NCT04209634

IND: 142063 Regeneron Pharmaceuticals, Inc.

**Clinical Study Protocol**

# AN OPEN-LABEL EFFICACY AND SAFETY STUDY OF POZELIMAB IN PATIENTS WITH CD55-DEFICIENT PROTEIN-LOSING ENTEROPATHY (CHAPLE DISEASE)

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|---|---|
| **Compound**: | REGN3918 (Pozelimab) |
| **Clinical Phase:** | 2/3 |
| **Protocol Number:** | R3918-PLE-1878 |
| **Protocol Version:** | R3918-PLE-1878 Amendment 6 |
| **Amendment 6 Date of Issue:** | *See appended electronic signature page* |
| **Amendment 5 Date of Issue:** | 18 Feb 2021 |
| **Amendment 4 Date of Issue:** | 09 Jun 2020 |
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| **Amendment 1 Date of Issue:** | 08 May 2019 |
| **Original Date of Issue:** | 02 Jan 2019 |
| **Medical /Study Director:** | [redacted] |

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# AMENDMENT HISTORY

## Amendment 6

The main purpose of this amendment is to extend the study duration to approximately 3 years.

| Description of Change | Brief Rationale | Sections Changed |
|---|---|---|
| The duration of the treatment period is extended from 104 weeks to 144 weeks, with an end-of-study follow-up at week 164, to a total duration of approximately 3 years | The longer term efficacy and safety of pozelimab treatment in CD55-deficient PLE are unknown; extending the on-treatment study period allows for description of a third year of treatment | Clinical Study Protocol Synopsis: Study Design, Study Duration<br>Section 6.1 Study Description and Duration<br>Figure 1 : Study Flow Diagram<br>Section 9.1.1 Footnotes for the Schedule of Events Table: #1 , #12<br>Section 9.1.2 Early Termination Visit |
| Updated endpoints and analyses to include the full 144-week study treatment period | Due to the extension of study duration, the end of treatment is at week 144 rather than week 104. Endpoints and analyses are updated to reflect this change | Clinical Study Protocol Synopsis: Objectives, Endpoints<br>Section 2.2 Secondary Objectives<br>Section 5.2 Secondary Outcomes<br>Section 5.3 Exploratory Outcomes<br>Section 11.4.3.2 Secondary Efficacy Analysis |
| Added a sample collection time point for pozelimab ADA at week 96 | The sampling schedule is adjusted due to the extension of the study duration | Table 1 Schedule of Events |
| Removed references to an open-label extension study | Text specifying the mechanism of post trial access has been deleted as the Sponsor is evaluating a number of options regarding this provision | Clinical Study Protocol Synopsis: Study Design<br>Section 6.1 Study Description and Duration<br>Section 9.1.2 Early Termination Visit |
| Updated confidentiality statement | This is a template language update for sponsor documents | Title page |
| Editorial changes and corrections | These are minor corrections | Throughout document |

### Amendment 5

The main purpose of this amendment is to remove the 1-year limitation on the study enrollment period and to align with prior correspondence with a regulatory agency.

| Description of Change | Brief Rationale | Sections Changed |
|---|---|---|
| Removed the 1-year limitation on the recruitment period. | This change was made to increase flexibility for study recruitment due to enrollment holds caused by the global pandemic. | Clincal Study Protocol Synopsis: Study Design, Sample Size<br>Section 6.1 Study Description and Duration<br>Section 7.1 Number of Patients Planned |
| The definition of evaluable for improvement for facial edema and peripheral edema was changed to require a severity of at least 3 points out of 5 at baseline rather than 2 points out of 5 at baseline. | This was a correction on the definition of an evaluable patient for facial and peripheral edema assessments. The 5-point scale used would not be able to accommodate a 2-point worsening for a patient with a score of 2 at baseline. | Clincal Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.1 Primary Outcome |
| For the primary endpoint, the definition was revised for improvement and worsening. An increase or decrease of 25 points or more, respectively, will be used for improvement or worsening on the Pediatric Quality of Life Inventory (PedsQL) gastrointestinal (GI) Symptoms Scale for the stomach pain and hurt sub-scale.<br>For the secondary endpoint on improvement in each patient's most bothersome sign/symptom, revised definition for improvement to an increase of 25 points or more on the PedsQL GI Symptoms Scale: nausea and vomiting subscale, and the definition for patients who are evaluable for improvement was revised to patients with a score of ≤75 at baseline. Correspondingly, for the diarrhea sub-scale, worsening is defined as a decrease of 25-points or more. | This change was made to address a comment from a regulatory agency regarding a more clinically meaningful within-patient change in scores. A 25-point change on the transformed score reflects a 1-category change on the raw score scale.<br>Corresponding changes were made for alignment to a related secondary endpoint on improvement in each patient's most bothersome sign/symptom and secondary endpoints on the proportion of patients who maintain disease control. | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 3.2.1 Rationale for Study Design<br>Section 5.1 Primary Outcome<br>Section 5.2 Secondary Outcomes |
| Removed screening value from the definition of baseline for facial and peripheral edema. The baseline value will be used. | This change was made to align the definitions of baseline for edema with those for albumin and symptom scales. | Section 11.4.3.1 Primary Efficacy Analysis |

| Description of Change | Brief Rationale | Sections Changed |
|---|---|---|
| Added time periods (12-48, 12-104, [new] 24-48, [new] 48-104 weeks) to secondary endpoints on maintenance of control:<br>• Proportion of patients with active disease at baseline who maintain disease control<br>• Proportion of patients with inactive disease on eculizumab at baseline who maintain disease control | These analyses were requested by a regulatory agency to evaluate durability of response during a review of the study analysis plan. | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.2 Secondary Outcomes |
| Replaced bowel movement with PedsQL GI Symptoms Scales diarrhea subscale in the definition of maintenance of disease control. A definition of worsening based on the PedsQL GI Symptoms Scales diarrhea subscale is provided. | This correction was necessary as bowel movement e-diary is not continued after week 24. The definition of worsening for the PedsQL GI Symptoms Scales diarrhea subscale is provided. | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.2 Secondary Outcomes |
| Removed language to exclude patients without an evaluable core symptom from the primary efficacy analysis. | This language was removed to align with regulatory agency feedback. | Clinical Study Protocol Synopsis: Statistical Plan<br>Section 11.4.3.1 Primary Efficacy Analysis |
| Included details of evaluable and non-evaluable patients for the secondary efficacy analysis.<br>Moved details on the identification of a patient's most bothersome sign/symptom to secondary efficacy analysis. | Details were included from the study statistical analysis plan.<br>The text did not pertain to the primary efficacy analysis and was moved to the relevant section. | Clinical Study Protocol Synopsis: Statistical Plan<br>Section 11.4.3.1 Primary Efficacy Analysis<br>Section 11.4.3.2 Secondary Efficacy Analysis |
| Corrected timing of primary analysis to be conducted when patients complete 24 weeks of treatment. | This correction was to align the first database lock with the primary endpoint at week 24. | Clinical Study Protocol Synopsis: Study Design<br>Section 6.1 Study Description and Duration<br>Section 11.6 Timing of Analyses |

### Amendment 4

The following table outlines the changes made to the protocol and the affected sections:

| Description of Change | Brief Rationale | Sections Changed |
|---|---|---|
| Allowed an extended screening period up to approximately 10 weeks for patients who:<br>(1) require additional time to complete meningococcal vaccinations<br>(2) must physically relocate to the vicinity of a study center<br>(3) are pending their screening laboratory results<br>(4) have other requirements, which will be evaluated on a case by case basis after a discussion between the sponsor and investigator. | This change allows flexibility in the screening period for patients who have extenuating circumstances but are otherwise eligible to participate in the study. | Clinical Study Protocol Synopsis: Study Design<br>Section 6.1 Study Description and Duration<br>Figure 1 Study Flow Diagram<br>Section 9.1.1 Footnotes for the Schedule of Events Table, #29<br>Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit |
| Revised exclusion criterion and study procedures to clarify that patients who are appropriately treated for an intercurrent illness (such as resolution of an infection) may be rescreened. | This change clarifies the language about rescreening patients who had an intercurrent illness during screening. | Section 7.2.2 Exclusion Criteria, #6<br>Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit |
| Incorporated exclusion criterion on hepatitis (and removed as a standalone exclusion), stating that viral hepatitis status should be determined by means of the patient's medical history.<br>Clarified that testing to establish activity status of hepatitis B or C may be performed at the discretion of the investigator. | This change clarifies that hepatitis screening is based on medical history, but optional hepatitis testing may be performed if warranted to determine eligibility. | Section 7.2.2 Exclusion Criteria, #14 (revised), #21 (removed)<br>Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events Table, #8<br>Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit |
| Added PGIC and CGIC assessments at week 48. | This change is a request from a health agency. | Table 1 Schedule of Events |
| Added clinical outcome assessments (CGIS, CGIC, PGIS, PGIC, and PedsQL questionnaires) at week 12. | This change allows an analysis of clinical outcome assessments at week 12 as requested by a health agency. | Table 1 Schedule of Events |
| Revised sample collection for immunogenicity assessment from week 96 to week 104 (end of treatment). | This change aligns immunogenicity analysis with other end of treatment assessments. | Table 1 Schedule of Events |
| Added time point for exit interview to be performed at early termination. | This change ensures that an exit interview is performed if a patient discontinues the study prior to the primary analysis at week 24 | Table 1 Schedule of Events |

| Description of Change | Brief Rationale | Sections Changed |
|---|---|---|
| Included definitions for improvement in nausea, vomiting, and stool consistency for efficacy endpoint. | This change provides additional detail for the analysis of efficacy endpoints as described in the Statistical Analysis Plan (v2.0). | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.2 Secondary Outcomes |
| Clarified the secondary endpoint on stool consistency to specify the parameter to be analyzed (number of days per week with ≥1 bowel movement of loose/watery consistency) | This change provides a more precise description of the secondary endpoint on stool consistency as described in the Statistical Analysis Plan (v2.0). | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.2 Secondary Outcomes |
| Increased the home dosing window to ±2 days | This change provides more flexibility for countries with 2-day national holidays. | Clinical Study Protocol Synopsis: Study Design, Treatment<br>Section 6.1 Study Description and Duration<br>Section 8.2 Drug Administration<br>Section 9.1.1 Footnotes for the Schedule of Events Table, #1 |
| Added language that, if a patient becomes pregnant during the study, the benefits and risks for the patient should be assessed and discussed with the medical monitor to determine whether study treatment should be continued. | This change provides guidance in the event that a patient becomes pregnant while on treatment. | Section 8.6.2.1 Reasons for Permanent Discontinuation of Study Drug<br>Section 10.1.3 Events that Require Expedited Reporting to Sponsor |
| Included language to provide flexibility in study procedures to address the continuity of study conduct during the COVID-19 pandemic. | This language addresses changes to study conduct due to impact from the COVID-19 pandemic, including screening and study visits. | Section 3.2.3.1 Study Conduct in Response to COVID-19 (new)<br>Section 9.1 Schedule of Events |
| Revised description of the trained interviewer who will conduct concept elicitation and exit interviews to “a trained external or internal interviewer”. | This is a correction. A trained interviewer will conduct the interviews. | Section 9.2.3.3 Clinical Outcome Assessments |

### Amendment 3

The following table outlines the changes made to the protocol and the affected sections:

| Description of Change | Brief Rationale | Sections Changed |
|---|---|---|
| Included an exception to allow patients under 6 years of age presenting with life-threatening disease to be enrolled into the study prior to the availability of week 12 data from the first 2 patients. The decision to allow exceptions will be made in conjunction with the medical director, steering committee, and will require approval from senior Regeneron medical staff and Ethics Committee/Institution Review Board. Depending on local policy, input from health authority may be sought before proceeding. | This change allows the enrollment of very young patients with life-threatening disease in exceptional cases. | Clinical Study Protocol Synopsis: Study Design, Target Population<br>Section 3.2.1 Rationale for Study Design<br>Section 6.1 Study Description and Duration<br>Section 7.2 Study Population<br>Section 7.2.1 Inclusion Criteria, #1 |
| Removed prohibition on intravenous albumin infusions during screening. This bullet has been moved to Section 8.10.2 Permitted Medications. | Albumin infusion is clinically appropriate for patients with very severe disease and stopping the infusions in such cases could result in catastrophic edema with hemodynamic compromise. | Section 8.10.1 Prohibited Medications<br>Section 8.10.2 Permitted Medications |

### Amendment 2

The following table outlines the changes made to the protocol and the affected sections:

| Change and Rationale for Change | Sections Changed |
|---|---|
| Revised primary endpoint to address health authority comments:<br>• Revised success criteria for normalization of serum albumin to include requirements for maintenance within normal range without the need for albumin infusion<br>• Removed stool consistency, clinician global impression of severity, and patient/caregiver global impression of severity to limit the number of clinical components.<br>• Provided pre-defined responder thresholds for the 4 prevalent aspects of disease selected for the primary endpoint (bowel movement frequency, peripheral edema, facial edema, and abdominal pain frequency). | Clinical Study Protocol Synopsis: Objectives, Outcomes/Endpoints, Statistical Plan<br>Section 2.1 Primary Objectives<br>Section 3.2.1 Rationale for Study Design<br>Section 5.1 Primary Outcomes<br>Section 11.1 Statistical Hypothesis<br>Section 11.4.3.1 Primary Efficacy Analysis |
| Added a secondary endpoint to evaluate improvement in the patient's most bothersome symptom, as determined prior to baseline using a concept elicitation interview. This change was made to address health authority comments. | Clinical Study Protocol Synopsis: Outcomes/Endpoints, Statistical Plan<br>Section 5.2 Secondary Outcomes<br>Section 9.2.3.3 Clinical Outcome Assessments |
| Added a secondary objective and endpoints to evaluate maintenance of efficacy for patients with active disease at baseline (at weeks 48 and 104) as well as the subgroup of patients with inactive disease who switched from eculizumab to pozelimab at baseline (at weeks 24, 48, and 104). Maintenance of disease control is based on normalization of serum albumin, no worsening of symptoms, and no increase of dosage of concomitant medication for the treatment of PLE. Medications considered concomitant medications for the treatment of PLE are clarified. This change was made to address health authority comments. | Clinical Study Protocol Synopsis: Objectives, Outcomes/Endpoints<br>Section 2.2 Secondary Objectives<br>Section 5.2 Secondary Outcomes<br>Section 8.10.2 Permitted Medications<br>Section 11.4.3.2 Secondary Efficacy Analysis |
| Increased minimum sample size to 6 patients and revised the study success criterion to show that at least 4 out of 6 patients with active disease are responders. The 90% confidence interval (CI) for 4 out of 6 responders is [0.27, 0.94]. Patients with fewer than 5 available albumin measurements between week 12 and week 24 will be considered non-evaluable for the primary endpoint. This change was made to address health authority comments. | Clinical Study Protocol Synopsis: Study Design, Sample Size, Statistical Plan<br>Section 6.1 Study Design<br>Section 7.1 Number of Patients Planned<br>Section 11.2 Justification of Sample Size<br>Section 11.4.3.1 Primary Efficacy Analysis<br>Section 11.6 Timing of Analyses |
| Clarified baseline definitions for the primary efficacy analysis. This change was made to address health authority comments | Section 11.4.3.1 Primary Efficacy Analysis |

