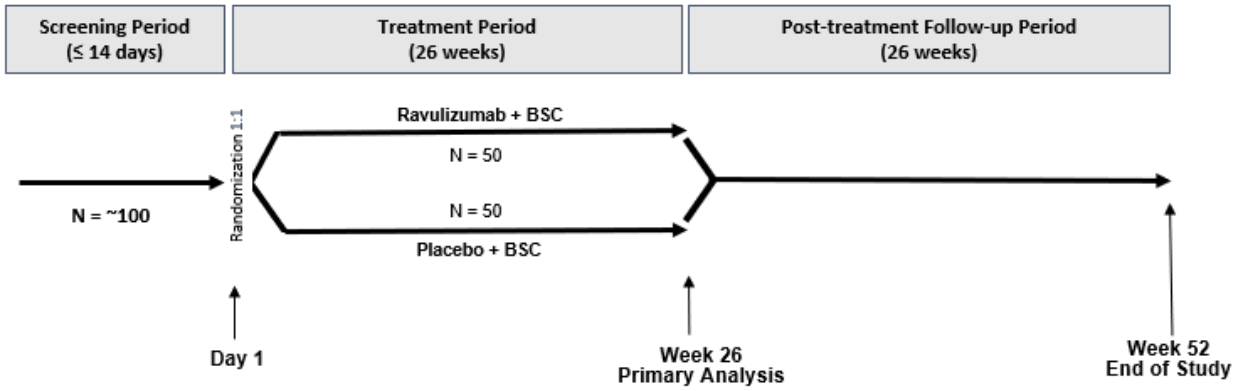
Eligible participants were enrolled into the study and were randomized in a 1:1 ratio to receive either ravulizumab intravenous (IV) infusion or placebo IV infusion in combination with BSC.

Ravulizumab was supplied as a sterile, preservative-free, 10-mg/mL solution in single-use vials, designed for administration via IV infusion by diluting into commercially available saline (0.9% sodium chloride injection). Placebo had an identical appearance to that of ravulizumab.

Ravulizumab has been shown to achieve immediate, complete, and sustained inhibition of terminal complement in adult patients with paroxysmal nocturnal hemoglobinuria and in pediatric and adult patients with atypical hemolytic uremic syndrome (aHUS). It is expected that

the same dosing regimen will also achieve comparable inhibition of complement-mediated damage in patients with TMA.

Figure 1: Study Design Schematic



Note: Randomized participants received a weight-based loading dose on Day 1, followed by weight-based maintenance dosing on Day 15 and then q8w. The weight-based dosing regimen was based on the last recorded study visit body weight. The schematic is based on the planned sample size (n = 100).
Abbreviations: BSC = best supportive care; q8w = every 8 weeks; TMA = thrombotic microangiopathy

4.1. Planned Analyses

A primary endpoint analysis to assess sample size re-estimation was planned to be conducted at the interim time point, when 50% of the 100 planned participants have been followed for 26 weeks from randomization or withdrawn from the initial 26 weeks of the study and have been assessed for the primary endpoint. The primary analysis was planned to be conducted after all participants complete Week 26 or withdraw from the study prior to Week 26. Analyses will be performed on data for the 26-week randomized Treatment Period. The final study analysis was planned to be conducted at the end of the study.

Due to the early termination of the study, the planned interim analysis for sample size re-estimation and the planned primary analysis will not be conducted, and the final study analysis will be performed after the last participant in the study has completed the 26-week Treatment Period.

4.2. Changes from Analyses Specified in the Protocol

As mentioned in Section 4.1, the planned interim analysis for sample size re-estimation and the planned primary analysis as specified in Protocol Amendment 2 (PA2) will not be conducted due to the termination of the study. Only the final study analysis after the last participant in the study has completed the 26-week Treatment Period will be performed.

In addition, no hypothesis testing or inferential statistics for the purpose of treatment comparisons will be performed due to the reduction in sample size because of few participants enrolled. Estimands defined in PA2 are no longer applicable and, thus, are removed from the SAP.

4.3. Changes from Analyses Specified in the Previous Version of the SAP

SAP Version	Version Date	Change	Rationale
1.0	29 Jun 2021	Not applicable	Original version

2.0	DD MMM 2022	Changes to align with PA2:
		• Added additional secondary endpoints:
		  o Loss of TMA response
		  o Changes from Baseline in hematologic parameters at all scheduled visits
		  o Increases in hemoglobin ≥ 1 g/dL at Week 26
		• Elevated "change in patient-reported outcomes as measured by FACIT-Fatigue" to the secondary endpoint
		• Added an exploratory endpoint to assess overall survival
		• Added the Modified Intent-to-Treat Set as the primary analysis set; removed the Enrolled Set
		• Updated the Per-Protocol Set definition to reflect the revised inclusion/exclusion criteria
		Changes from analyses specified in PA2:
		• Removed the interim analysis for sample size re-estimation and the primary analysis
		• Removed hypothesis testing and inferential statistics
		• Removed descriptions on estimands corresponding to the primary and key secondary endpoints
		• Combined key secondary endpoints and additional secondary endpoints to reflect that all secondary endpoints will be summarized in descriptive statistics
			To reflect changes made in PA2 and in the planned analyses due to the early termination of the study

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; PA2 = Protocol Amendment 2; SAP = statistical analysis plan; TMA = thrombotic microangiopathy

5. DEFINITIONS

5.1. Primary Endpoint

The primary efficacy endpoint of the study is complete TMA response during the 26-week randomized Treatment Period.

Complete TMA response is defined as normalization of hematologic parameters (platelet count and LDH) and ≥ 30% improvement in estimated glomerular filtration rate (eGFR) from Baseline (Table 2).