| Change and Rationale for Change | Sections Changed |
|---|---|
| The following outcome assessments were moved from the primary and secondary outcomes to exploratory assessments:<br>• Patient/caregiver assessment of severity of disease<br>• Patient/caregiver assessment of change<br>• Physician assessment of severity of disease<br>• Physician assessment of change<br>This change was made to address health authority comments. | Section 2.3 Exploratory Objectives<br>Section 5.3 Exploratory Outcomes |
| Added Haemophilus influenzae and pneumococcal vaccinations as part of study pre-treatment requirements, unless the patient has adequate documentation of prior administration. This change was made to address health authority comments. | Section 6.1 Study Description and Duration<br>Section 8.3.1 Vaccinations<br>Section 9.2.2 Study Drug Administration |
| Included details regarding the composition of the steering committee. This change was made to address health authority comments. | Section 6.3.1 Steering Committee |
| Included additional details to help standardize physician assessment of edema and facial edema. Assessment of abnormal findings of facial edema, peripheral edema, and ascites should be accompanied by clinical photography, which will be read centrally by an independent physician blinded to the time point at which the photograph was taken. This change was made to address health authority comments. | Clinical Study Protocol Synopsis: Statistical Plan<br>Section 9.1.1 Footnotes for the Schedule of Events, #15<br>Section 9.2.3.2 Physician Assessment of Edema and Ascites<br>Section 11.4.3.1 Primary Efficacy Analysis |
| Added individual patient stopping rules and study stopping rules. This change was made to address health authority comments. | Section 6.1.1 Study Stopping Rules [new section]<br>Section 6.1.1.1 Individual Patient Stopping Rules [new section]<br>Section 6.1.1.2 Study Stopping Criteria [new section] |
| Added a new footnote to allow for early monitoring of anti-drug antibody (ADA) response. This change was made to address health authority comments. | Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events, #28 (new footnote) |
| Reordered effect on stool consistency as a secondary objective. This assessment was originally part of the primary objective. | Clinical Study Protocol Synopsis: Objectives, Outcomes/Endpoints, Statistical Plan<br>Section 2.2 Secondary Objectives |
| Strengthened rationale for study design and revised to align with other changes to the protocol. | Section 3.2.1 Rationale for Study Design |
| Included additional details regarding clinical outcome assessments (concept elicitation interview and exit interview). | Section 9.2.3.3 Clinical Outcome Assessments |
| Revised secondary endpoint on total complement activity (CH50) for clarity. | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.2 Secondary Outcomes |

| Change and Rationale for Change | Sections Changed |
|---|---|
| Removed the exclusion of patients with allergy or hypersensitivity to doxycycline as the incidence of serious hypersensitivity reactions is very low. Exposure with Regeneron antibody administration is lower than levels of exposure from animal meat, milk, and fish. | Section 7.2.2 Exclusion Criteria, #13 |
| Revised list of exploratory biomarkers and removed sampling time points to reduce the amount of blood volume collected per patient. | Section 4.5 Exploratory Biomarker Variables<br>Section 5.3 Exploratory Outcomes<br>Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events, #24<br>Section 9.2.7 Pharmacodynamic and Exploratory Biomarker Procedures |
| Added C-reactive protein to routine chemistry laboratory analysis to monitor systemic inflammation. | Section 9.2.4.4 Laboratory Testing |
| Revised language to allow serum or urine pregnancy testing per local practice, and clarified that pregnancy testing is mandatory at screening and at baseline. | Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events, #22<br>Section 9.2.4.4 Laboratory Testing |
| Added a note to assess for fractionated bilirubin if the total bilirubin is above the upper limit of normal. | Section 9.2.4.4 Laboratory Testing |
| Revised to allow the sponsor to be consulted regarding the interpretation of electrocardiograms (ECGs). | Section 9.2.4.3 Electrocardiogram |
| Updated REGN3918 with approved name, pozelimab | Section 8.1 Investigational Treatment |
| Clarified that samples for drug concentration and ADA analyses will be collected prior to study drug administration. In addition, samples for drug concentration and ADA analyses will be collected in the event of anaphylactic reactions, serious adverse events, or severe injection site reactions. | Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events, #27 (new footnote)<br>Section 9.2.5 Drug Concentration and Measurements |
| Revised to allow the storing of samples that are positive for ADA for further analysis when a neutralizing antibody (NAb) assay is available. | Section 4.4 Immunogenicity Variables<br>Section 9.2.6 Anti-Drug Antibody Measurements and Samples |
| Clarified that albumin infusions may be permitted as described in Section 8.10.1, Prohibited Medications. Patients who receive an albumin infusion between week 12 and week 24 will be considered a non-responder for the primary endpoint. | Clinical Study Protocol Synopsis: Outcomes/Endpoints<br>Section 5.2 Secondary Outcomes |
| Added a section header to improve organization of statistical section related to the timing of analyses. | Section 11.6 Timing of Analyses (new section header) |
| Updated immunogenicity-related sections based on updates to the protocol template language. | Section 2.2 Secondary Objectives<br>Section 4.4 Immunogenicity Variables<br>Section 11.3.4 Immunogenicity Analysis Sets<br>Section 11.4.6 Analysis of Immunogenicity Data |

| Change and Rationale for Change | Sections Changed |
|---|---|
| Minor corrections | Section 1 Introduction<br>Section 3.2.1 Rationale for Study Design<br>Section 3.2.3 Risk-Benefit Assessment<br>Section 4.2 Outcome Variables<br>Section 7.1 Number of Patients Planned<br>Section 7.2 Exclusion Criteria, #3<br>Table 1 Schedule of Events<br>Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit<br>Section 9.2.3.3 Clinical Outcome Assessments<br>Section 9.2.4.4 Laboratory Testing<br>Section 10.2.5 Severity<br>Section 19 References<br>Throughout document |

### Amendment 1

The following table outlines the changes made to the protocol and the affected sections:

| Change and Rationale for Change | Sections Changed |
|---|---|
| Provided additional details pertaining to the background of the disease and the study drug. | Section 1 Introduction<br>Section 3.2.1 Rationale for Study Design |
| Study objectives, study outcomes/endpoints, and study design revised to include clinical outcomes as part of the primary analysis in keeping with Health Authority advice. | Clinical Study Protocol Synopsis: Objectives, Study Design, Outcomes/Endpoints, Statistical Plan<br>Section 2 Study Objectives<br>Section 3.2.1 Rationale for Study Design<br>Section 5 Primary and Secondary Outcomes<br>Section 6.1 Study Description and Duration<br>Section 7.1 Number of Patients Planned<br>Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events Table, footnote 8<br>Section 9.2.3.3 Clinical Outcome Assessments<br>Section 11.1 Statistical Hypothesis<br>Section 11.2 Justification of Sample Size<br>Section 11.4.3.1 Primary Efficacy Analysis<br>Section 11.5 Interim Analysis |
| Amended study population to begin enrollment with older pediatric patients in order to mitigate the potential for risk in very young patients.<br>Additionally, for patients switching from eculizumab, removed 3-month washout requirement to mitigate risks associated with the discontinuation of treatment. | Section 3.2.1 Rationale for Study Design<br>Section 6.1 Study Description and Duration<br>Section 7.2 Study Population<br>Section 7.2.1 Inclusion Criteria |
| Screening procedures amended to remove nasal and throat swab screening for Nesseria meningitidis.<br>Screening procedures amended to allow genetic testing for Inclusion Criterion #2 to be performed at screening if needed. | Section 7.2.2 Exclusion Criterion #1<br>Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events Table, footnote 5<br>Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit |
| Additional blood samples collected for laboratory analyses, enabled by optimization of blood volume requirements. | Section 4.5 Exploratory Biomarker Variables<br>Table 1 Schedule of Events<br>Section 9.2.4.4 Laboratory Testing<br>Section 9.2.7 Pharmacodynamic and Exploratory Biomarker Procedures |
| Provide updated information about study drug. | Section 8.1 Investigational Treatment |

| Change and Rationale for Change | Sections Changed |
|---|---|
| For consistency across the pozelimab development program, added exclusion criteria for hepatitis B/C and tuberculosis. | Section 7.2.2 Exclusion Criteria #21 and #22<br>Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events Table, footnote 7 (added)<br>Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit |
| For consistency across the pozelimab development program, amended follow-up period to 21 weeks after the last dose of study drug. | Section 7.2.2 Exclusion Criteria<br>Section 8.3.2 Oral Antibiotics<br>Section 9.1.2 Early Termination Visit<br>Section 11.4.4.1 Adverse Events |
| For consistency across the pozelimab development program, revised language regarding recommended risk mitigation strategies for meningococcal vaccinations, oral antibiotic prophylaxis, and risk assessment of *Neisseria gonorrhea*. | Section 6.1 Study Description and Duration<br>Section 8.3.2 Oral Antibiotics<br>Section 8.4 Risk Management of *Neisseria Gonorrhea*<br>Table 1 Schedule of Events<br>Section 9.1.1 Footnotes for the Schedule of Events Table, footnotes 6 and 9 |
| For consistency across the pozelimab development program, included clarification on methods of contraception. | Section 7.2.2 Exclusion Criteria #20 |
| Revised sections with updated sponsor protocol template language for consistency with current processes. | Section 4.4 Immunogenicity Variables<br>Section 10 Safety Evaluation and Reporting<br>Section 12 Quality Control and Quality Assurance<br>Section 13.5 Clinical Study Data Transparency (added)<br>Section 14 Protocol Amendments |
| Corrected numbering of study days and updated Schedule of Events to reflect changes made in this amendment. | Table 1 Schedule of Events<br>Throughout document |
| Revised to add clarification or correct inconsistencies | Section 4.2 Outcome Variables<br>Section 8.2 Drug Administration<br>Section 8.6.1 Dose Modification<br>Section 9.2.3.1 Serum Albumin, Total Protein, and Immunoglobulin<br>Section 9.2.3.2 Physician Assessment of Edema and Ascites<br>Section 9.2.4.2 Physical Examination and Body Weight<br>Throughout document |

# CLINICAL STUDY PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title** | An Open-Label Efficacy and Safety Study of Pozelimab in Patients with CD55-Deficient Protein-Losing Enteropathy (CHAPLE Disease) |
| **Site Locations** | Multiple International Sites |
| **Principal Investigator** | [redacted] |
| **Objectives** | The primary objective of the study is to determine the effect of pozelimab on active CD55-deficient protein-losing enteropathy (PLE; CHAPLE), as measured by:<br>1. Normalization of serum albumin, and<br>2. Improvement in the following clinical outcomes that are evaluable for improvement at baseline, without worsening of the others, after 24 weeks of treatment (assessed at week 24):<br>• Daily bowel movement frequency<br>• The presence and severity of facial or peripheral edema<br>• The patient/caregiver assessment of abdominal pain frequency<br>The secondary objectives of the study are:<br>• To evaluate the safety and tolerability of pozelimab in patients with CD55-deficient PLE disease<br>• To evaluate the effect of pozelimab on CD55-deficient PLE (both patients with active disease at baseline and those with inactive disease on eculizumab, switching to pozelimab)<br>• To determine the effects of pozelimab on albumin and other serum proteins (total protein, immunoglobulins)<br>• To determine the effects of pozelimab on ascites<br>• To determine the effects of pozelimab on stool consistency<br>• To determine the effect of pozelimab on health-related quality of life<br>• To determine the effect of pozelimab on lab abnormalities observed in CD55-deficient PLE such as hypertriglyceridemia, thrombocytosis, and hypovitaminosis B12<br>• To describe the effects of pozelimab on the sparing of concomitant medications and reduction in hospitalization days<br>• To determine the effects of pozelimab on growth<br>• To characterize the concentration of pozelimab in patients with CD55-deficient PLE<br>• To assess the occurrence of anti-drug antibody (ADA) for pozelimab in patients with CD55-deficient PLE |

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| **Study Design** | R3918-PLE-1878 is an open label, single arm, 144-week treatment study in patients aged 1 year and older with active clinical signs and symptoms of CD55-deficient PLE/CHAPLE disease, and a CD55 loss-of-function mutation detected by genotype analysis (frameshift, nonsense mutations). In the case of missense or suspected splice site mutations, CD55-deficient PLE is to be confirmed by flow cytometry of peripheral blood cells. The first 2 patients enrolled will be of age 6 years or older (exception will be made for patients under 6 years of age with life-threatening disease).<br>A minimum of 6 patients with active PLE will be enrolled, up to approximately 20 patients. The primary analysis will occur when approximately 6 patients with active PLE have received 24 weeks of treatment. Subsequent analyses will occur 1 and 2 years after the first dose in the last patient enrolled.<br>The study consists of a screening period (up to 4 weeks [or up to 10 weeks for patients with extenuating circumstances]) followed by a 144-week treatment period (from week 0 to week 144, with final dose at week 143), and a follow-up period (from week 145 to week 164).<br>Patients will be given a single loading dose of pozelimab 30 mg/kg intravenously (IV) on day 1, then fixed doses subcutaneously (SC) (based on body weight) QW (±2 days) over the treatment period.<br>Only patients with active PLE will be included in the primary analysis. Active PLE is defined as hypoalbuminemia of less than or equal to 3.2 g/dL within the screening period, and within the last 6 months, at least 7 days (which do not have to be consecutive) of 1 or more of the following symptoms or signs: diarrhea, vomiting, abdominal pain, peripheral or facial edema, an episode of infection with concomitant hypogammaglobulinemia, or a new thrombotic event. |
| **Study Duration** | The duration of the study for a patient is approximately 165 weeks (from week 0 to week 164), excluding the screening period. |
| **End of Study Definition** | The end of study is defined as the last visit of the last patient. |
| **Population** | |
| **Sample Size:** | A minimum of 6 patients with active PLE will be enrolled, up to approximately 20 patients.<br>Eligible patients with inactive PLE may also be enrolled, but their data will not be included in the primary analysis. |
| **Target Population:** | Patients aged 1 year and older with a clinical diagnosis of CD55-deficient PLE disease, with CD55 loss of function mutation determined by genetic analysis (frameshift, nonsense mutations) and confirmed (only necessary in the case of missense or suspected splice site mutations) by flow cytometry or western blotting CD55 on peripheral blood cells. The first 2 patients must be aged 6 years and older (exception will be made for patients under 6 years of age with life-threatening disease). |

**Treatment**

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|---|---|
| **Study Drug** | Pozelimab |
| **Dose/Route/Schedule:** | Patients will be given a single loading dose of pozelimab 30 mg/kg IV on day 1, then fixed doses SC (based on body weight) QW (±2 days) over the treatment period. |

**Outcomes/Endpoints**

**Primary:**

The primary endpoint at week 24 is the proportion of patients with active disease at baseline achieving both of the following:

- Normalization of serum albumin, defined as
  - serum albumin within the normal range at at least 70% of measurements between week 12 and week 24, and
  - no single albumin measurement of <2.5 g/dL between week 12 and week 24, and
  - no requirement for albumin infusion between week 12 and week 24
- Improvement in the following clinical outcomes that were evaluable for improvement at baseline, with no worsening of the others (ie, those not evaluable for improvement) at week 24:
  - The number of bowel movements per day, based on a 1-week average, captured by e-diary. Improvement is defined as a reduction of 50% or more in the number of daily bowel movements based on a 1-week average. Patients evaluable for improvement are defined as those with an average of 3 or more bowel movements per day at baseline. Worsening is defined as an increase of 30% or more
  - Physician assessment of facial edema (based on a 5-point Likert scale). Improvement is defined as a reduction of 2 points or more. Patients evaluable for improvement are defined as those with a severity of at least 3 points out of 5 at baseline. Worsening is defined as an increase of 2 points or more
  - Physician assessment of peripheral edema (based on a 5-point Likert scale). Improvement is defined as a reduction of 2 points or more. Patients evaluable for improvement are defined as those with a severity of at least 3 points out of 5 at baseline. Worsening is defined as an increase of 2 points or more
  - Patient/caregiver assessment of abdominal pain frequency as assessed by the Stomach pain and hurt sub-scale of the Pediatric Quality of Life Inventory (PedsQL™) Gastrointestinal (GI) Symptom Scale. Improvement is defined as an increase of 25 points or more. Patients evaluable for improvement are those with a score of 70 points or less at baseline. Worsening is defined as a decrease of 25 points or more

**Secondary:**

- Incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables from baseline to week 144
- Improvement in each patient's most bothersome sign/symptom at week 24, as determined prior to baseline using a semi-structured concept elicitation interview, from amongst the 'core' clinical endpoints of frequency of bowel movements, peripheral edema, facial edema, abdominal pain frequency (as described previously), nausea, vomiting, and stool consistency:
  - Improvement in nausea and vomiting will be defined as an increase of 25 points or more on the 0 to 100 transformed nausea and vomiting subscale of the PedsQL GI Symptom Scale score where lower scores indicate worse nausea and vomiting. Patients will be evaluable for improvement in nausea and vomiting if they have a score ≤75 on the nausea and vomiting subscale at baseline
  - Improvement in stool consistency will be defined as a reduction of ≥50% in the number of days per week that the patient has a bowel movement of loose/watery consistency. A bowel movement is considered to be loose/watery if it corresponds to 3 images of loose or watery stools on the Brussels Infant and Toddler Stool Scale (BITSS), the images and descriptors for categories 4 or 5 on the modified Bristol Stool Form Scale for Children (mBSFS-C), and the images and descriptors for categories 6 or 7 of the Bristol Stool Form Scale (BSFS). To be evaluable for improvement in stool consistency, patients must have a bowel movement of loose/watery stool consistency for ≥2 days/week at baseline
- The proportion of patients with active disease at baseline who maintain disease control in these time periods (in weeks) 12-48, 12-144, 24-48, 48-96, 96-144 as defined by:
  - Normalization of serum albumin, defined as serum albumin within the normal range at at least 70% of measurements and no single albumin measurement of <2.5 g/dL and no requirement for albumin infusion .
  - No worsening (definitions in parentheses), from the beginning of the stated time period, at any single visit during the stated time period, of: facial or peripheral edema (≥2-point increase); or stomach pain and hurt sub-scale (≥25-point decrease); or diarrhea subscale of the PedsQL GI Symptom Scale (≥25-point decrease)
  - No increase in doses of permitted concomitant medications for the treatment of PLE at any time, no re-introduction of any permitted concomitant medication once withdrawn, where permitted concomitant medication is as follows: corticosteroids, IV or SC immunoglobulin, IV albumin, biologic immunomodulators (anti-tumor necrosis factor [TNF], vedolizumab), small molecule immunomodulators (eg, azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation

- The proportion of patients with inactive disease on eculizumab at baseline who maintain disease control in these time periods (in weeks) 12-48, 12-144, 24-48, 48-96, 96-144 as defined by:
  - Normalization of serum albumin, defined as serum albumin within the normal range at at least 70% of measurements and no single albumin measurement of <2.5 g/dL and no requirement for albumin infusion and
  - No worsening (definitions in parentheses), from the beginning of the stated time period, at any single visit during the stated time period, of: facial or peripheral edema (≥2-point increase); or stomach pain and hurt sub-scale (≥25-point decrease); or diarrhea subscale of the PedsQL GI Symptom Scale (≥25-point decrease)
  - No increase in dose of permitted concomitant medication for the treatment of PLE at any time, no re-introduction of any permitted concomitant medication once withdrawn, where permitted concomitant medication is as follows: corticosteroids, IV or SC immunoglobulin, IV albumin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (eg, azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation
- The number of bowel movements per day, based on a 1-week average, captured by e-diary from baseline to week 24
- The number of days/week with ≥1 bowel movement of loose/watery stool consistency, as measured by BSFS for patients who are 18 years of age and older, mBSFS-C for patients who are toilet-trained and less than 18 years of age, or the BITSS who are not toilet-trained, and captured by e-diary from baseline to week 24
- Physician assessment of facial edema (based on a 5-point Likert scale) from baseline to week 144
- Physician assessment of peripheral edema (based on a 5-point Likert scale) from baseline to week 144
- Change in abdominal symptoms, as assessed by the PedsQL™ GI Symptom Scale stomach pain and hurt sub-scale and food and drink limits sub-scale from baseline to week 144
- Health-related quality of life as measured by the PedsQL™ Generic Core Scales from baseline to week 144; additionally, the following sub-scales will be reported separately:
  - About my work/studies and school functioning sub-scale
  - Physical functioning sub-scale
- Assessment of abdominal ascites (assessed by measurement of abdominal circumference) from baseline to week 24
- Frequency of albumin infusions up to week 144, expressed as number per half-year. Albumin infusions are permitted during the treatment phase in the event that the albumin level is below 3.0 g/dL at 2 consecutive visits with accompanying symptoms of facial or peripheral edema or ascites. Any albumin infusions

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| | between week 12 and week 24 will render the patient a non-responder for the primary endpoint.<br>• Total albumin, protein, total Ig, IgG, IgM, IgA, expressed as:<br>– Absolute value at every scheduled time point including week 24<br>– Absolute and percent change from baseline over time<br>– Time to first normalization<br>• Vitamin B12, folate, iron, iron binding capacity, ferritin, magnesium, fasting cholesterol/triglycerides, expressed as:<br>– Absolute value at every scheduled time point including week 24<br>– Absolute and percent change from baseline over time<br>– Time to first normalization<br>• Alpha-1 antitrypsin levels in blood and stool, and change from baseline to week 12 and week 24<br>• Use and dose/frequency from baseline to week 144 of: corticosteroids, IV or SC immunoglobulin, IV albumin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (eg, azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation, anti-coagulants (eg, low-molecular-weight heparin), antibiotics (with the exception of those used for the purpose of Neisserial prophylaxis), anti-platelet agents (eg, low-dose aspirin)<br>• Hospitalization days (percentage of days hospitalized) over time<br>• Body weight and height, (expressed as z scores) over time<br>• Concentrations of total pozelimab in serum assessed throughout the study<br>• Incidence of treatment-emergent ADAs to pozelimab in patients over time<br>• Change and percent change from baseline of total complement CH50 assay over time |
| **Procedures and Assessments** | The efficacy procedures include laboratory measurements of serum albumin, protein, and immunoglobulins, and other laboratory abnormalities characteristic of PLE. Clinical assessments include those for global disease activity, edema, and ascites (characteristic clinical features of PLE). Patient or caregiver-reported outcomes include those for global disease assessment, common PLE symptoms, and health-related quality of life. Effect on healthcare utilization will be determined by quantifying the sparing and withdrawal of concomitant therapies and the reduction of hospitalization days. Effects on growth and maturation will be assessed using weight, height, and pubertal Tanner staging. Evaluation of dosing regimen will be assessed using blood concentration of pozelimab and CH50, a pharmacodynamic marker.<br>Overall safety will be assessed by monitoring/evaluation of TEAEs, physical examinations, and clinical safety laboratory tests at prespecified time points. Samples for drug concentration will be collected, and the potential emergence of anti-pozelimab antibodies will also be evaluated. |

**Statistical Plan**

The primary objective of the study is to determine the effect of pozelimab on CD55-deficient PLE/CHAPLE disease in patients with active disease at baseline. The primary outcome is the achievement of both of the following: (1) normalization of serum albumin, and (2) improvement from baseline to week 24 in the prespecified clinical outcomes that were evaluable for improvement at baseline, with no worsening of the others. The primary endpoint is the proportion of patients achieving the primary outcome.

**Justification for the sample size**. The study is regarded as successful if at least 4 of 6 patients achieve the primary endpoint. Unpublished patient-level data of 14 patients treated with eculizumab were made available to the study sponsor. In the historical control period before initiating eculizumab, 0 of 14 patients met the primary endpoint (90% exact confidence interval (CI): [0.00, 0.19]). If 4 of 6 evaluable patients treated with pozelimab achieve the primary endpoint, the 90% exact CI for the probability of achieving the primary endpoint is (0.27, 0.94), with the lower limit of 0.27 clearly greater than the upper limit of 0.19 for the historical control period of the 14 patients. By a Bayesian analysis, a comparison between 4 of 6 pozelimab-treated patients achieving the primary endpoint and 0 of 14 in the historical data by a Beta-Binomial analysis with the Jefferys prior of Beta(0.5, 0.5) would conclude that there is a >99% posterior probability that pozelimab has a greater response rate than untreated patients. There would also be a 90% posterior probability that the response rate with pozelimab is at least 0.37 higher than that of untreated patients. Thus, the study success criterion of observing at least 4 of 6 evaluable patients achieving the primary endpoint provides strong evidence of effectiveness.

All of the 14 eculizumab-treated patients achieved a normalized serum albumin level by 12 weeks of treatment and required no albumin infusions subsequent to treatment initiation (90% exact CI: [0.81, 1.00]). If the true rate of achieving the primary endpoint for patients on pozelimab is 0.81 (the lower limit of the CI for eculizumab), then a sample size of 6 gives a probability of 91% for achieving the study success criterion.

**Primary Efficacy Analysis.** The subset of the full analysis set (FAS) with patients having active PLE at baseline will provide the data for the primary efficacy analysis. The percentage of patients achieving normalization of albumin and achieving improvement in the prespecified evaluable clinical outcomes will be calculated and its 90% CI will be reported.

There are 7 planned albumin measurements between week 12 and week 24, inclusive. Patients will be considered non-evaluable for the primary analysis if there are fewer than 5 available albumin measurements between week 12 and week 24. Albumin measurements outside of the visit windows and/or carried out at local laboratories will be considered as valid measurements. To be considered responders, at least 70% of available measurements must be normal (≥3.5 g/dL). Thus, patients with the minimum of 5 available measurements must have 4 out of 5 normal. Patients with the planned number of 7 measurements must have at least 5 normal. Patients who have more than 7 available measurements (due to unplanned albumin measurement in local labs) must have at least 70% of all available measurements normal. Non-responder imputation for patients with fewer than 5 available albumin measurements between 12 and week 24 will be carried out as a sensitivity analysis. The mean changes from baseline in albumin over time and the mean number of albumin infusions per half-year will also be estimated. Patient profiles of albumin over time will be plotted.

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| | There are 4 clinical outcomes that can contribute to the clinical improvement component of the primary endpoint. Patients are evaluable for improvement in each of these based on activity at baseline. Patients evaluable for only 1 of the 4 clinical outcomes must show improvement (as defined) in that clinical outcome and no worsening in the other 3. Patients evaluable for more than 1 clinical outcome must show improvement for all of their evaluable outcomes and no worsening in any non-evaluable outcomes.<br>For facial and peripheral edema, the primary analysis will be performed using the investigating physician's report. Clinical photographs will be rated by a single, independent central reader blinded to the time point at which the photograph was taken. The correlation of central read to physician's assessment will be described. The central read will be used as a sensitivity analysis on the primary endpoint. |

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
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| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| aHUS | Atypical hemolytic uremic syndrome |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BID | Twice daily |
| BITSS | Brussels infant and toddler stool scale |
| BSFS | Bristol Stool Form Scale |
| BUN | Blood urea nitrogen |
| BW | Body weight |
| CareGIC | Caregiver global impression of change |
| CareGIS | Caregiver global impression of severity |
| CGIC | Clinical global impression of change |
| CGIS | Clinical global impression of severity |
| ClinRO | Clinical reported outcome |
| COA | Clinical Outcome Assessment |
| COVID-19 | Coronavirus Disease 2019 |
| CRF | Case report form (electronic or paper) |
| CRP | C-reactive protein |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FPFD | First patient first dose |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| HBsAG | Hepatitis B surface antigen |
| HBeAg | Hepatitis B e antigen |
| HCV RNA | Hepatitis C virus RNA |
| HDL | High-density lipoprotein |
| HRQoL | Health-related quality of life |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |

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| IRB | Institutional Review Board |
| IV | Intravenous |
| LDL | Low-density lipoprotein |
| LLOQ | Lower limit of quantification |
| mBSFS-C | modified Bristol Stool Form Scale for Children |
| MID | Minimum important difference |
| NAbs | Neutralizing antibodies |
| NOAEL | No observable adverse effect level |
| ObsOR | Observer reported outcome |
| PD | Pharmacodynamics |
| PedsQL™ | Pediatric Quality of Life Inventory™ |
| PGIC | Patient global impression of change |
| PGIS | Patient global impression of severity |
| PK | Pharmacokinetic |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| PLE | Protein-losing enteropathy |
| PRO | Patient reported outcome |
| PT | Preferred term |
| PT/aPTT | Prothrombin time/activated partial thromboplastin time |
| RBC | Red blood cell |
| Regeneron | Regeneron Pharmaceuticals, Inc. |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |
| SAS | Statistical Analysis System |
| SC | Subcutaneous |
| SOC | System organ class |
| TB | Tuberculosis |
| TEAE | Treatment-emergent adverse event |
| TNF | Tumor necrosis factor |
| WBC | White blood cell |

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# 1. INTRODUCTION

CD55-deficient protein-losing enteropathy (CD55-deficient PLE) is a newly described disease and potential indication for C5 blockade, also referred to as complement hyperactivation, angiopathic thrombosis, protein-losing enteropathy (CHAPLE disease) (Kurolap, 2017) (Ozen, 2017b). Of the 11 patients described by Ozen et al., 9 were from Turkey, 1 was from Syria and 1 was from Morocco. Eight of these patients were <2 years old at presentation. Unlike paroxysmal nocturnal hemoglobinuria (PNH), another disease being evaluated for REGN3918 (also known as pozelimab), hemolysis has not been observed in CD55-deficiency patients.

CD55-deficient PLE/CHAPLE disease is caused by biallelic loss-of-function mutations in the CD55 gene. Clinically, it manifests as a familial form of protein-losing enteropathy (PLE) caused by primary intestinal lymphangiectasia (PIL) or Waldmann's disease that is frequently severe and can be accompanied by lethal systemic manifestations. CD55 is a glycophosphatidylinositol (GPI)-anchored membrane protein that inhibits the enzymatic activity of C3b and C4b, thus preventing the formation of C3 and C5 convertases that lead ultimately to the assembly of the membrane-attack complex (C5b–C9). Thus, the absence of CD55 causes overactivation of the complement system, causing the production of various complement products including anaphylatoxins and the membrane-attack complex. When absent due to somatic mutation of the PIGA gene (required for the biosynthesis of GPI anchors) in hematopoietic stem cells, CD55 loss, as well as CD59 loss, is specific to hematopoietic cells (CD59 is another GPI-linked complement regulatory protein). The resultant complement-mediated lysis of red cells and platelets gives rise to intravascular hemolysis and thrombosis, in a disease termed PNH. In CD55-deficient PLE, isolated germ line loss of CD55 expression in all tissues manifests in the GI tract, as primary intestinal lymphangiectasia, which causes PLE. The majority of patients suffer from early-onset GI manifestations, including bloody diarrhea, vomiting, and abdominal pain, and occasionally develop partial or complete intestinal obstruction and intestinal failure. The loss of proteins through the GI tract leads to hypoalbuminemia and subsequent peripheral and facial edema and ascites, as well as hypogammaglobulinemia which predisposes to repeat infections. Due to loss of nutrients in the intestinal lumen, a malabsorption syndrome ensues, leading to vitamin and micronutrient deficiencies and severely impaired growth. As for PNH and other examples of complement disorders, atypical hemolytic uremic syndrome (aHUS), and transplant thrombotic microangiopathy, CD55-deficient PLE patients are susceptible to thrombosis, particularly in mesenteric and hepatic veins, and it is the thrombotic manifestation that leads to intestinal and hepatic failure, and most frequently leads to early mortality. Patients with CD55 deficiency frequently manifest with thrombocytosis.