Table 2: Overview of Complete Thrombotic Microangiopathy Response

		TMA Response Parameter
Complete TMA response	Hematologic response	• Normalization of platelet count (defined as platelet count ≥ 150000/μL) without transfusion support during the prior 7 days
		• Normalization of LDH (defined as LDH ≤ 1.5 × upper limit of normal)
	Renal response	• Improvement in eGFR of ≥ 30% compared to Baseline

Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy

If a participant is not on dialysis at Baseline, baseline eGFR will be defined as the last nonmissing assessment value prior to the start of study treatment. If a participant is on dialysis at Day 1, baseline eGFR will be set to 10 mL/min/1.73 m^2. If a participant is on dialysis during the entire 26-week randomized Treatment Period or through early discontinuation of study drug, then the change in eGFR will not be calculated.

For complete TMA response, participants must have met all 3 TMA response parameters simultaneously, with each component meeting the requirement at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. The first laboratory value will be assessed based on central laboratory results; the second laboratory value will be assessed based on the earliest value obtained ≥ 24 hours after the first value and may be based on central or local laboratory results.

Participants will be classified as nonresponders if they do not have any TMA response observed before the following intercurrent events: treatment discontinuation or start of disallowed therapy or medicine, regardless of whether the TMA response is observed after these intercurrent events. For other participants without the above intercurrent events, whether the TMA response occurs by 26 weeks will be assessed using all available assessments within the 26-week randomized Treatment Period.

5.2. Secondary Endpoints

The following is a list of secondary efficacy endpoints. Due to early termination of the study, there are no longer any "key secondary endpoints" with multiplicity adjustment.

1. Time to complete TMA response (measured in days from Day 1 to the first day that the participant satisfies the criteria for complete TMA response) during the 26-week randomized Treatment Period.
    - TMA response occurs on the first day when all components of TMA response are met simultaneously, with each component meeting the requirement at 2 separate assessments obtained at least 24 hours apart, and any measurement in between.
2. Achievement of hematologic response at Week 26.
3. Change from Baseline in eGFR at Week 26.
4. On dialysis at Week 26.
5. Time to response for each TMA parameter (Table 2) during the 26-week randomized Treatment Period
    - Hematologic response
    - Renal response
6. Achievement of individual component of complete TMA response at all scheduled assessments
    - Hematologic response
    - Renal response
    - At least one of the TMA parameters
7. Changes from Baseline in hematologic response parameters at all scheduled assessments
    - Platelets
    - LDH
    - Hemoglobin
8. Increase in hemoglobin at Week 26 of
    - ≥ 2 g/dL
    - ≥ 1 g/dL
9. Change in kidney function
    - Change from Baseline in eGFR at all scheduled assessments
    - Change from Baseline in dialysis requirement at Week 26 and Week 52
    - Duration of dialysis (for participants who had dialysis within the 26-week randomized Treatment Period or within the study)

10. Complete TMA response at Week 52 among participants who achieved complete TMA response during the 26-week randomized Treatment Period
11. Loss of TMA response during the 26-week randomized Treatment Period (for participants who achieved complete TMA response during the 26-week randomized Treatment Period)
12. TMA relapse during the Post-Treatment Follow-up Period (for participants who achieved complete TMA response during the 26-week randomized Treatment Period)
13. Change in patient-reported outcomes as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) at all scheduled assessments

5.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

1. Exploratory biomarkers will be assessed in blood and urine for change from Baseline and may include, but are not limited to, markers of vascular damage, renal injury, and complement dysregulation (eg, soluble terminal complement complex, factor Ba). Exploratory biomarker assessments will be detailed in a separate, exploratory biomarker SAP.
2. Change in patient-reported outcomes as measured by EuroQol 5-Dimension 5-Level (EQ-5D-5L) and Kidney Disease Quality of Life instrument™–36 items (KDQOL-36) at scheduled visits
3. Incidence of complement dysregulation-related mutations
4. Health resource utilization by Week 26 and Week 52 including:
    - Number, underlying reason, and duration of hospitalizations (including stays in intensive care unit, if applicable)
    - Number of outpatient medical encounters (including physician or emergency room visits)
5. Overall survival by Week 26 and Week 52

5.4. Pharmacokinetic and Pharmacodynamic Endpoints

The pharmacokinetic (PK) endpoints of the study are as follows:

1. Serum concentrations of ravulizumab over time
2. Serum free complement component 5 (C5) concentrations (absolute value, change from Baseline, and percentage change from Baseline) over time
3. Serum total C5 concentrations (absolute value, change from Baseline, and percentage change from Baseline) over time
4. Incidence of antidrug antibodies (ADAs) and assessment of immunogenicity

5.5. Safety Endpoints

The safety and tolerability endpoints of the study are as follows:

1. Incidence of adverse events (AEs) and serious adverse events (SAEs) by Week 26 and Week 52
2. Incidence of major adverse cardiovascular events (MACEs) by Week 26 and Week 52
3. Changes from Baseline in vital signs and laboratory parameters at scheduled assessments

5.5.1. Adverse Events

AEs are defined in Protocol Section 10.3.

MACEs as determined by the Investigator will be assessed as part of the planned evaluation of AEs. A MACE is defined as any of the following:

- Nonfatal myocardial infarction
- Nonfatal stroke
- Death from cardiovascular disease

Adverse events of special interest (AESIs) include meningococcal infections as defined in PA2 Section 8.4.6.

5.5.2. Vital Signs

Vital signs are systolic and diastolic blood pressure [mm Hg], heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]), and pulse oximetry (%).

5.5.3. Laboratory Assessments

Laboratory assessments are defined in Protocol Section 10.2, where the laboratory tests as detailed will be performed by the central laboratory or designated ancillary laboratories. Local laboratory results are only required in the event that the central laboratory results were not available in time for either study drug administration and/or response evaluation. In the event of duplicate samples from local and central laboratories (for any time point), central laboratory results will be used for analysis.

5.5.4. Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be conducted according to the schedule of activities (SoA) in the protocol to obtain heart rate, PR, QRS, QT, and corrected QT (QTc) intervals. The QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

5.5.5. Physical Examination

A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, musculoskeletal, and neurological state. An abbreviated physical

examination will include, at a minimum, a body-system relevant examination based on Investigator judgment and participant symptoms.

5.5.6. Immunogenicity

Blood samples will be collected to test for the presence of ADAs to ravulizumab in serum according to the SoA in the protocol. Samples with confirmed positive ADA will further be tested for ADA titer and the presence of neutralizing antibodies.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

The analysis sets are defined as follows.

6.1. Intent to Treat Set

The Intent-to-treat (ITT) Set will include all randomized participants.

The ITT Set was used for disposition summaries.

6.2. Modified Intent-to-Treat Set

The Modified Intent-to-Treat (mITT) Set will include all randomized participants, excluding participants who enrolled prior to the availability of Shiga toxin-related hemolytic uremic syndrome (ST-HUS) and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) central laboratory results and are subsequently found to be ineligible after randomization.

The mITT Set was selected as the primary efficacy population to ensure the exclusion of participants with thrombotic thrombocytopenic purpura (TTP) or ST-HUS as potential confounders in the efficacy analyses, as these conditions present similarly to the target population but have distinct clinical prognosis and management. For the efficacy assessments, participants will be assessed according to the treatment they were randomized to receive, regardless of the treatment they actually received ("as randomized" approach).

6.3. Per-Protocol Set

The Per-Protocol Set (PPS) will consist of mITT participants who met all of the following criteria. The primary analysis will be repeated on the PPS as supplementary analyses. PPS will be analyzed according to the participants' randomized treatment assignment.

1. Participants who received full randomized intervention during the 26-week randomized Treatment Period
2. Did not receive any disallowed medications or undergo any disallowed therapeutic procedures as described in Protocol Section 6.6.2:
    - Experimental interventions or therapies
    - Eculizumab or other agents that act on the complement pathway
    - Therapeutic plasma exchange/plasma infusion following randomization
3. Met inclusion criteria (IC) in the study:
    - IC 4: TMA within ≤ 14 days prior to Screening is associated with at least one of the following triggers:
        a) Autoimmune (lupus nephritis or systemic sclerosis-associated TMA [SSc-TMA])
        b) Infection
        c) Solid organ transplant (eg, kidney, pancreas, liver, heart, or small bowel)
        d) Drugs
        e) Malignant hypertension

- IC 5: Confirmation of all of the following laboratory findings during the Screening Period and/or ≤ 14 days prior to the start of the Screening Period:
    a) Platelet count < 150,000/μL
    b) LDH ≥ 1.5 × upper limit of normal and hemoglobin ≤ LLN (based on age and sex)
    c) Acute kidney injury as defined by meeting 1 or more of the following criteria (for kidney transplant recipients, the pre-TMA value is based on post-transplant eGFR):
        – Acute decline in eGFR ≥ 50% from pre-TMA value (the pre-TMA value must be ≤ 12 months prior to Screening)
        – New acute kidney injury with an eGFR ≤ 30 mL/min/1.73 m^2
        – New initiation of dialysis due to TMA requiring > 1 session and for no more than 14 days prior to Screening

4. Did not violate important exclusion criteria (EC) in the study, including the following:
    - EC 1: Any known gene mutation that causes aHUS
    - EC 3: Known chronic kidney disease (CKD):
        - In participants with native kidneys: eGFR ≤ 45 mL/min/1.73 m^2 by the CKD-Epidemiology Collaboration (CKD-Epi) equation (Levey, 2009) due to any cause or ongoing acute kidney injury requiring dialysis treatment lasting for > 14 days prior to Screening.
        - In kidney transplant recipients: determination of the CKD threshold will be based on Investigator judgment.
    - EC 5: Primary and secondary glomerular diseases other than lupus
    - EC 6: Diagnosis of primary antiphospholipid antibody syndrome
    - EC 7: Shiga toxin-producing *E coli* infections, including, but not limited to, ST-HUS
    - EC 8: Known familial or acquired ADAMTS13 deficiency (activity < 5%)
    - EC 9: Positive direct Coombs test result, which, in the judgement of the Investigator, is indicative of a clinically significant immune-mediated hemolysis not due to TMA
    - EC 10: Clinical diagnosis of disseminated intravascular coagulation in the judgment of the Investigator, utilizing the International Society on Thrombosis and Haemostasis scoring criteria
    - EC 11: Presence of sepsis requiring vasopressors within 7 days prior to or during Screening
    - EC 13: Known bone marrow insufficiency or failure as evidenced by cytopenias
    - EC 14: Kidney biopsy (if available) showing any of the following in glomeruli:
        - ≥ 50% interstitial fibrosis tubular atrophy
        - ≥ 50% glomerulosclerosis

- ≥ 50% crescent formation

- EC 22: Respiratory failure from any cause requiring mechanical ventilation (including intubation, bilevel positive airway pressure, or continuous positive airway pressure) within 72 hours prior to randomization
- EC 23: Use of any complement inhibitors within the past 3 years
- EC 24: Participation in the following types of interventional treatment studies within 30 days before Day 1 in this study or within 5 half-lives of that investigational treatment, whichever is greater:
  - Interventional treatment study of any unapproved therapy regardless of indication
  - Interventional treatment study of any therapy (approved or unapproved) being evaluated for TMA intervention

6.4. Safety Set

The Safety Set will include all participants who receive at least 1 dose of study drug. Participants will be analyzed according to the study treatment they actually received. For a participant to be analyzed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for all their study drug exposure visits. All safety analyses will be performed on the Safety Set.

6.5. Pharmacokinetic and Pharmacodynamic Analysis Set

All participants who receive at least 1 dose of ravulizumab and who have evaluable PK or pharmacodynamic (PD) data will be included in the PK/PD Analysis Set. PK and PD analyses will be performed on the PK/PD Analysis Set.