Following its discovery in 2017, CD55-deficient PLE/CHAPLE disease has to date been described in 14 patients (Kurolap, 2017) (Ozen, 2017b). Age of onset in these 14 patients was less than 1 year in three, 1 year of age in five, 2-3 years in three, and 4 to 10 years in three. Severity ranges from subclinical PLE (described in 3 relatives of 14 published patients) to early fatality (in 3 of the 14 published patients). A hallmark of CD55-deficient PLE disease, and PLE in general, is a decrease in serum proteins: all described patients demonstrate hypoalbuminemia and hypogammaglobulinemia. While a proportion of patients with CD55-deficient PLE display features of inflammatory bowel disease (IBD) and receive IBD medications (to which they are generally refractory), a greater percentage present with symptoms attributable to hypoalbuminemia, namely, edema. A typical case is a child with infantile onset of facial and

extremity edema in relation to hypoalbuminemia, with or without diarrhea, who requires frequent hospital admissions to receive albumin infusion. Due to malabsorption, these patients commonly show growth failure, and some have delay in pubertal development. The more severely affected cases develop mesenteric venous thrombosis that is frequently associated with retrograde extension and cardiac involvement, as well as embolic complications. It appears that once the thrombotic complications develop, the patients follow a chronic course of increasing debilitation, eventually leading to premature death. Treatment has typically included corticosteroids, IVIg or SCIg, intravenous (IV) albumin, biologic immunomodulators (anti-tumor necrosis factor [TNF], vedolizumab), small molecule immunomodulators (e.g. azathioprine, mesalazine), micronutrients, enteral or parenteral feeding, anti-coagulants (low-molecular-weight heparin, aspirin), antibiotics, anticoagulants, and anti-platelet agents (Kurolap, 2017). In spite of these therapies, the long-term morbidity and risk of mortality remains high. In keeping with the role of CD55 absence in pathogenesis, eculizumab, which is a humanized monoclonal antibody directed against the terminal complement protein C5, alleviates disease, with an immediate recovery of PLE and in children, improved growth, with the cessation of other medications. Eculizumab has been made available to some patients through a compassionate use program but is not currently approved for the treatment of CD55-deficient PLE/CHAPLE disease nor, based on a search of public records, does there appear to be an ongoing development program.

Regeneron Pharmaceuticals, Inc. intends to develop pozelimab for the treatment of CD55-deficient PLE/CHAPLE. Pozelimab is a fully human, monoclonal immunoglobulin G4P (IgG4P) antibody directed against the terminal complement protein C5 that inhibits terminal complement activation by blocking cleavage of C5 into C5a (anaphylatoxin) and C5b, thereby blocking the formation of the membrane-attack complex (C5b-C9, a structure-mediating cell lysis. Pozelimab is being developed for the treatment of PNH and other diseases in which tissue damage is mediated by the terminal complement pathway activity. Pozelimab can be administered by IV or subcutaneous (SC) administration. Additionally, pozelimab binds to polymorphic variations in C5 that are not recognized by eculizumab.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

# 2. STUDY OBJECTIVES

## 2.1. Primary Objective

The primary objective of the study is to determine the effect of pozelimab on active CD55-deficient protein-losing enteropathy (PLE; CHAPLE), as measured by:

1. Normalization of serum albumin, and
2. Improvement in the following clinical outcomes that are evaluable for improvement at baseline, without worsening of the others, after 24 weeks of treatment (assessed at week 24):
    - Daily bowel movement frequency
    - The presence and severity of facial or peripheral edema
    - The patient/caregiver assessment of abdominal pain frequency

## 2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of pozelimab in patients with CD55-deficient PLE disease
- To evaluate the effect of pozelimab on CD55-deficient PLE (both patients with active disease at baseline and those with inactive disease on eculizumab, switching to pozelimab)
- To determine the effects of pozelimab on albumin and other serum proteins (total protein, immunoglobulins)
- To determine the effects of pozelimab on ascites
- To determine the effects of pozelimab on stool consistency
- To determine the effect of pozelimab on health-related quality of life
- To determine the effect of pozelimab on lab abnormalities observed in CD55-deficient PLE such as hypertriglyceridemia, thrombocytosis, and hypovitaminosis B12
- To describe the effects of pozelimab on the sparing of concomitant medications and reduction in hospitalization days
- To determine the effects of pozelimab on growth
- To characterize the concentration of pozelimab in patients with CD55-deficient PLE
- To assess the incidence of treatment-emergent ADA for pozelimab in patients with CD55-deficient PLE disease

## 2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To characterize the effect of pozelimab on the incidence of new thromboembolic events and the extension of existing thromboses
- To assess the effect of pozelimab on sexual maturation
- To assess the effect of pozelimab on complement pathway activity
- To assess the effect of pozelimab on inflammation and thrombosis markers
- To determine the effects of pozelimab on patient/caregiver assessment of change and severity of disease
- To determine the effects of pozelimab on physician assessment of change and severity of disease
- To explore the effect of pozelimab on gastrointestinal (GI) symptoms (nausea and vomiting and diarrhea) and on caregiver quality of life/burden

# 3. HYPOTHESIS AND RATIONALE

## 3.1. Hypothesis

Pozelimab treatment will result in normalization of serum albumin and improvement in clinical signs and symptoms in CD55-deficient PLE/CHAPLE disease.

## 3.2. Rationale

### 3.2.1. Rationale for Study Design

CD55-deficient PLE is a life-threatening, ultra-orphan disease of infants, children, adolescents, and young adults with no current approved therapy. There are approximately 40 patients across the world known to have this disease as of December 2018. R3918-PLE-1878 is an open-label study to evaluate the safety and efficacy of pozelimab in 4 to 20 patients with CD55-deficient PLE, as an addition to standard-of-care therapies (excluding eculizumab). The rationale for an open-label study is that the disease is too severe for patients to be allocated to a placebo group, and that there are no suitable active comparator therapies available. There are reports of cases that suggest that a similar anti-C5 monoclonal antibody drug, eculizumab, significantly improves the clinical condition of patients with CD55-deficient PLE and there is a very high likelihood, given the similar mechanism of action of eculizumab and pozelimab, that pozelimab will have a similar effect. CD55-deficient PLE is a serious condition for which patients may experience disease progression over the period of the study if they do not receive active treatment. The expected effect of treatment is expected to be large enough to distinguish the effect of treatment with pozelimab from the underlying disease progression accounting for its variability over time. The intent of this study is to generate the first efficacy and safety data from a clinical study for the anti-C5 therapeutic class in this indication, and to support licensure for the treatment of CD55-deficient PLE with pozelimab. The study population has been designed (based on an analysis of data obtained from 13 patients prior to and after eculizumab treatment) to maximize the inclusion of patients from among the known global patient population (which currently stands at 23 individuals, of which 17 are known to be on eculizumab treatment and in remission). The following types of patients may be included:

- Patients with active PLE who are naïve to eculizumab therapy. Active PLE is defined as: hypoalbuminemia of less than or equal to 3.2 g/dL within the screening period; and, within the last 6 months, at least 7 days (which do not have to be consecutive) of 1 or more of the following symptoms or signs: diarrhea, vomiting, abdominal pain, peripheral or facial edema, or an episode of infection with concomitant hypogammaglobulinemia, or a new thrombotic event.
- Patients with active PLE who were previously taking eculizumab, and stopped it because of access issues, or because their physician withdrew it in the expectation that they would remain inactive, or because they were refractory to it due to the Arg885His variant in the C5 gene (which is unable to bind to eculizumab).

- Patients on treatment with eculizumab, with inactive or controlled disease, who elect to switch from an IV to an SC anti-C5 treatment. These patients will switch from eculizumab to pozelimab without an interruption of anti-C5 treatment to limit the risk of loss of disease control. In these patients, eculizumab should be discontinued during the screening period, and pozelimab started at the time that the next scheduled eculizumab dose would have taken place. These patients will not contribute data towards the primary endpoint but will provide supportive safety and efficacy data.

The definition of inactive PLE is any case of PLE which fails to meet the definition of active disease as per definition above. This should not include patients whose future access to eculizumab would be compromised, ie, those on the Alexion compassionate use program, with no likelihood of finding alternative reimbursement for eculizumab. Regeneron will not provide for patients to be treated with eculizumab at any time during or after the study.

**Rationale for a study in pediatric patients**: CD55-deficient PLE is a life-threatening, ultra-orphan disease with no current approved therapy. Pozelimab was well-tolerated in toxicology studies in adolescent (13-week study) and adult (26-week study) cynomolgus monkeys at doses up to 100 mg/kg/week via IV administration for up to 26 weeks. The no observable adverse effect level (NOAEL) based on the results of these toxicology studies was determined to be 100 mg/kg, the highest dose tested. To date, toxicology studies in juvenile animals have not been conducted for pozelimab. Available adult safety data, known target biology, and the lack of target organs identified in nonclinical toxicology (13- and 26-week) studies are expected to support dosing in the proposed patient population. Enhanced pre- and post-natal development (ePPND) data generation will run in parallel and is expected to be supportive of marketing authorization/BLA in pediatric patients. The safety and effectiveness of Soliris® for the treatment of aHUS have been established in pediatric patients and supported by evidence from 4 adequate and well-controlled clinical studies (Soliris package insert, 2019). To mitigate the potential risk in very young patients, the first 2 patients recruited into the trial should be 6 years of age or older and safety through week 12 will be assessed before inclusion of pediatric patients 1 year and older. Exceptions to this rule will be made if patients younger than 6 years of age present with life-threatening disease prior to the availability of 12 weeks of data in 2 patients aged 6 years or older. Examples of life-threatening disease include, but are not limited to: hemodynamic compromise from severe edema or from evolving thrombosis, bowel intussusception or ileus. The decision to allow exceptions will be made in conjunction with the medical director, steering committee, and will require approval from senior Regeneron medical staff and Ethics Committee (EC)/Institutional Review Board (IRB). Depending on local policy, input from health authority may be sought before proceeding. As of 13 March 2020, 1 patient (aged greater than 6 years) has been recruited. There is a patient aged 5 years and 5 months with severe edema and serum albumin as low as 1.0 g/dL, requiring high dose intermittent steroids and intermittent albumin infusions, daily at their most frequent. Intravenous access is unreliable and when not available the edema has progressed to life-threatening hemodynamic compromise. An expedited request for EC approval to enroll this patient is currently in progress.

Evidence of pozelimab efficacy will be based on (a) an induction and maintenance of response with respect to normalization of serum albumin in active patients and (b) improvement in a clinical endpoint in active patients, as the 2 components of the primary endpoint (Section 5.1). Maintenance of response in switch patients will be measured and reported as supportive evidence. Given the ultra-rare nature of this condition and very small size of the study, the albumin endpoint has been designed to capture both induction and maintenance, and maintenance alone, so that it can be applied to every patient. Namely, that albumin measured between week 12 (allowing time for both the active patients to respond, and the switch patients to wash-out residual eculizumab) and week 24 (allowing for time to demonstrate maintenance of effect) is normalized. Sustained normalization of albumin as a primary endpoint is objective and stringent and has never been achieved through the use of existing standard of care prior to the advent of anti-C5 therapy in all known patients. Serum albumin also has clinical meaning: Facial and peripheral edema and GI symptoms are directly correlated with the albumin level, since they are caused by a decrease in the oncotic pressure that is maintained by albumin. Furthermore, IV albumin infusions are an established standard therapy in PLE and temporarily improve these clinical manifestations, in parallel with a temporary increase in the albumin level. The decision to treat with albumin is made based on monitoring of the albumin level. Taken together, these factors argue that the albumin level is clinically meaningful. The first component of the primary endpoint is: the proportion of patients with at least 70% of albumin measurements within the normal range between week 12 (allowing time for both the active patients to respond, and the switch patients to wash-out residual eculizumab) and week 24 (allowing a full 3 months to demonstrate maintenance). Albumin normal range varies little between labs and is typically 3.5 to 5.5 g/dL. The upper limit for active PLE patients was set at 3.2 g/dL based on a review of data from 7 Turkish and 3 Israeli patients (Ozen unpublished data; Baris-Feldman unpublished data). In up to 15 years of pre-eculizumab follow-up in these patients, the albumin never went above 3.2 g/dL nor showed a short-term increase of 1 g/dL (absent having received an albumin infusion). Following eculizumab treatment, all 10 patients showed a normalization of the mean albumin level using measurements taken between weeks 12 and 24, and all 10 patients showed an increase from baseline of at least 1 g/dL on at least 1 occasion between weeks 12 and 24. We will collect all available pre-study albumin (as well as other relevant laboratory and clinical) data on all patients. A patient who receives an albumin infusion between weeks 12 and 24 will be considered a non-responder: in the historical data set, no patient required any albumin infusion while on treatment with eculizumab. Patients will also be considered a non-responder if any single albumin value is <2.5 g/dL after between weeks 12 and 24 .

An improvement in clinical endpoints will be the second component of the primary endpoint. A range of clinical endpoints have been designed to capture patient benefit, due to the paucity of quantitative data regarding the clinical effect of eculizumab, and due to variability of clinical manifestations: there is no single clinical manifestation that occurs in every patient. Some of the clinical endpoints are included within the primary endpoint; others are included as secondary. Four clinical endpoints were selected for inclusion in the primary endpoint on the basis of: a relatively higher prevalence in the patient population, a relatively stronger face validity for meaningfulness, and a relatively greater degree of objective quantification. Frequent bowel movements emerged as commonly experienced by patients with the disease. In an analysis of data from 13 patients prior to and following eculizumab treatment, 8/13 patients had average daily bowel movements (measured over a week) of 3 or more. Of these 8 patients, 7 showed a reduction of at least 50%.

Only 4/13 patients had bowel movements of more than 4 times a day, and all 4 patients showed an improvement of at least 50%. Based on published literature and discussions with physicians with experience treating patients with CD55-deficient PLE, abdominal pain was also identified as a prevalent aspect of disease. Frequency of abdominal pain is quantifiable using an existing patient reported outcome measure, the PedsQL GI Symptoms Scales' Stomach Pain and Hurt Subscale (Varni, 2012). The definition of a responder, ie, a 25-point change on the transformed score, reflects a 1-category change on the raw score scale. The scores at which patients will be considered evaluable for improvement is 70 or less because the average score on the subscale tended to be less than 70 for patients with GI diseases (range: 63.8 to 71.9) (Varni, 2015b) (Varni, 2015c) (Varni, 2016). Facial and peripheral edema was also a prevalent aspect of disease but due to a lack of suitable existing measurement tools (with nothing available for children and for facial edema), we have developed Likert scales for the physician to grade the severity of edema. For the peripheral edema scale we have adopted response options from an existing developed clinician-reported outcome assessment (Brodovicz, 2009).

To mitigate the risk that our pre-defined responder thresholds do not perform adequately, we will use anchor-based methods using the patient/caregiver globals as anchors to assess the responder definition for the individual endpoints. Concept elicitation interviews conducted during the screening period will also be used to elicit each patient's most bothersome sign/symptom from amongst those included in the core sign/symptom concepts of disease. Exit interviews will also be conducted on the date the primary endpoints will be assessed. The qualitative data from the exit interviews will also be used to interpret trial results and to further understand whether the observed changes were meaningful from the perspective of the patient/caregiver.