7. STATISTICAL ANALYSIS

7.1. General

All analyses will be performed using Statistical Analysis Software® (SAS®) Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software.

Summary statistics will be computed and displayed by treatment group, and by visit, where applicable. Descriptive statistics for continuous variables will include the number of participants, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented.

7.1.1. Handling Missing Data

For binary endpoints, a nonresponder imputation (NRI) method will be used by categorizing any participants who have a missing value for categorical variables at a specific visit as a nonresponder for that visit. In addition, participants who have the following intercurrent events will be assigned as nonresponders, regardless of whether any response is observed after these intercurrent events: premature discontinuation of the study treatment or initiation of disallowed therapy or medicine, before observing the response for an endpoint in analysis.

For time-to-event endpoints (time to complete TMA response, time to response for each individual TMA parameter), missing data and data after intercurrent events of premature discontinuation of study treatment or initiation of disallowed therapy or medicine will be censored.

For the continuous secondary endpoint, no missing data handling will be performed. Summary statistics will be provided using observed data.

7.1.2. Multicenter Studies

The number of participants at each site is expected to be very small. Therefore, there will be no summarization of efficacy analyses by site.

7.2. Study Participants

7.2.1. Disposition of Participants

The summary of disposition will include the number and percentage of screened participants, randomized participants, and treated participants. In addition, the number and percentage of participants who discontinued from study treatment, the primary reason for treatment discontinuation (including coronavirus disease 2019 [COVID-19]-related reason) or discontinued from the study and the primary reason for study discontinuation (including COVID-19 related reason) will be summarized for all randomized participants by treatment group and overall. A table will also summarize the number and percentage of participants included in each analysis set defined in Section 6.

7.2.2. Protocol Deviations

Protocol deviations will be determined per the standard operating procedure (SOP) “Identification, Handling, and Documentation of Protocol Deviations” (SOP-G-CL-0044). The

number and percentage of participants with specific protocol deviations will be summarized for all enrolled participants by important and nonimportant deviations. To ensure completeness of the list of protocol deviations, the following will be verified programmatically from the database:

1. Participants from whom informed consent was not obtained
2. Participants who violated any IC/EC
3. Participants who received any disallowed medication or underwent any disallowed therapeutic procedure
4. Participants randomized to the ravulizumab treatment group who did not receive all of the planned number of infusions during the 26-week randomized Treatment Period

Protocol deviations from monitoring reports and other relevant sources will also be reviewed, and any important deviations will be included in the list that is summarized and reported.

Summary statistics will be presented by treatment group and overall.

7.2.3. Demographics, Disease Characteristics, and History

All demographics, baseline characteristics, and disease characteristics will be summarized using the mITT Set. Summary statistics will be presented by treatment group and overall. By-participant listings of these data will be provided.

7.2.3.1. Demographics and Baseline Characteristics

The following demographic variables will be summarized:

- Sex (female, male)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Age at Screening (years)
- Age categories (18 to < 40 years, 40 to < 65 years, ≥ 65 years)
- Baseline weight (kilogram): Descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: 30 to < 40, 40 to < 60, 60 to < 100, ≥ 100 kg
- Baseline height (centimeter)
- Geographical region (EU, US, Japan, rest of the world)
- Time from TMA diagnosis to randomization
- TMA laboratory values (platelets, hemoglobin, LDH)

7.2.3.2. Disease Characteristics

The following characteristics will be summarized by treatment group and overall:

- Primary and additional trigger type
  - Autoimmune (lupus nephritis, SSc-TMA)
  - Infection
  - Solid organ transplant (eg, kidney, pancreas, liver, heart, small bowel)
  - Drugs
  - Malignant hypertension
- Organ dysfunction
  - Dialysis status during the Screening Period
  - eGFR
- PLASMIC score at Baseline (refer to Section 9.3.3)

7.2.3.3. Medical History and Baseline Physical Examination

Medical history will be classified by System Organ Class (SOC) and Preferred Term using the latest available version of standardized Medical Dictionary for Regulatory Activities (MedDRA) and will be reported by treatment group and overall for the Safety Set. Baseline physical examination information will be summarized by treatment group and overall for the Safety Set. By-participant listings of medical/surgical history and physical examinations will be presented.

7.2.4. Prior and Concomitant Medications/Procedures

Prior and concomitant medications (including vitamins and herbal preparations) and nonpharmacologic therapies and procedures will be summarized using the Safety Set. Prior medications or procedures are defined as medications or procedures taken within the 30 days prior to the first dose of study drug. Concomitant medications or procedures are defined as medications or procedures received by the participants on or after the first dose of study drug, including those started before the first dose of study drug and continued after the first dose of study drug.

Medications will be coded using the World Health Organization (WHO) Drug Dictionary version in use by Alexion at the time of the analysis, while nonpharmacologic therapies and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) will be coded using MedDRA.

Medication summaries by treatment group (ie, number [%]) of participants using prior and concomitant medications will be presented by WHODrug Anatomical Therapeutic Chemical Level 3 and by WHO-Drug generic name. Procedures will be summarized similarly, but by MedDRA SOC and Preferred Term. Protocol-required vaccinations will be summarized similarly and will also be presented separately.

By-participant listings of these data will be provided separately.

7.3. Efficacy Analyses

The mITT Set is the primary analysis set for all efficacy analyses. The primary analysis will be repeated on the PPS as supplementary analyses.

7.3.1. Primary Analysis

The primary efficacy endpoint of the study is complete TMA response during the 26-week randomized Treatment Period.

Analysis of the primary endpoint will be conducted on the mITT Set based on randomized treatment groups using NRI for missing data handling. Point estimate and 95% confidence interval (CI) will be provided for the response rate for each treatment group. For participants who withdraw from the study, data up to the time of withdrawal will be used to assess complete TMA response.

Additionally, the primary efficacy endpoint will be analyzed based on the PPS.

7.3.1.1. Subgroup Analysis

Summaries of the primary efficacy endpoint will be presented by trigger type (including the primary trigger).

7.3.2. Secondary Analyses

All secondary analyses will be performed on the mITT Set.

For time-to-event endpoints, Kaplan-Meier cumulative distribution curves will be generated for each treatment group. A corresponding summary table will present by treatment group the cumulative distribution function estimate, the number of participants at risk, the number of participants responding, and the number of participants censored at each post-Baseline time point. The table will also present the first quartile, median, and third quartile, along with the corresponding 2-sided 95% CI, of time to response.

The binary additional secondary endpoints will be summarized by randomized treatment group by calculating the point estimate and 2-sided 95% CI for the response rate, based on exact confidence limits using the Clopper-Pearson method (Clopper, 1934). NRI will be used to handle missing data.

For continuous additional secondary endpoints, descriptive statistics, including the number of participants, mean, SD, minimum, median, and maximum, will be provided based on observed data.

For participants who require dialysis, change from Baseline in dialysis requirements will be summarized. An analysis will present the number and proportion of participants who require dialysis over time. A 2-sided 95% CI for the proportion will be provided. A participant will be considered as not requiring dialysis at a specific post-Baseline time point if they have been dialysis free for at least 14 days prior to that time point.

7.4. Interim Analysis

No interim analysis would be performed due to early termination of the study.

7.5. Exploratory Analyses

7.5.1. Biomarkers

Planned analyses on exploratory biomarkers will be detailed in a separate, exploratory biomarker SAP. Exploratory biomarker assessments will be reported in a separate biomarker report.

7.5.2. Patient-Reported Outcomes

Quality of life will be analyzed for EQ-5D-5L and KDQOL-36.

For EQ-5D-5L, a visual analogue scale (VAS) and the health state index score using US time trade-off (TTO) will be calculated (based on Section 9.3.13) and summarized at Baseline and each scheduled post-Baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from Baseline.

For KDQOL-36, Short-Form Health Survey 12 Item (SF-12, item 1-12), burden of kidney disease (item 13-16), symptoms/problems of kidney disease (item 17-28b), and effects of kidney disease scales on daily like (item 29-36) as subscales will be calculated separately by taking the sum of the component items. Descriptive statistics as well as the change from Baseline by visits will be presented separately for each subscale.

7.5.3. Health Resource Utilization

Hospitalizations will be summarized in a table presenting the number and proportion of participants requiring hospitalization, as well as the number of hospitalizations, the duration, the reason for hospitalization, and the hospitalization setting (intensive care unit or general ward).

Outpatient medical encounters will be summarized by presenting the number and proportion of participants requiring physician or emergency-room visits and the underlying reason.

7.6. Pharmacokinetic and Pharmacodynamic Analyses

Individual PK/PD data will be collected for all participants. PK/PD analyses will be performed on the PK/PD Analysis Set.

Serum ravulizumab concentration will be summarized over time with descriptive statistics, including the number of observations, arithmetic mean, SD, median, minimum, maximum, coefficient of variation, geometric mean, and geometric coefficient of variation.

The PD effects of ravulizumab will be evaluated by assessing the observed values, changes and percentage changes from Baseline in serum free and total C5 concentrations over time, as appropriate. Summaries will present descriptive statistics at each sampling time, as appropriate.

7.7. Safety Analyses

All safety analyses will be conducted on the Safety Set and based on the actual treatment received. All safety data will be provided by treatment group, in participant listings. AEs will be coded in MedDRA and presented by MedDRA SOC and Preferred Term. No formal hypothesis testing is planned. Safety data will be presented separately for the 26-week randomized Treatment Period and Post-Treatment Follow-up Period.

7.7.1. Study Treatment Duration and Treatment Compliance

Study treatment duration, numbers of infusions received, and treatment compliance will be summarized for the Safety Set. Study treatment duration will be calculated (in weeks) starting from the first infusion of study drug.

Treatment compliance will be calculated as a percentage based on the number of infusions received out of the number of infusions expected.

7.7.2. Adverse Events

The following definitions will be used for AEs:

- Pretreatment AEs: Any AE that starts after providing informed consent/assent, but before randomization or before the start of the first infusion of study drug.
- Treatment-emergent adverse event (TEAE): Any AE that starts between the first infusion of study drug and up to 8 months after the last infusion of study drug.
- Treatment-emergent serious adverse event (TESAE): A TEAE that is serious.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, drug-related TEAEs, TEAEs during study drug administration, and SAEs will be summarized by treatment group. All AEs will be coded using MedDRA version 23 or higher and will be summarized by SOC and Preferred Term overall, severity, and relationship to treatment. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity/relationship tables, the participant's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated participants in the Safety Set within a treatment group and overall. Tables will be sorted by descending frequency of SOC and by descending frequency of Preferred Term within an SOC.

Detailed by-participant listings of pretreatment AEs, TEAEs, SAEs, related TEAEs, TEAEs during study drug administration, TEAEs leading to withdrawal from the study, and TEAEs leading to study treatment discontinuation will be provided.

7.7.2.1. Overall Summary of Adverse Events

An overall summary of AEs and SAEs will be presented. The number of events (n) and number of participants with events (n, %) will be shown for the following event subcategories:

- Any TEAE
- Any TESAE
- TEAEs leading to withdrawal from the study
- TEAEs leading to study treatment discontinuation
- Study drug-related TEAEs
- TEAEs during study drug administration

Additionally, the number and percentage of participants who died during the study will be presented. AEs and SAEs by SOC and Preferred Term. The number of AEs and the number and

percentage of participants with events will be presented by SOC and Preferred Term. Participants are counted once in each SOC and Preferred Term. Percentages will be based on the total number of treated participants in the treatment group. SAEs will be summarized similarly.