### 3.2.2. Rationale for Dose Selection

Following an IV loading dose of 30 mg/kg, pozelimab will be administered SC weekly at doses depending on body weight (BW) as follows:

- For BW < 10 kg: 125 mg
- For BW ≥10 kg and <20 kg: 200 mg
- For BW ≥20 kg and <40 kg: 350 mg
- For BW ≥40 kg and <60 kg: 500 mg
- For BW ≥60 kg: 800 mg

These doses were selected to achieve, in modeling, similar peak and trough pozelimab concentrations in serum as those shown to completely inhibit C5 activity (as assessed by suppression of ex vivo hemolysis through the CH50 assay) in healthy adult subjects. These are the doses chosen for the study of adult PNH patients (30 mg/kg IV loading dose followed by a weekly dose of 800 mg SC) in study R3918-PNH-1852. The predicted peak concentrations of 600 to 700 mg/L have been observed in study R3918-HV-1659 in healthy volunteers and have been shown to be well tolerated; the predicted trough concentration of 400 mg/L is above the concentration considered minimally necessary to achieve maximal suppression of C5 activity for all patients, and allows for the variability and uncertainty in pharmacokinetics/ pharmacodynamics (PK/PD). There is a theoretical consideration that increased enteric protein loss very early in treatment might require an upwards correction of the loading dose. However, the published data

on eculizumab-treated patients report that free C5 concentrations fall to the lower limit of quantification within 3 days of first infusion, along with clinical improvement in all 3 patients within the first 12 hours of treatment, using a standard IV dose of eculizumab (ie, the maintenance dose tiered by body weight according to the label for pediatric patients with atypical hemolytic uremic syndrome, in which there is no enteric protein loss) (Kurolap, 2017) (Soliris package insert, 2019). These data suggest that increased enteric protein loss early in treatment is unlikely to result in a pharmacologically meaningful reduction in therapeutic monoclonal antibody concentration.

Pozelimab has been evaluated in a randomized, placebo-controlled double-blind study (R3918-HV-1659) in 56 healthy subjects in 7 dose cohorts (N=8, randomized 6:2 pozelimab:placebo for each cohort). Pozelimab was found to be generally well tolerated in ascending single doses of 1, 3, 10, and 30 mg/kg IV and 300 and 600 mg SC. The seventh cohort, a multiple-dose cohort of 4 weekly SC doses of 400 mg following a 15 mg/kg IV loading dose, resulted in one resolved serious adverse event (SAE) in the study, an episode of salpingitis of undetermined etiology. The range of concentrations of pozelimab observed in study R3918-HV-1659 encompasses the predicted concentrations expected in pediatric patients at the proposed dosing regimen. In all 4 IV dosing cohorts, suppression of hemolysis was observed as early as 15 minutes post-injection. Transient, complete suppression of hemolysis was achieved with ≥ 3 mg/kg dosing. At 30 mg/kg, complete suppression of hemolysis was maintained for 4 weeks, consistent with observed, prolonged pozelimab exposure following this dose. In the multiple-dose cohort 5, complete suppression of CH50 was observed over the 4-week dosing period and up to 2 weeks after the last SC dosing.

Pozelimab was well-tolerated in toxicology studies in adolescent (13-week study) and adult (26-week study) cynomolgus monkeys at doses up to 100 mg/kg/week via IV administration for up to 26 weeks. The NOAEL based on the results of these toxicology studies was determined to be 100 mg/kg, the highest dose tested. To date, toxicology studies in juvenile animals have not been conducted for pozelimab. Juvenile toxicology data are not expected to be required to initiate trials in a limited number of pediatric (<12 years of age) patients with life-threatening, ultra-orphan condition and no approved therapy. Available adult safety data, known target biology, and the lack of target organs identified in nonclinical toxicology (13- and 26-week) studies are expected to support dosing in the proposed patient population. Enhanced pre- and post-natal development (ePPND) data generation will run in parallel and is expected to be supportive of marketing authorization/BLA in pediatric patients.

Additional background information can be found in the Investigator's Brochure.

### 3.2.3. Risk-Benefit Assessment

CD55-deficient PLE is a life-threatening, ultra-orphan disease with no current approved therapy. Current treatments typically include: corticosteroids, IVIg or SCIg, IV albumin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (e.g. azathioprine, mesalazine), micronutrients, enteral or parenteral feeding, anti-coagulants (low-molecular-weight heparin, aspirin), antibiotics, and anti-coagulants (Kurolap, 2017). In spite of these therapies, the long-term morbidity and risk of mortality remains.

The benefit of blocking C5 complement activity in PLE is supported from reports of eculizumab, which alleviates disease, with an immediate recovery of signs and symptoms of PLE and in children, improved growth, along with the cessation of other medications (Kurolap, 2017). Pozelimab offers potential additional benefits of better control by providing maximal and durable inhibition of C5 throughout the dosing interval, improving the dosing regimen, binding to the polymorphic variant C5 protein which renders eculizumab ineffective, and development of a SC formulation.

An established risk of blocking C5 complement activity is an increased susceptibility to infections, specifically to encapsulated organisms, the most potentially severe of which is infection with *Neisseria meningitidis* (Figueroa, 1991). Experience with eculizumab suggests that pretreatment with appropriate vaccinations covering multiple serotypes and concurrent therapy with oral antibiotics are effective at mitigating this risk (Hill, 2013)(Soliris package insert, 2019). Current treatment guidelines for PNH and the eculizumab package insert recommend such vaccination prior to dosing. In various disease settings such as asplenia in sickle cell disease, and with terminal complement deficiency, use of long-term prophylactic antibiotics has been safely implemented for the prevention of encapsulated organisms including N. meningitidis (Gaston, 1986) (Wedzicha, 2008). Because vaccination does not provide 100% coverage to all strains and there are no proven titer levels associated with 100% protection, prophylactic oral antibiotics are also commonly given to patients with genetic or pharmacologic deficiency in terminal complement activity. Therefore, vaccination prior to administration (or at the time of administration, based on local practice, per Section 8.3.1) will sufficiently mitigate the risks of single and multiple doses of pozelimab in patients to a level that has been considered acceptable in other anti-C5 clinical development programs. In addition, concurrent therapy with oral antibiotics should be considered according to local practice (Section 8.3.2).

Recently, serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported during eculizumab treatment (Soliris package insert, 2019). Counseling about *Neisseria gonorrhea* prevention, testing, and treatment is to be performed in accordance with local practice/national guidelines (see Section 8.4).

There is a potential risk of immune complex formation when switching from eculizumab to pozelimab. SKY59, a humanized antibody against C5, is being administered in a clinical trial to 7 patients with PNH who had been on eculizumab for at least 3 months (Röth, 2018). SKY59 is administered as IV loading dose 2 weeks after the last dose of eculizumab, and then 1 week later patients receive SC administration either weekly, every 2 weeks, or every 4 weeks. In 2 out of 7 patients, mild to moderate, non-serious, likely drug-target-drug complex-mediated reactions with clinical manifestations similar to serum sickness were observed in the initial post-switch

period (days 9 and 10, respectively). These manifestations were treated with topical steroids and resolved by day 21 with no interruption in study treatment. The authors noted that in patients switching from eculizumab to SKY59, the formation of drug-target-drug complex composed of SKY59, C5, and eculizumab is expected due to the different binding epitopes of the 2 antibodies.

Therefore, during the transition of therapy in patients currently being treated with eculizumab and who switch to pozelimab treatment, immune complex formation comprising eculizumab, C5, and pozelimab may occur. Although the consequences of this hypothetical complex formation are unknown, a potential risk includes immune adverse events (AEs). To mitigate this risk, the investigator will maintain heightened awareness, and appropriate safety monitoring during this early phase will be included. Also, the loading dose of pozelimab has been designed to generate an excess of pozelimab over eculizumab, a measure intended to avoid the equimolar stoichiometric conditions (Regeneron data; report in preparation) that may give rise to higher-order immune complexes. Guidance on the management of a suspected immune AE due to drug-target-drug immune complex formations of eculizumab-C5-pozelimab is provided in Section 8.5.

A risk-benefit statement for pozelimab is provided in the Investigator's Brochure.

#### 3.2.3.1. Study Conduct in Response to COVID-19

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any subjects in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and subjects can safely participate in this study. Until then, the sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

# 4. STUDY VARIABLES

## 4.1. Demographic and Baseline Characteristics

Baseline characteristics (as allowed to be collected per local regulations) will include standard demographic information (eg, age, race, weight, height, etc.), disease characteristics, medical history, and medication history for each patient.

## 4.2. Outcome Variables

The outcome variables include albumin and albumin infusion, protein, immunoglobulins, micronutrients, laboratory markers, α-1 trypsin, AEs, vital signs, frequency of bowel movements and diarrhea, gastrointestinal symptoms, health-related quality of life, clinician assessment of disease activity (current and change), assessment of edema and ascites, use of concomitant medications to treat PLE, outcome assessments, hospitalization days, and height and weight. A list and details of outcome variables can be found in Sections 9.2.2 (Efficacy Procedures) and 9.2.4 (Safety Procedures).

## 4.3. Pharmacokinetic Variables

The PK variable is the concentration of total pozelimab at time points shown in Table 1.

## 4.4. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, status of neutralizing antibodies (NAbs), and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1. Samples positive in the ADA assay will be further characterized for NAbs.

## 4.5. Exploratory Biomarker Variables

Exploratory variables may include but are not limited to:

- Markers of thrombosis: D-dimer, and N terminal prothrombin fragments [F1+2]
- Levels of total C5 protein
- Markers of complement pathway activation: soluble C5b-9
- A sample for additional exploratory biomarkers (PD, predictive, and prognostic) potentially related to pozelimab treatment exposure, clinical activity, or underlying disease may be collected and archived.

# 5. PRIMARY AND SECONDARY OUTCOMES

## 5.1. Primary Outcome

The primary endpoint at week 24 is the proportion of patients with active disease at baseline achieving both of the following:

- Normalization of serum albumin, defined as
  - serum albumin within the normal range at at least 70% of measurements between week 12 and week 24, and
  - no single albumin measurement of <2.5 g/dL between week 12 and week 24, and
  - no requirement for albumin infusion between week 12 and week 24
- Improvement in the following clinical outcomes that were evaluable for improvement at baseline, with no worsening of the others (ie, those not evaluable for improvement) at week 24:
  - The number of bowel movements per day, based on a 1-week average, captured by e-diary. Improvement is defined as a reduction of 50% or more in the number of daily bowel movements based on a 1-week average. Patients evaluable for improvement are defined as those with an average of 3 or more bowel movements per day at baseline. Worsening is defined as an increase of 30% or more.
  - Physician assessment of facial edema (based on a 5-point Likert scale). Improvement is defined as a reduction of 2 points or more. Patients evaluable for improvement are defined as those with a severity of at least 3 points out of 5 at baseline. Worsening is defined as an increase of 2 points or more.
  - Physician assessment of peripheral edema (based on a 5-point Likert scale). Improvement is defined as a reduction of 2 points or more. Patients evaluable for improvement are defined as those with a severity of at least 3 points out of 5 at baseline. Worsening is defined as an increase of 2 points or more.
  - Patient/caregiver assessment of abdominal pain frequency as assessed by the Stomach pain and hurt sub-scale of the PedsQL™ GI Symptom Scale. Improvement is defined as an increase of 25 points or more (on the 0 to 100 transformed total subscale score where lower scores indicate worse GI stomach pain and hurt). Patients evaluable for improvement are defined as those with a score of 70 points or less at baseline. Worsening is defined as a decrease of 25 points or more.

## 5.2. Secondary Outcomes

The secondary endpoints are:

- Incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables from baseline to week 144
- Improvement in each patient's most bothersome sign/symptom at week 24, as determined prior to baseline using a semi-structured concept elicitation interview, from amongst the 'core' clinical endpoints of frequency of bowel movements, peripheral edema, facial edema, abdominal pain frequency (as described in Section 5.1), nausea, vomiting, and stool consistency:
  - Improvement in nausea and vomiting will be defined as an increase of 25 points or more on the 0 to 100 transformed nausea and vomiting subscale of the PedsQL GI Symptom Scale score where lower scores indicate worse nausea and vomiting. Patients will be evaluable for improvement in nausea and vomiting if they have a score ≤75 on the nausea and vomiting subscale at baseline
  - Improvement in stool consistency will be defined as a reduction of ≥50% in the number of days per week that the patient has a bowel movement of loose/watery consistency. A bowel movement is considered to be loose/watery if it corresponds to 3 images of loose or watery stools on the Brussels Infant and Toddler Stool Scale (BITSS), the images and descriptors for categories 4 or 5 on the modified Bristol Stool Form Scale for Children (mBSFS-C), and the images and descriptors for categories 6 or 7 of the Bristol Stool Form Scale (BSFS). To be evaluable for improvement in stool consistency, patients must have a bowel movement of loose/watery stool consistency for ≥2 days/week at baseline
- The proportion of patients with active disease at baseline who maintain disease control in these time periods (in weeks) 12-48, 12-144, 24-48, 48-96, 96-144 as defined by:
  - Normalization of serum albumin, defined as serum albumin within the normal range at at least 70% of measurements and no single albumin measurement of <2.5 g/dL and no requirement for albumin infusion
  - No worsening (definitions in parentheses) from the beginning of the stated time period, at any single visit during the stated time period, of: facial or peripheral edema (≥2-point increase); or stomach pain and hurt sub-scale (≥25-point decrease); or diarrhea subscale of the PedsQL GI Symptom Scale (≥25-point decrease)
  - No increase in dose of permitted concomitant medication for the treatment of PLE at any time, no re-introduction of any permitted concomitant medication once withdrawn, where permitted concomitant medication is as follows: corticosteroids, IV or SC immunoglobulin, IV albumin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (eg, azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation

- The proportion of patients with inactive disease on eculizumab at baseline who maintain disease control in these time periods (in weeks) 12-48, 12-144, 24-48, 48-96, 96-144 as defined by:
  - Normalization of serum albumin, defined as serum albumin within the normal range at at least 70% of measurements and no single albumin measurement of <2.5 g/dL and no requirement for albumin infusion
  - No worsening (definitions in parentheses), from the beginning of the stated time period, at any single visit during the stated time period, of: facial or peripheral edema (≥2-point increase); or stomach pain and hurt sub-scale (≥25-point decrease); or diarrhea subscale of the PedsQL GI Symptom Scale (≥25-point decrease)
  - No increase in dose of permitted concomitant medication for the treatment of PLE at any time, no re-introduction of any permitted concomitant medication once withdrawn, where permitted concomitant medication is as follows: corticosteroids, IV or SC immunoglobulin, IV albumin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (eg, azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation
- The number of bowel movements per day, based on a 1-week average, captured by e-diary from baseline to week 24
- The number of days/week with ≥1 bowel movement of loose/watery stool consistency, as measured by BSFS for patients who are 18 years of age and older, mBSFS-C for patients who are toilet-trained and less than 18 years of age, or the BITSS who are not toilet-trained, and captured by e-diary from baseline to week 24
- Physician assessment of facial edema (based on a 5-point Likert scale) from baseline to week 144
- Physician assessment of peripheral edema (based on a 5-point Likert scale) from baseline to week 144
- Change in abdominal symptoms, as assessed by the PedsQL™ GI Symptom Scale stomach pain and hurt sub-scale and food and drink limits sub-scale from baseline to week 144
- Health-related quality of life as assessed by the PedsQL™ Generic Core Scales from baseline to week 144; additionally, the following sub-scales will be reported separately:
  - About my work/studies and school functioning sub-scale
  - Physical functioning sub-scale
- Assessment of abdominal ascites (assessed by measurement of abdominal circumference) from baseline to week 24