7.7.2.2. AEs and SAEs by SOC, Preferred Term, and Relationship

The number of AEs and the number and percentage of participants with events will be presented by SOC and Preferred Term as described above by relationship (related, not related). If a participant has more than 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

7.7.2.3. AEs by SOC, Preferred Term, and Severity

The number of AEs and the number and percentage of participants with events will be presented by SOC and Preferred Term as described above by severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5). If a participant has more than 1 occurrence of an AE, the most severe occurrence will be used in the summary table.

7.7.2.4. MACE

Descriptive statistics for the number and percentage of participants with MACEs will be presented by treatment group. Pretreatment and treatment-emergent MACE rates through Day 183 (Week 26) and Day 365 (Week 52) (number per 100 patient-years) along with patient-years of follow-up and total number of MACEs will be displayed by treatment group.

7.7.2.5. Deaths and Other Significant Adverse Events

A listing of participant deaths will be produced, as well as a listing of AESI (including meningococcal infections).

7.7.3. Other Safety

7.7.3.1. Analyses for Laboratory Tests

Observed values and changes from Baseline in clinical chemistry, hematology, and urinalysis will be summarized descriptively by treatment group at Baseline and at each post-Baseline time point. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized by treatment group for all study visits. For purposes of analyses, laboratory results based on standardized units will be used.

7.7.3.2. Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, O_2 saturation, and temperature) and weight will be summarized descriptively by treatment group at Baseline and post-Baseline time point s for observed values and for changes from Baseline.

A listing of vital signs will also be presented by treatment group, participant, vital sign parameters, and visit.

7.7.3.3. Electrocardiograms

ECGs will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. A shift from baseline to worst on-study ECG table will be presented by treatment group for ECG results. Observed values and change from Baseline in ECG intervals (PR, RR, QT, and QTc) will be summarized descriptively by treatment group at Baseline and each post-Baseline time point. QT interval will be corrected using QTcF.

A listing of ECG results will also be presented by treatment group, participant, and visit.

7.7.3.4. Immunogenicity

The incidence of ADAs to ravulizumab will be summarized descriptively by treatment group at each post-Baseline time point. In addition, the number and percentage of participants ever positive and always negative will be summarized. Any confirmed ADA-positive samples will be tested for ADA titer and the presence of neutralizing antibodies to ravulizumab, and the results will also be summarized.

7.7.3.5. Physical Examination

Adverse changes from Baseline in physical examination findings will be classified as AEs and analyzed accordingly.

7.7.3.6. COVID-19 Related Analysis

The following analysis will be performed to assess the pandemic impact of COVID-19 on the study as supplementary analyses.

Patients with COVID-19-related screen failure will be summarized and presented.

The number and proportion of participants who experience the following COVID-19 impact will be summarized by treatment group and visit in the mITT Set:

- Those who miss the scheduled visits due to COVID-19
- Those with visits modified due to COVID-19 and details relating to visit modification
- Those who miss the scheduled doses of study treatment due to COVID-19
- Those who partially or completely miss primary endpoint assessments due to COVID-19 and those who received vaccination against COVID-19 or COVID-19-related treatment

The number of missing doses per participant will be summarized by treatment group in the mITT Set.

For safety analysis, AEs, including SAEs that are considered as COVID 19 related, will be summarized.

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9. APPENDICES

9.1. Protocol Schedule of Activities

Refer to Protocol Section 1.3 for the SoA.

9.2. Sample Size, Power, and Randomization

The planned sample size determination was based on a 2-sided Fisher's exact test performed at a 2-sided significance level of 0.05, comparing the proportion of participants achieving complete TMA response at Week 26 in participants randomized to ravulizumab versus placebo. A sample size of 100 (50 participants per treatment group) has approximately 90% power to detect a statistically significant ($p \leq 0.05$) treatment difference of 35% in the proportion of responders at a 2-sided significance level of 0.05, assuming the responder rate is 35% with placebo plus BSC and 70% with ravulizumab plus BSC and an anticipated 10% dropout rate (Caires, 2012; Humphreys, 2004; Lee, 2012; Schwarz, 2010; Song, 2013; Wu, 2013).

9.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

9.3.1. Definition of Baseline Values

Baseline for all parameters summarized during the 26-week randomized Treatment Period is defined as the last nonmissing assessment value prior to the start of study treatment (data from Screening or Day 1), prior to the date of randomization, with the exception for eGFR, for which the baseline definition is provided in Section 5.1.

9.3.2. Loss of TMA Response

For participants who meet the criteria for complete TMA response during the 26-week randomized Treatment Period, loss of TMA response is defined as when the participant fails to meet the criteria for 1 or more components of TMA response at a subsequent visit during the 26-week randomized Treatment Period. At least 1 parameter must fail to meet the response criteria at 2 separate assessments obtained at least 24 hours apart and any measurement in between. The first laboratory value will be assessed based on central laboratory results; the second laboratory value will be assessed based on the earliest value obtained $\geq$ 24 hours after the first value and may be based on central or local laboratory results.

9.3.3. PLASMIC Score

The PLASMIC score is the sum of points from each qualifying component. The score will be used to stratify participants into low (0 to 4), intermediate (5), and high (6 to 7) risk categories for TTP (Table 3).

Table 3: PLASMIC Score Derivation

Components	Point
Platelet count < 30×10^9/L	1
Hemolysis: Reticulocyte count > 2.5%, haptoglobin undetectable, or indirect bilirubin > 2.0 mg/dL (34.2 µmol/L)	1
No active cancer: Not treated for cancer within the past year	1
No history of solid-organ or stem-cell transplant	1
MCV < 9.0×10^{-14} L (< 90 fL)	1
INR < 1.5	1
Creatinine < 2.0 mg/dL (176.8 µmol/L)	1

Abbreviations: INR = international normalized ratio; MCV = mean corpuscular volume

9.3.4. Change from Baseline

Change in values from Baseline will be calculated as follows:

Change in value = (subsequent value – baseline value), given that both the baseline value and subsequent value are nonmissing.