- Frequency of albumin infusions up to week 144, expressed as number per half-year. Albumin infusions are permitted during the treatment phase in the event that the albumin level is below 3.0 g/dL at 2 consecutive visits with accompanying symptoms of facial or peripheral edema or ascites. Any albumin infusions between week 12 and week 24 will render the patient a non-responder for the primary endpoint.
- Total albumin, protein, total Ig, IgG, IgM, IgA, expressed as:
  - Absolute value at every scheduled time point including week 24
  - Absolute and percent change from baseline over time
  - Time to first normalization
- Vitamin B12, folate, iron, iron binding capacity, ferritin, magnesium, fasting cholesterol/triglycerides, expressed as:
  - Absolute value at every scheduled time point including week 24
  - Change from baseline over time
  - Time to first normalization
- Alpha-1 antitrypsin levels in blood and stool, and change from baseline to week 12 and week 24
- Use and dose/frequency from baseline to week 144 of: corticosteroids, IV or SC immunoglobulin, IV albumin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (eg, azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation, anti-coagulants (eg, low-molecular-weight heparin), antibiotics (with the exception of those used for the purpose of Neisserial prophylaxis), anti-platelet agents (eg, low-dose aspirin)
- Hospitalization days (percentage of days hospitalized) over time
- Body weight and height (expressed as z scores) over time
- Concentrations of total pozelimab in serum assessed throughout the study
- Incidence of treatment-emergent anti-drug antibodies (ADA) to pozelimab in patients over time
- Change and percent change from baseline of total complement activity CH50 over time

## 5.3. Exploratory Outcomes

- Total C5 concentrations in plasma over time
- Markers of thrombosis: D-dimer, and N terminal prothrombin fragments (F1+2)
- Complement assays : sC5b-9
- Change in GI symptoms (Diarrhea sub-scale and Nausea and vomiting sub-scale) as measured by the Pediatric Quality of Life Inventory (PedsQL™) GI Symptoms Scales from baseline over time
- Change in caregiver well-being and burden as measured by the PedsQL™ Family Impact Module from baseline over time
- Clinician global impression of change (CGIC) from baseline to week 144
- Clinician global impression of severity (CGIS) from baseline to week 144
- Patient/caregiver global impression of change (PGIC/CareGIC) from baseline to week 144
- Patient/caregiver global impression of severity (PGIS/CareGIS) from baseline to week 144
- If appropriate to age and stage of sexual maturation, the Tanner pubertal stage
- Whole exome sequencing (if not already done)

# 6. STUDY DESIGN

## 6.1. Study Description and Duration

R3918-PLE-1878 is an open-label, single-arm, 144-week treatment study in patients aged 1 year and older with active clinical signs and symptoms of CD55-deficient PLE/CHAPLE disease, and a CD55 loss-of-function mutation detected by genotype analysis (frameshift, nonsense mutations). In the case of missense or suspected splice site mutations, CD55-deficient PLE is to be confirmed by flow cytometry of peripheral blood cells. The first 2 patients enrolled will be of age 6 or older (exception will be made for patients under 6 years of age with life-threatening disease, see Section 3.2.1).

A minimum of 6 patients with active PLE will be enrolled, up to approximately 20 patients. The primary analysis will occur when approximately 6 patients with active PLE have received 24 weeks of treatment. Subsequent analyses will occur 1 and 2 years after the first dose in the last patient enrolled.

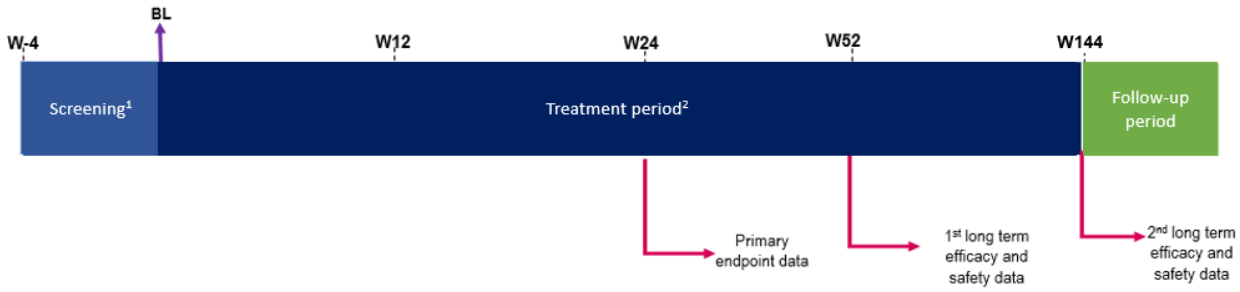
Patients will be given a single loading dose of pozelimab 30 mg/kg IV on day 1, then fixed doses SC (based on body weight) QW (±2 days) over the treatment period (Section 3.2.2).

The study consists of a screening period (up to 4 weeks [or up to 10 weeks for patients with extenuating circumstances, Section 9.2.1]) followed by a 144-week treatment period (from week 0 to week 144, with last dose at week 143), and a follow-up period (from week 145 to week 164; Figure 1).

Active PLE is defined as hypoalbuminemia of less than or equal to 3.2 g/dL within the screening period, and within the last 6 months, at least 7 days (which do not have to be consecutive) of one or more of the following symptoms or signs: diarrhea, vomiting, abdominal pain, peripheral or facial edema, or an episode of infection with concomitant hypogammaglobulinemia, or a new thrombotic event. Active patients should not be on current therapy with eculizumab.

As part of risk mitigation for this study, patients should receive updated meningococcal, Haemophilus influenzae type B, and pneumococcal vaccinations (Section 8.3.1) and are recommended to receive daily oral antibiotic prophylaxis (Section 8.3.2) as well as counselling regarding risk of *Neisseria gonorrhea* (Section 8.4), as applicable. Subsequent to the first 2 patients, in addition to the active patient population heretofore described, patients who are well-controlled on eculizumab may consider switching to pozelimab to avoid IV infusion. Patients switching to pozelimab from eculizumab will be switched with no wash-out, due to the risk of thrombosis with a return to active disease. In this case, eculizumab should be discontinued at the baseline visit, which should be scheduled within the window for the next eculizumab dose. Pozelimab should be started at the time that the next scheduled eculizumab dose would have taken place (the dosing interval for eculizumab is typically 2 weeks). The first pozelimab dose will be administered instead of eculizumab. Due to a theoretical risk of formation of higher order complexes of pozelimab/C5/eculizumab in these patients in the initial weeks of active treatment, the protocol contains guidance for investigators to create awareness of the symptoms and signs of type III hypersensitivity reactions and provides for clinical management of such reactions (Section 8.5).

**Figure 1: Study Flow Diagram**




1. Screening period may be extended to approximately 10 weeks for patients with extenuating circumstances, as described in Section 9.2.1.
2. Patients will receive an IV loading dose of pozelimab on week 0/day 1 and then receive SC pozelimab weekly until week 143 for a total treatment duration of 144 weeks.

After the first administration of pozelimab at the study site, subsequent administrations may either be continued at the clinical site, or by the site personnel or another healthcare professional at patient's home (if possible) or local clinic, or self-administered/administered by the patient or designated person, respectively.

### 6.1.1. Study Stopping Rules

#### 6.1.1.1. Individual Patient Stopping Rules

If a patient experiences 1 SAE, or 2 AEs of severe intensity (in either case possibly or definitely attributable to pozelimab) (Section 10.2.5), or 1 of the reasons for discontinuation outlined in Section 8.6.2, a meeting of the Steering Committee (Section 6.3.1) will take place to review the event and make recommendations as to whether the patient may continue treatment.

#### 6.1.1.2. Study Stopping Criteria

Decisions to discontinue or suspend the study will be made by the Steering Committee (Section 6.3.1).

Enrollment of new patients will be paused should the following occur:

- Two or more patients experience 1 or more SAEs judged to be possibly or definitely attributable to pozelimab

Following the review of all available safety data by the Steering Committee, a consensus opinion that the totality of the data suggests that this event is unlikely to be related to pozelimab will lead to resumption of study enrollment. Conversely, an unfavorable benefit-risk assessment will lead to a recommendation to terminate the study. Any recommendation to terminate the study made by the Steering Committee must be approved by the Regeneron Safety Oversight Committee (RSOC), which includes senior clinical, regulatory, and pharmacovigilance leaders at Regeneron.

### 6.1.2. End of Study Definition

The end of study is defined as the last visit of the last patient.

## 6.2. Planned Interim Analysis

There will not be a formal interim analysis of efficacy data for an early stopping of the study.

## 6.3. Study Committees

### 6.3.1. Steering Committee

There will be a Steering Committee comprised of key investigators and individuals representing the sponsor (including representatives from clinical, safety, and statistics) who will meet regularly to review available data throughout the study, and ad hoc triggered by individual or study stopping rules. Impartial input will be provided by committee members who are not directly involved in the conduct of the study, including at least 1 physician experienced in treating patients with PLE and at least 1 member experienced in pediatric rare diseases and/or pediatric ethics. If 1 individual is identified with both these areas of expertise, there will be only 1 additional member. The Steering Committee may recommend to continue, discontinue, suspend, or alter the study on the basis of accumulating efficacy and safety information.

The composition and meeting schedule for this committee will be described further in a charter.

# 7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

## 7.1. Number of Patients Planned

A minimum of 6 patients with active PLE will be enrolled, up to approximately 20 patients. Eligible patients with inactive disease may also be enrolled, but their data will not contribute to the primary analysis.

Selected sites are those in Turkey, Israel, and the USA that have diagnosed and provided care for these patients. Other countries (including those in the EU) may be added depending on patient availability, without amending this protocol. Patients may attend some visits at a site in a country other than their country of residence on a case-by-case basis.

## 7.2. Study Population

Patients aged 1 year and older with a clinical diagnosis of CD55-deficient PLE disease, with CD55 loss-of-function mutation determined by genetic analysis (frameshift, nonsense mutations) and confirmed (only necessary in the case of missense or suspected splice site mutations) by flow cytometry or western blotting CD55 on peripheral blood cells. The first 2 patients must be aged 6 years or older, except in a case whereby severity of disease is life-threatening (Section 3.2.1).

### 7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female aged 1 year and older. The first 2 patients recruited must be aged 6 years or older (exception will be made for patients under 6 years of age with life-threatening disease, see Section 3.2.1).
2. Clinical diagnosis of CD55-deficient PLE/CHAPLE disease (based on a history of PLE), confirmed by biallelic CD55 loss-of-function mutation detected by genotype analysis (frameshift, nonsense mutations). In the case of missense or suspected splice site mutations, CD55-deficient PLE is to have been confirmed by flow cytometry of peripheral blood cells or western blot. These diagnostic tests can be performed as part of the study screening procedures, or as part of standard clinical evaluation prior to screening.
3. Patient either has:
    a. Active disease, defined as:
        i Hypoalbuminemia of less than or equal to 3.2 g/dL within the screening period, and
        ii Within the last 6 months and attributable to CD55-deficient PLE, at least 7 days (which do not have to be consecutive) of at least one of the following symptoms or signs: diarrhea, vomiting, abdominal pain, peripheral or facial edema, or an episode of infection with concomitant hypogammaglobulinemia, or a new thromboembolic event

    NOTE: The first 2 patients enrolled in the study must fall into inclusion criterion 3a.

b. Inactive disease on eculizumab therapy (and whose treating physician has the expectation of future access to renewed eculizumab treatment should this be required), and is willing to discontinue eculizumab during screening and start pozelimab at baseline with no eculizumab wash-out.

4. Willing and able to comply with clinic visits and study-related procedures.
5. Written informed consent from parent/guardian for minor patients.
6. Written assent from minor patients as appropriate (eg, above the age of 6 years or the applicable age per local regulatory requirements).
7. Patient either alone or with the help of their parents/legal guardians, as required, must be able to understand and complete study-related questionnaires.

### 7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. History of meningococcal infection.
2. No documented meningococcal vaccination within 3 years prior to screening and patient unwilling to undergo vaccination during the study (if fully available according to local practice). Refer to Section 8.3.1 for further details.
3. No documented vaccination for *Haemophilus influenzae* and *Streptococcus pneumoniae* if applicable based on local practice or guidelines prior to screening and patient unwilling to undergo vaccination during the study if required per local practice or guidelines. Refer to Section 8.3.1 for further details.
4. Presence of a concomitant disease that leads to hypoproteinemia at the time of starting pozelimab, including a urinary protein loss or a hepatic disease that affects production of proteins by liver.
5. A concomitant disease that leads to secondary intestinal lymphangiectasia such as a fontan procedure for congenital heart disease.
6. Recent infection requiring systemic treatment with antibiotics, antivirals, or antifungals (within 2 weeks of screening or during the screening period). If the patient is appropriately treated, the patient may be rescreened.
7. PLE previously refractory to eculizumab, with the exception of patients with the Arg885His variant in the C5 gene.
8. Known hereditary complement deficiency other than CD55 deficiency.
9. Documented history of active, ongoing systemic autoimmune diseases.
10. Known or suspected infectious colitis at screening. Once this has resolved, patient may be rescreened.
11. Patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 $m^2$ (according to Chronic Kidney Disease - Epidemiology Collaboration equation 2009 [adults] or creatinine-based Schwartz equation [pediatric patients]).

12. Recent, unstable medical conditions, excluding PLE and related complications, within the past 3 months prior to screening visit. Option to rescreen after 3 months has elapsed.
13. Known sensitivity to any of the components of the pozelimab formulation or drug product.
14. Any clinically significant abnormality identified at the time of screening that, in the judgment of the investigator or any sub-investigator, would preclude safe completion of the study or constrain endpoints assessment, such as major systemic diseases, including a medical history of hepatitis B or C. Patients known to have had hepatitis B or C in the past can enroll only if these diseases are no longer active, as demonstrated by negative hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), hepatitis B virus DNA, and negative hepatitis C virus RNA (HCV RNA), respectively.

    Note: Testing for hepatitis B and C is not mandatory for enrollment in the trial but may be performed at the discretion of the investigator.
15. Participation in another interventional clinical study or use of any experimental therapy within 30 days before screening visit or within 5 half-lives of that investigational product, whichever is greater, with the exception of complement inhibitors (see Section 7.2.1)
16. Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, eg:
    - Deemed unable to meet specific protocol requirements, such as scheduled visits and/or
    - Deemed unable to tolerate long-term injections as per the patient, the investigator, sub-investigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the study, etc. and/or
    - Presence of any other conditions (eg, geographic, social, etc.), actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
17. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
18. Women who are pregnant, breastfeeding, or who have a positive pregnancy test at screening visit or day 1
19. Pregnant or breastfeeding women
20. Women of childbearing potential* and girls beyond menarche (and not sexually abstinent) who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 21 weeks after the last dose. Highly effective contraceptive measures include:
    a. Stable use of combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. Intrauterine device (IUD); intrauterine hormone-releasing system (IUS)

c. Bilateral tubal ligation

d. Vasectomized partner

e. And/or sexual abstinence†, ‡.

* Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

21. *Intentionally left blank*

22. Documented history of unresolved tuberculosis (TB), or evidence of active or latent tuberculosis infection (LTBI) during screening period. Assessment for active TB and LTBI should accord with local practice or guidelines, including those pertaining to risk assessment, and the use of tuberculin skin test or T-cell interferon-gamma release assay.

## 7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.6.2.

## 7.4. Replacement of Patients

Patients prematurely discontinued from study will not be replaced.

# 8. STUDY TREATMENTS

## 8.1. Investigational Treatment

Pozelimab drug product will be provided in a sterile, single-use glass vial for either IV or SC administration and will be supplied by the sponsor.

Pozelimab drug product will be initially provided in lyophilized form in a sterile, single use glass vial for IV or SC administration that requires reconstitution with sterile water for injection, and then transitioned to a sterile, single-use glass vial or pre-filled syringe containing a liquid 200 mg/mL pozelimab formulation for IV or SC administration that will not require reconstitution. The compositions of the lyophilized and liquid formulations differ, mainly as a result of the inclusion of a viscosity reducer in the high concentration liquid formulation.

Study drug will be supplied by the sponsor. The admixture solutions needed for delivery of the lyophilized or liquid drug product for IV administration will be sourced locally, or may be supplied by the sponsor, as necessary. Detailed information about the drug product and dose preparation is provided in the pharmacy manual. Detailed information about the drug product and dose preparation is provided in the pharmacy manual.

## 8.2. Drug Administration

Patients will be given a single loading dose of pozelimab 30 mg/kg IV on day 1, then SC dosing QW (±2 days) over the treatment period based on body weight. The last dose of study drug is administered at week 143.

Dose regimen:

- For BW < 10 kg: 125 mg.
- For BW ≥10 kg and < 20 kg: 200 mg.
- For BW ≥20 kg and < 40 kg: 350 mg.
- For BW ≥40 kg and < 60 kg: 500 mg.
- For BW ≥60 kg: 800 mg.

The location and administration options for SC route of administration will depend on the preference of the investigator and patient (eg, abdomen, thigh, or upper arm), the availability of clinical supply, and home healthcare visiting professional. Clinic visits for SC administration may or may not be needed.

If self-administration/administration by patient/designated person is allowed locally, then sufficient injection training at the scheduled injection with pozelimab will be provided. After training, observation of self-administration/administration by patient/designated person will be conducted by clinical site personnel or visiting healthcare professional. Once this observation is considered satisfactory, then the study drug can be subsequently administered independently by patient/designated person for the remainder of the study.

In addition, a patient diary will be provided prior to initiation of self-administration (ie, day 29). The diary should be completed upon each study drug administration. A study drug kit will be dispensed at the clinical site visit, using a direct-to-patient (DTP) service provider, or transported by a healthcare professional, as applicable.

Detailed information about the study drug administration is provided in the pharmacy manual.

## 8.3. Pretreatments

Enrolled patients will require evidence of meningococcal immunization or administration of vaccination during the screening period, and oral antibiotics are recommended during the treatment period, according to local or national practice and investigator's assessment.

### 8.3.1. Vaccinations

Enrolled patients will require immunization with meningococcal vaccinations. Administration of vaccination should occur preferably at least 2 weeks prior to initiation of pozelimab, or at another time point according to local practice or national guidelines. It is suggested that patients undergo vaccination for serotypes A, C, Y, W, and, if available, serotype B. Patients who have had previous, documented vaccination for meningococcus will be re-immunized based on local practice. Patients should be closely monitored for early signs and symptoms of meningococcal infection and evaluated immediately if an infection is suspected. Patients will be provided with a patient safety card describing signs and symptoms of meningococcal infection, along with instructions in case of a potential meningococcal infection, as well as information for the non-investigator healthcare provider.

In addition, patients are also required to have evidence of Haemophilus influenzae and pneumococcal immunizations, unless the patient has a medical contraindication. If adequate documentation of prior administration is not available *or* if the patient is not up-to-date with the recommended administration, the vaccines will be administered prior to the initiation of treatment with the study drug, according to local practice, guidelines, and availability.

The vaccinations will be sourced locally by the investigator or designee and reimbursed by the sponsor.

### 8.3.2. Oral Antibiotics

Daily, oral antibiotic prophylaxis may commence on the day of first dosing, unless the risks outweigh the benefits, or it is inconsistent with local practice, and continue for the duration of the study. It is recommended that patients who prematurely discontinue pozelimab receive at least 21 weeks of oral antibiotic prophylaxis after discontinuing pozelimab, or a duration consistent with local guidelines, whichever is longer (Section 9.1.2). For adults, it is suggested that antibiotic prophylaxis be penicillin V 500 mg twice a day (BID), and in the case of penicillin allergy, erythromycin 500 mg BID may be used at the discretion of the investigator. For pediatric patients, it is suggested that antibiotic prophylaxis be penicillin VK 125 mg orally BID in patients who are < 5 years of age, and 250 mg BID if ≥ 5 years of age. If pediatric patients are penicillin-allergic, then erythromycin 125 mg orally BID in patients who are < 3 years of age and 250 mg orally BID in patients who are ≥ 3 years of age. Ultimately, the decision to administer prophylaxis with oral antibiotics, the duration of prophylaxis, the choice and dosage regimen of oral antibiotics will be

at the discretion of the investigator. The oral antibiotics will be sourced locally by the investigator or designee and reimbursed by the sponsor.

## 8.4. Risk Management of *Neisseria Gonorrhea*

Patients should be counseled about *Neisseria gonorrhea* prevention and regular testing should be advised for at-risk patients, as applicable.

A risk factor assessment should be based on local practice or national guidelines. The investigator should make his/her own assessment of risk (and if needed, consultation with other healthcare provider) to determine if the patient is at risk, which would lead to further management on prevention, testing, and treatment of *Neisseria gonorrhea*.

Testing and treatment should be in accordance with local practice/national guidelines.

General preventive measures include abstinence and use of a condom. Additional preventive measures should be considered based on local practice or national guidelines.

## 8.5. Risk Management of Immune Complex Formation

During the transition of therapy from eculizumab to pozelimab, investigators should have heightened awareness for possible immune AEs as a result of the risk of drug-target-drug immune complex formations of eculizumab-C5-pozelimab. Patients may present with a variety of signs and symptoms such as fever, malaise, rash, and polyarthralgia. Less common manifestations include edema, neuropathy, GI complaints, nephropathy (including systemic hypertension), and vasculitis. If a rash does develop, the site may consider taking pictures of the skin lesions, as allowed based on local requirements. If photos are obtained, then copies should be kept as source documents, which may later be collected by the Sponsor. Laboratory tests should include an unscheduled CBC, ESR, CRP, chemistry, C3, C4, and urinalysis. Hematuria of ++ or more on urinalysis should be followed up with urine microscopy for red blood cell (RBC) and white blood cell (WBC) quantification. Proteinuria of ++ or more should be followed up with a protein:creatinine ratio from a spot urine sample. Further investigations are at the discretion of the investigator. Investigators should consider treatment with an additional dose of SC pozelimab. This dose should be in accordance with the tiered, weight-based regimen and be administered 3 to 4 days prior to the next scheduled dose. This additional dose will establish conditions of pozelimab excess in the circulation and minimize the risk of further formation of immune complexes. In addition, further management should be based on clinical experience with type III hypersensitivity reactions (ie, serum sickness) which include antihistamines, non-steroidal anti-inflammatory drugs, topical corticosteroids for localized skin rash, and systemic corticosteroids for generalized skin rash, internal organs, or systemic manifestations.

## 8.6. Dose Modification and Study Treatment Discontinuation Rules

### 8.6.1. Dose Modification

Dose regimen modification/reduction is not allowed for an individual patient.

- Patients will increase dose as specified by the dose regimen in the event that they move into a higher BW bracket. For the purposes of these dose increases, body weight will be measured at the study visits as specified in the schedule of assessments (Table 1) and not at each weekly administration. Pozelimab will be supplied initially in vials as lyophilized powder for reconstitution, so a single presentation will support all the weight-based dosing regimen The correct number of vials and volume for SC injection drawn up will be administered by a healthcare practitioner (not necessarily a doctor) at the study site, during a visit, or at a local primary healthcare clinic in between visits or at home; self-administration/administration by patient/designated person may also be allowed (Section 8.2). Each SC dose may be administered by more than one injection if necessary; each injection should not exceed a 2 mL volume. Further details will be described in the Pharmacy Manual.

### 8.6.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study may be asked to complete study assessments, per Section 9.1.2.

#### 8.6.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Serious or severe allergic reactions considered related to study drug
- Liver impairment as evidenced by one or more of the following criteria occurring without evidence of another etiology:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 x ULN or
  - ALT or AST > 5 x ULN for more than 2 weeks or
  - ALT or AST > 3 x ULN and total bilirubin > 2 x ULN (or international normalized ratio [INR] > 1.5) and no other reason can be found to explain the combination of increased AST/ALT and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury
- Patient withdraws consent

- Patient noncompliance (eg, not complying with protocol-required visits, assessments, and/or dosing instructions)
- Investigator's clinical judgment that it is in the best interest of the patient

Note: Evidence of pregnancy is not considered an automatic reason for permanent discontinuation and should be discussed with the medical monitor. Pregnancy may be a reason for permanent discontinuation if the benefit-risk assessment of continuing treatment with pozelimab is deemed unfavorable.

#### 8.6.2.2. Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation may be considered by the investigator because of suspected AEs. The investigator can reinitiate treatment with study drug under close and appropriate clinical and/or laboratory monitoring once the investigator will have considered, according to his/her best medical judgment, that the responsibility of the study drug in the occurrence of the concerned event was unlikely.

## 8.7. Management of Acute Reactions

### 8.7.1. Acute Intravenous Infusion Reactions

**Patients should be observed for 30 minutes after the infusion.**

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

#### 8.7.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

#### 8.7.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

### 8.7.2. Acute Injection Reactions

#### 8.7.2.1. Systemic Injection Reactions

Patients should be observed for 30 minutes after the first SC injection.

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.5.

Acute systemic reactions following SC injection of study drug should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

#### 8.7.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to the Food and Drug Administration (FDA) September 2007 Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see also Section 10.2.5).

## 8.8. Method of Treatment Assignment

All patients who sign the informed consent form (ICF) will be assigned a patient number. Treatment assignment will be performed in an unblinded fashion. To demonstrate a clear effect of pozelimab as early as possible, the first 2 patients recruited should have active PLE.

### 8.8.1. Blinding

This is an open-label study.

## 8.9. Treatment Logistics and Accountability

### 8.9.1. Packaging, Labeling, and Storage

Pozelimab for injection will be provided as open-label supplies packaged in carton boxes. Each carton box will contain 1 labeled vial. Carton box and vial label will indicate the protocol number, product identity and strength, medication/reference number, batch number, directions for use, route of administration, expiry date, sponsor information, and storage conditions, and will correspond to all regulatory requirements.

If provided by sponsor, diluent for pozelimab for IV and SC injections will be provided as open-label supplies packaged in carton boxes. Each carton box will contain 1 labeled vial. Carton box and vial label will indicate the protocol number, product identity and strength, medication/reference number, batch number, directions for use, route of administration, expiry date, and sponsor.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

### 8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed on site or at a destruction depot after accountability and reconciliation.

### 8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- Dispensed to each patient,
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

### 8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

## 8.10. Concomitant Medications

Any treatment administered from the time of informed consent to the end of the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

### 8.10.1. Prohibited Medications

The following medications are prohibited, with the exception of those listed in Section 8.10.2, as described below:

- Within 24 hours prior to each clinic visit when blood is drawn, patients should not consume any alcohol.
- Beginning on day 1 and continuing throughout the study, while the patient is continuing pozelimab, the patient should not take eculizumab.
- Add any experimental therapy, including complement inhibitors even if they become approved during study conduct.
- No Vitamin B12 supplementation during the first 4 weeks of pozelimab treatment (ie, cannot be initiated prior to week 4 visit)

### 8.10.2. Permitted Medications

Permitted medication is any medication that is not prohibited. The following medications and procedures will be permitted, under the following conditions:

- Albumin infusions are permitted during screening for disease of life-threatening severity only, and after start of study drug in the event that the albumin level is below 3.0 g/dL with accompanying symptoms of facial or peripheral edema or ascites. This limitation only applies to albumin infusions given specifically for the PLE.
- Any medication required to treat an AE, including non-steroidal anti-inflammatory drugs, antihistamines, or topical or systemic corticosteroids, at the discretion of the investigator
- Meningococcal vaccination, as described in Section 8.3.1
- Oral antibiotic prophylaxis, as described in Section 8.3.2
- Medications for treatment of type III hypersensitivity reactions as described in Section 8.5
- Oral contraceptives or hormone replacement therapy may continue or be started during the study
- Acetaminophen/paracetamol, aspirin, or ibuprofen at the recommended dose per the local label
- Immunosuppressive drugs, biologic therapies, immunoglobulins, corticosteroids, iron supplements, vitamins, and enteral and parenteral feeding are permitted and considered treatments of PLE. Any changes to these concomitant medications will be at the discretion of the investigator. Weaning and/or withdrawal of any of these medications is permitted at the discretion of the investigator, in the context of response in the underlying disease to treatment with pozelimab. Anti-thrombotic agents, anticoagulants, antibiotics are permitted.
- Any medication required for the treatment of patient's background medical conditions

# 9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

## 9.1. Schedule of Events

Study assessment and procedures are presented by study period and visit in Table 1.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

## Table 1: Schedule of Events

| **Study Procedure** | **Screening** [29] | **Baseline** | **Treatment Period**[1] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
| Day | -28 | 1 | 2 | 8±3 | 15±3 | 22±3 | 29±3 | 43±3 | 57±3 | 71±3 | 85±3 |
| Week | -4 | 0 | | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 |
| **Screening/Baseline:** | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion[2] | X | X | | | | | | | | | |
| Genetic testing (if needed)[2] | X | | | | | | | | | | |
| Medical History[3] | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Prior Medications[4] | X | | | | | | | | | | |
| Lab Parameter History[5] | X | | | | | | | | | | |
| Vaccination History[6] | X | X | | | | | | | | | |
| Risk assessment for *Neisseria gonorrhea* (as applicable)[7] | X | | | | | | | | | | |
| Hepatitis/TB history and assessment[8] | X | | | | | | | | | | |
| Electrocardiogram | X | | | | | | | | | | |
| Concept Elicitation Interview[9] | X | | | | | | | | | | |
| **Treatment:** | | | | | | | | | | | |
| Administer Study Drug[10] | | X[11] | | X[12] | | | | | | | |
| Patient Diary (for self-admin) | | | | | | | X | X | X | X | X |
| Concomitant Meds and Interventions | X | X | X | X | X | X | X | X | X | X | X |
| **Efficacy:** | | | | | | | | | | | |
| Tanner Staging[13] | | X | | | | | | | | | X |
| e-Diary | X[14] | X | X | X | X | X | X | X | X | X | X |
| BSFS, mBSFS-C, or BITSS | X[14] | X | X | X | X | X | X | X | X | X | X |
| CGIS | | X | | X | X | X | X | | X | | X |
| CGIC | | | | X | X | X | X | | X | | X |
| Physician Assessment of Facial Edema[15] | X | X | X | X | X | X | X | X | X | X | X |
| Physician Assessment of Peripheral Edema[15] | X | X | X | X | X | X | X | X | X | X | X |
| Abdominal Circumference[15] | X | X | X | X | X | X | X | X | X | X | X |
| Body Weight with z Score | X[16] | X | | | | | X | | X | | X |
| Height with z Score | X[16] | X | | | | | X | | X | | X |
| PedsQL Generic Core Scales | | X | | X | X | X | X | | X | | X |
| PedsQL GI Symptom Scales | | X | | X | X | X | X | | X | | X |

| **Study Procedure** | **Screening** [29] | **Baseline** | **Treatment Period**[1] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
| Day | -28 | 1 | 2 | 8±3 | 15±3 | 22±3 | 29±3 | 43±3 | 57±3 | 71±3 | 85±3 |
| Week | -4 | 0 | | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 |
| PedsQL Family Impact Module | | X | | X | X | X | X | | X | | X |
| PGIS/CareGIS | | X | | X | X | X | X | | X | | X |
| PGIC/CareGIC | | | | X | X | X | X | | X | | X |
| Hospitalization Days | X[17] | X | X | X | X | X | X | X | X | X | X |
| **Safety:** | | | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events[18] | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Testing and Biomarkers:** | | | | | | | | | | | |
| Blood Chemistry Panel[19] | X | X | X | X | X | X | X | X | X | X | X |
| Micronutrients and Lipid Panel[20] | | X | | X | | | X | | X | | X |
| Blood Immunoglobulin Panel[21] | | X | | X | | | X | | X | | X |
| Alpha-1 Antitrypsin (fecal and serum) | | X | | | | | | | | | X |
| Pregnancy Test[22] | X | X | | | | | | | | | |
| Urinalysis | X | X | | X | X | X | X | | | | X |
| Hematology | X | X | | X | X | | X | | X | | X |
| Coagulation Panel (APTT/PT) | X | | | X | | | X | | | | X |
| Complement Hemolytic Assay (CH50)[23] | | X | | X | | | X | | X | | X |
| Total C5[23] | | X | | X | | | X | | X | | X |
| Total Complement C3 and C4 Levels | X | | | | | | | | | | |
| Thrombosis Biomarkers[24] | | X | | X | | | X | | | | X |
| sC5b-9 (plasma) [23] | | X | | X | X | | X | | X | | X |
| Buccal Swab for DNA Isolation (optional)[25] | | X | | | | | | | | | |
| Future biomedical research (optional, weight >20 kg only) | | X | | | | | X | | X | | X |
| **Drug Concentration and ADA Samples:** | | | | | | | | | | | |
| Drug Conc. Sample [23, 27] | | X | | X | X | | X | X | X | | X |
| ADA Sample [23, 27, 28] | | X | | | | | | | | | X |