9.3.5. Percent Change from Baseline

Percent change in values from Baseline will be calculated as follows:

Percent change in value = (change in value / baseline value) × 100

where change in value = (subsequent value – baseline value), given that the baseline value is nonmissing and nonzero and the subsequent value is nonmissing.

9.3.6. Analysis Visits

Summaries over post-Baseline time points or analyses at specific post-Baseline time points will be performed based on the list of visits described in the SoA of the protocol. For all assessments in the 26-week randomized Treatment Period, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of Day 1 visit) + 1. This number of days will be used to assign analysis visit.

The analysis visit assignment for a specific assessment will be based on visit windows around each scheduled visit for that specific assessment. The windows for each scheduled visit will go from the midpoint (in days) between the current visit and the previous scheduled visit to the midpoint between the current visit and the subsequent scheduled visit. If the interval separating 2 scheduled visits is an even number of days, that middle day will be included in the later visit window and excluded from the prior visit window. For example, for an assessment with a scheduled visit on Day 71, a prior scheduled visit on Day 57, and a subsequent scheduled visit on Day 85, the window will start at 64 days from Baseline and will go to 77 days from Baseline.

9.3.7. Analysis Values

The values being considered for analysis at a specific post-Baseline time point will be based on the analysis visit assigned to that value. If there is more than 1 nonmissing value for a specific assessment with the same analysis visit, the value used for analysis will be the one for which the calculated number of days from baseline is closest to the scheduled visit day. If 2 values have the

same analysis visit and are the at same distance away from the scheduled visit day, the earlier of the 2 values will be used for analysis.

9.3.8. Adverse Events

TEAEs are events with start dates on or after the date of the start of the first infusion of study drug and up to 8 months after the last infusion of study drug. If the start date of an AE is partially or completely missing and the end (stop) date of the AE does not indicate that it occurred prior to first dose or 8 months after last dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the start of first infusion of study drug and before the year of last infusion of study drug, then the AE is treatment emergent.
- If the start year is the same as the year of the start of the first infusion of study drug and
  - The start month is missing, then the AE is treatment emergent

    OR
  - The start month is present and is the same or after the month of the first infusion of study drug, then the AE is treatment emergent
- If the start date is completely missing, then the AE is treatment emergent.

9.3.9. Concomitant Medications/Therapies

Concomitant medications or therapies are defined as any nonstudy medications or therapies that were taken or given while the participant also received study treatment. A medication or therapy will be considered concomitant if the start date is on or after the date of the start of study treatment or if the start date is before the start of study treatment date and the end (stop) date is after the start of study treatment date. If the start date of a medication/therapy is partially or completely missing and the end (stop) date of the medication/therapy does not indicate that it ended prior to the start of study treatment, then the determination of the concomitant status will be based on the following:

- If the start year is after the year of the start of study treatment, then the medication/therapy is concomitant; else
- If the start year is the same as the year of the start of study treatment and
  - The start month is missing, then the medication/therapy is concomitant; else if
  - The start month is present and is the same or after the month of the start of study treatment, then the medication/therapy is concomitant; else
- If the start date is completely missing, then the medication/therapy is concomitant.

All other medications/therapies are considered prior medications/therapies.

9.3.10. Serum Creatinine and eGFR

Serum creatinine measurements are not reliable with concurrent dialysis. Therefore, all serum creatinine values obtained while a participant is on dialysis will be excluded from all analyses. The eGFR rate will be imputed with a value of 10 (in mL/min/1.73 m^2) while a participant is on dialysis. A participant will be considered on dialysis from the first day of dialysis through 5 days after the end of dialysis. A participant will be considered as not requiring dialysis at a specific post-Baseline time point if they have been dialysis free for at least 14 days prior to that time point. This rule will only be applied to postbaseline assessments of serum creatinine and eGFR.

The eGFR will be calculated based on creatinine using CKD-Epi equation in patients ≥ 18 years of age:

eGFR = 141 × min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 × 0.993Age x 1.018 [if female] × 1.159 [if Black]

9.3.11. Platelets and Hemoglobin

Platelet and hemoglobin measurements are not reliable with concurrent red blood cell (RBC) and/or platelet transfusions. Therefore, platelet values obtained on the day of a blood transfusion of platelets through 7 days after the transfusion will be excluded from all analyses. Hemoglobin values obtained on the day of a blood transfusion of either whole blood or packed RBCs through 7 days after the transfusion will be excluded from all analyses. This rule will only be applied to postbaseline assessments of platelets and hemoglobin.

9.3.12. Hypertension

Hypertension will be defined as follows.

Two consecutive blood pressure measurements obtained at least 1 hour apart, where

- The systolic pressure is greater than 139 mm Hg or
- The diastolic pressure is greater than 80 mm Hg

9.3.13. EQ-5D-5L Scoring Algorithm for US TTO

EQ-5D-5L is assessed using the index scored according to the TTO value set for the US as well as the response on the VAS question.

The standard US TTO value set is used to assign a value based on the health state indicated on the questionnaire.

The following will be used to calculate STATES at each time point:

MOBILITY: 0.000 if response = 1, -0.096 if response = 2, -0.122 if response = 3, -0.237 if response = 4, -0.322 if response = 5

SELF CARE: 0.000 if response = 1, -0.089 if response = 2, -0.107 if response = 3, -0.220 if response = 4, -0.261 if response = 5

USUAL ACTIVITIES: 0.000 if response = 1, -0.068 if response = 2, -0.101 if response = 3, -0.255 if response = 4, -0.255 if response = 5

PAIN/DISCOMFORT: 0.000 if response = 1, -0.060 if response = 2, -0.098 if response = 3, -0.318 if response = 4, -0.414 if response = 5

ANXIETY/DEPRESSION: 0.000 if response = 1, -0.057 if response = 2, -0.123 if response = 3, -0.299 if response = 4, -0.321 if response = 5

US TTO score = 1 + MOBILITY + SELF CARE + USUAL ACTIVITIES + PAIN/DISCOMFORT + ANXIETY/DEPRESSION

If data for some but not all dimensions are missing at a specific time point, data for the missing dimension(s) from the last available assessment prior to the time point with missing data will be used in the US TTO calculation. If all dimensions are missing, the last available US TTO score prior to the time point with missing data will be used.

9.3.14. FACIT-Fatigue Scoring Algorithm

The FACIT-Fatigue Scale (Version 4) is a short, 13-item, self-reported, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a 4-point scale (0 to 4). The fatigue scale ranges from 0 to 52, with a higher score indicating less fatigue.

Negatively stated items (all 13 items except for items An5 and An7) will be reversed by subtracting the response from "4." The FACIT-Fatigue total score will then be calculated by taking the sum of the items from the 13-item questionnaires divided by the number of items answered and then multiplied by 13, the total number of items in the scale. A total score will not be calculated if more than 50% of the items are missing.

9.3.15. KDQOL-36

The KDQOL-36 health survey includes 36 health questions consisting of 5 multi-item measures: physical component score (items 1, 2, 3, 4, 5, and 8), mental component score (items 6, 7, 9, 10, 11, and 12), burden of kidney disease (items 13 to 16), symptoms/problems of kidney disease (items 17 to 28b), and effects of kidney disease scales on daily life (items 29 to 36). The scoring procedure for the KDQOL-36 first transforms the raw precoded numeric values of items to a 0 to 100 possible range (Table 4). Each subscale score will then be calculated separately by taking the sum of the transformed items divided by the number of items answered and then multiplied by the number of items in the subscale. A subscale will not be calculated if more than 50% of the items in the subscale are missing.

Table 4: KDQOL-36 Item Score Transformation

Number of levels within an item [items]	2-level [i4-i7]	3-level [i2-i3]	5-level [i12-i16]	5-level (reverse) [i1, i8, i17-i27, i28a, i28b, i29-i36]	6-level [i11]	6-level (reverse) [i9, i10]
Item raw score transformation	1 → 0	1 → 0	1 → 0	1 → 100	1 → 0	1 → 100
	2 → 100	2 → 50	2 → 25	2 → 75	2 → 20	2 → 80
	NA	3 → 100	3 → 50	3 → 50	3 → 40	3 → 60
	NA	NA	4 → 75	4 → 25	4 → 60	4 → 40
	NA	NA	5 → 100	5 → 0	5 → 80	5 → 20
	NA	NA	NA	NA	6 → 100	6 → 0

Abbreviations: KDQOL-36 = Kidney Disease Quality of Life instrument™–36 items; NA = not applicable

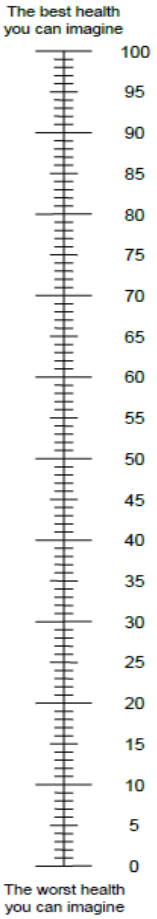
9.4. Questionnaires and Patient-Reported Outcomes

9.4.1. EQ-5D-5L

EQ-5D-5L	
Under each heading, please check the ONE box that best describes your health TODAY.	
MOBILITY	☐ I have no problems walking. ☐ I have slight problems walking. ☐ I have moderate problems walking. ☐ I have severe problems walking. ☐ I am unable to walk.
SELF-CARE	☐ I have no problems washing or dressing myself. ☐ I have sight problems washing or dressing myself. ☐ I have moderate problems washing or dressing myself. ☐ I have severe problems washing or dressing myself. ☐ I am unable to wash or dress myself.
USUAL ACTIVITIES *(eg, work, study, housework, family, or leisure activities)*	☐ I have no problems doing my usual activities. ☐ I have slight problems doing my usual activities. ☐ I have moderate problems doing my usual activities. ☐ I have severe problems doing my usual activities. ☐ I am unable to do my usual activities.
PAIN/DISCOMFORT	☐ I have no pain or discomfort. ☐ I have slight pain or discomfort. ☐ I have moderate pain or discomfort. ☐ I have severe pain or discomfort. ☐ I have extreme pain or discomfort.
ANXIETY/DEPRESSION	☐ I am not anxious or depressed. ☐ I am slightly anxious or depressed. ☐ I am moderately anxious or depressed. ☐ I am severely anxious or depressed. ☐ I am extremely anxious or depressed.
Your Health Today (0-100)	See sample below

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

9.4.2. FACIT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

9.4.3. KDQOL-36

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
3. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

KDQOL-36 (Continued, Page 2)

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
4. Accomplished less than you would like.....	☐ 1	☐ 2
5. Were limited in the kind of work or other activities	☐ 1	☐ 2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
6. Accomplished less than you would like.....	☐ 1	☐ 2
7. Didn't do work or other activities as carefully as usual.....	☐ 1	☐ 2

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

KDQOL-36 (Continued, Page 3)

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

KDQOL-36 (Continued, Page 4)

Your Kidney Disease

How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
13. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

KDQOL-36 (Continued, Page 5)

During the <u>past 4 weeks</u>, to what extent were you bothered by each of the following?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
17.	Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18.	Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.	Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.	Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21.	Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22.	Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23.	Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24.	Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25.	Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26.	Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27.	Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[a].	(Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[b].	(Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

KDQOL-36 (Continued, Page 6)

Effects of Kidney Disease on Your Daily Life

Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease bother you in each of the following areas?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
29. Fluid restriction?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Dietary restriction?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Being dependent on doctors and other medical staff?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5