**Table 1 Schedule of Events (contd)**

| Study Procedure | Treatment Period[1] | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | End of TX Analysis | End of Study | Early Term |
| **Visit Number** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | |
| Day | 99 ±3 | 113 ±3 | 127 ±3 | 141 ±3 | 155 ±3 | 169 ±3 | 253 ±3 | 337 ±3 | 421 ±3 | 505 ±3 | 589 ±3 | 673 ±3 | 1009 ±3 | 1149 ±3 | |
| Week | 14 | 16 | 18 | 20 | 22 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 144 | 164 | |
| **Treatment:** | | | | | | | | | | | | | | | |
| Administer Study Drug[10] | X[12] | | | | | | | | | | | | | | |
| Patient Diary (self-admin) | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Concomitant Meds and Interventions | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Efficacy** | | | | | | | | | | | | | | | |
| Tanner Staging[13] | | | | | | X | | X | | X | | | X | | |
| E-Diary | X | X | X | X | X | X | | | | | | | | | |
| BSFS, mBSFS-C, or BITSS | X | X | X | X | X | X | | | | | | | | | |
| CGIS | | X | | | | X | | X | | X | | X | X | | |
| CGIC | | X | | | | X | | X | | | | | X | | |
| Physician Assessment of Facial Edema[15] | | X | | X | | X | X | X | X | X | X | X | X | | |
| Physician Assessment of Peripheral Edema[15] | | X | | X | | X | X | X | X | X | X | X | X | | |
| Abdominal Circumference[15] | | X | | X | | X | | | | | | | | | |
| Body Weight with z Score[16] | | X | | X | | X | X | X | X | X | X | X | X | | |
| Height with z Score[16] | | X | | X | | X | X | X | X | X | X | X | X | | |
| PedsQL Generic Core Scales | | X | | | | X | | | | | | | X | | |
| PedsQL GI Symptom Scales | | X | | | | X | | X | | X | | X | X | | |
| PedsQL Family Impact Module | | X | | | | X | | | | | | | | | |
| PGIS/CareGIS | | X | | | | X | | X | | X | | X | X | | |
| PGIC/CareGIC | | X | | | | X | | X | | | | | X | | |
| Exit interview[9] | | | | | | X | | | | | | | | | X |
| Hospitalization Days | | X | | X | | X | X | X | X | X | X | X | X | X | X |
| **Safety:** | | | | | | | | | | | | | | | |
| Vital Signs | | X | | X | | X | X | X | X | X | X | X | X | | |
| Physical Examination | | X | | X | | X | X | X | X | X | X | X | X | | |
| Adverse Events[18] | | X | | X | | X | X | X | X | X | X | X | X | X | X |

| **Study Procedure** | **Treatment Period[1]** | | | | | | | | | | | | | **Follow-up** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **End of TX Analysis** | **End of Study** | **Early Term** |
| **Visit Number** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | |
| Day | 99 ±3 | 113 ±3 | 127 ±3 | 141 ±3 | 155 ±3 | 169 ±3 | 253 ±3 | 337 ±3 | 421 ±3 | 505 ±3 | 589 ±3 | 673 ±3 | 1009 ±3 | 1149 ±3 | |
| Week | 14 | 16 | 18 | 20 | 22 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 144 | 164 | |
| **Laboratory Testing and Biomarkers:** | | | | | | | | | | | | | | | |
| Blood Chemistry Panel[19] | X[26] | X | X[26] | X | X[26] | X | X | X | X | X | X | X | X | | X |
| Micronutrients and Lipid Panel[20] | | X | | X | | X | X | X | | X | | X | X | | X |
| Blood Immunoglobulin Panel[21] | | X | | X | | X | X | X | X | X | X | X | X | | X |
| Alpha 1-Antitrypsin (fecal and serum) | | | | | | X | | | | | | | | | |
| Pregnancy Test[22] | | | | | | X | | | | | | | X | X | X |
| Hematology | | X | | X | | X | X | X | | X | | X | X | | |
| Coagulation Panel (APTT/PT) | | | | | | X | | X | | | | | X | | |
| Complement Hemolytic Assay (CH50) [23] | | X | | X | | X | X | X | | X | | X | X | | |
| Total C5[23] | | X | | X | | X | X | X | | X | | X | X | | |
| Total Complement C3 and C4 Levels | X | | | | | | | | | | | | | | |
| Thrombosis Biomarkers[24] | | | | | | X | | X | | | | | X | | |
| sC5b-9 (plasma) [23] | | | | | | X | | X | | X | | | X | | |
| Buccal Swab for DNA Isolation (optional) [25] | | | | | | | | | | | | | | | |
| Future biomedical research (optional, body weight >20 kg only) | | X | | X | | X | | X | | | | | X | | |
| **Drug Concentration and ADA Samples:** | | | | | | | | | | | | | | | |
| Drug Conc. Sample [23, 27] | | X | | X | | X | X | X | | X | | X | X | X | X |
| ADA Sample [23, 27] | | | | | | X | | X | | | | X | X | X | X |

### 9.1.1. Footnotes for the Schedule of Events Table

1. Treatment period is from week 0 to week 144, with first dose given on day 1 [week 0] and last dose at week 143. All visits in the Schedule of Events table are mandatory in-clinic visits, and do not reflect the dosing schedule, which is weekly (±2 days). Study procedures within each visit may be conducted on different days, within the stated visit window.
2. Including history of CD55 gene mutation analysis and if necessary CD55 protein analysis, confirmed by flow cytometry or western blot, respectively. If this data is unavailable, a blood sample may be collected, as needed, for analysis. Refer to Section 9.2.1 for details.
3. Including history of albumin infusions and prior thromboembolic events since birth
4. Including eculizumab administration history
5. Albumin, total protein, total immunoglobulin data including everything available from the patient's birth onwards
6. All patients require meningococcal, pneumococcal, and *Haemophilus influenzae* vaccination, either prior to the study or during screening, according to local availability and practice guidelines. Refer to Section 8.3.1 for details.
7. Risk assessment for *Neisseria gonorrhea* is described in Section 8.4.
8. Screening by tuberculin skin test or T-cell interferon-gamma release assay may be performed according to local practice or guidelines at the discretion of the investigator. Optional hepatitis B/C testing may be performed at the discretion of the investigator.
9. Patients (and caregivers, as appropriate) will be undergo a concept elicitation interview at screening and an exit interview at the time point of the primary endpoint as part of clinical outcomes evaluation. Details are described in Section 9.2.3.3.
10. Meningococcal vaccination is required and daily oral antibiotic prophylaxis is recommended as described in Section 8.3.
11. IV loading dose
12. Subcutaneous dosing to be administered weekly either at study site or in local community healthcare setting close to patient or at home. Weekly dosing is not noted as visits on this SOE table. The last dose of study drug is administered at week 143.
13. Only for patients between ages 8 to 20 years
14. Patients to begin completion of e-diary recording bowel movements and consistency at least 7 days prior to the baseline visit
15. In the presence of facial or peripheral edema or ascites, assessment should be always accompanied by clinical photography.
16. Including all available historical height and weight data from birth
17. Collect all available information pertaining to previous hospitalization dates since birth.
18. Including new thromboses and extension of existing thromboses

19. Total protein and albumin are tested in this panel (see blood chemistry panel in Section 9.2.4.4 Laboratory Testing). Testing will use either adult or small-volume pediatric kits as specified in a manual or kit instruction. If patient receives IV albumin infusion, this panel should be drawn either prior to the infusion or 2 weeks after the infusion.
20. See Micronutrients Panel and Lipids Panel in Section 9.2.4.4 Laboratory Testing.
21. See Blood Immunoglobulin Panel in Section 9.2.4.4 Laboratory Testing.
22. A pregnancy test is mandatory at screening and baseline for all women of childbearing potential (as defined in exclusion criterion #20). According to local practice in the study country, pregnancy testing (serum or urine) after enrollment is mandatory for all females from the age of sexual maturity, or for married females and, at the discretion of the investigator, for non-married females from the age of sexual maturity.
23. Intensity of blood sampling for these analytes will be reduced if necessary to comply with local body weight-specific limitations on blood withdrawal volume. The blood draw schedule in Table 1 is designed for patients with body weight equal or greater than 20 kg. It is expected that patients below 20 kg in weight will require reduction in blood-draw intensity. A separate blood draw schedule will be provided for patients with body weight between 10 kg and 20 kg in the sample handling manual. For patients with body weight less than 10 kg, an order of priority of blood draws will be provided in the sample handling manual or kit instruction, and samples should be drawn in this order until the volume limit is reached. The chemistry panel will have highest priority followed by full blood count and drug concentration.
24. Includes D-dimer, and F(1+2). Refer to lab manual for procedure.
25. Sample should be collected at baseline visit but may be collected at any time.
26. Kits may be provided locally so that the chemistry panel may be taken locally to the patient without needing a site visit.
27. Drug concentration and ADA samples are to be collected prior to study drug administration. In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to study drug and require treatment, or severe injection site reaction lasting longer than 24 hours, drug concentration and ADA samples will be collected at or near the onset of the event for any additional analysis.
28. In the event a patient sample is positive in the pozelimab ADA assay at week 12 or the first time point analyzed, the week 4 PK sample may be analyzed in the ADA assay, provided there is sufficient volume.
29. The screening period may be extended to approximately 10 weeks for patients with extenuating circumstances as described in Section 9.2.1.

### 9.1.2. Early Termination Visit

Patients who discontinue treatment and do not withdraw from study should continue all study visits as scheduled. If the week 164 visit does not include at least 21 weeks of follow-up, then patient should continue with site visits until 21 weeks after last dose of study drug.

Patients who discontinue treatment and study should be requested to have an early termination visit consisting of assessments listed for end of treatment visit (Table 1). If the patient agrees to a follow-up safety phone visit, then a follow-up phone call will be scheduled for 21 weeks after last dose of study drug.

Patients who discontinue study treatment after completing the treatment period should have a follow-up visit 21 weeks after last dose of study drug. This visit will consist of the safety assessments including laboratory tests (Section 9.2.4.4) listed for the week 144 visit in Table 1.

Patients who are withdrawn from the study before the primary endpoint visit (week 24) will be asked to return to the clinic for 2 visits: once for an early termination visit consisting of the end of study assessments described in Table 1, and again at the primary endpoint visit (week 24, day 169/visit 17). Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments, only.

In all instances, every attempt will be made to conduct a safety follow-up at 21 weeks after the last dose of study drug.

### 9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

## 9.2. Study Procedures

### 9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Medical history, including demonstration of CD55 gene loss of function (and absence of CD55 protein, if necessary) and collection of all available genetic sequencing data. All available genetic sequencing data and flow cytometry data are to be collected in its entirety. If at the time of screening, the patient does not have documentation of what mutation he/she carries or it cannot be retrieved, then the study site staff should collect a blood sample for genetic testing by the investigator to determine the mutation type prior to randomization. This testing will be performed on an as needed basis.
- History of albumin infusions and prior thromboembolic events since birth
- Demographics
- Prior medications including eculizumab
- Hospitalizations including dates, since birth if available

- Historical laboratory parameters, including albumin, total protein, and total immunoglobulins, since birth if available
- Vaccination history
- Risk assessment for *Neisseria gonorrhea*, as applicable. See Section 8.4
- Tuberculosis history and assessment. Screening by tuberculin skin test or T-cell interferon-gamma release assay may be performed according to local practice or guidelines at the discretion of the investigator
- Optional hepatitis B/C testing may be performed at the discretion of the investigator and may include: HBsAg, HBeAg, hepatitis B virus DNA, or HCV RNA
- ECG as described in Section 9.2.4.3
- Concept elicitation interview as described in Section 9.2.3.3

For screening purposes, multiple retest of laboratory testing is permitted for non-clinically significant abnormality. Additionally, patients who are appropriately treated for an intercurrent illness (eg, after a successful resolution of an infection) may be rescreened.

The screening period may be extended to approximately 10 weeks for patients who meet any of the following criteria:

- Patient requires additional time to complete meningococcal vaccinations
- Patient must physically relocate to the vicinity of a study center
- Patient is pending his/her screening laboratory results (Note: Samples for screening must be collected within 6 weeks of baseline)
- Patient has another requirement, which will be evaluated on a case by case basis after a discussion between the sponsor and investigator

### 9.2.2. Study Drug Administration

Study drug will be administered as described in Section 8.2. Immunization with meningococcal, *Haemophilus influenzae*, and pneumococcal vaccines are to be performed according to local practice (Section 8.3.1). Daily oral antibiotic prophylaxis is recommended (Section 8.3.2).

Compliance with study drug administration may be monitored with a patient diary according to Table 1.

### 9.2.3. Efficacy Procedures

#### 9.2.3.1. Serum Albumin, Total Protein, and Immunoglobulin

Samples will be collected at visits according to Table 1, and tested in the blood chemistry or immunoglobin panel (see Section 9.2.4.4) at a central lab.

#### 9.2.3.2. Physician Assessment of Edema and Ascites

Physicians will assess peripheral edema as follows*: Following a general inspection and palpation of all 4 limbs, the investigator will rate the overall severity of peripheral edema, taking into account

both degree and distribution, on a 5-point rating scale: 1) no edema; 2) mild edema: slight pitting, no visible change in the shape of the extremity; 3) moderate edema: definite pitting, slight change in the shape of the extremity; 4) severe edema: deep pitting, swollen extremity; and 5) very severe edema: very deep pitting, very swollen, distorted extremity.

Physicians will assess facial edema as follows*: Following a general inspection of the face, the investigator will rate the overall severity of facial edema, taking into account both degree and distribution, on a 5-point rating scale: 1) no edema, 2) mild edema, slight puffiness around the eyes with some flattening of superficial creases, 3) moderate edema, definite periorbital swelling with some flattening of deep creases with or without puffiness of the cheeks, 4) severe edema, marked periorbital swelling with loss of deep periorbital creases and definite swelling of the cheeks, 5) very severe edema, marked swelling of the entire face, eyes can only open to slit-like apertures.

Ascites severity will be assessed by measurement of abdominal circumference, as follows*:

1. Palpate for the lower rib margin (costal margin) and mark with a short horizontal line.
2. Palpate for the iliac crest and mark with a short horizontal line.
3. Using the tape measure, measure the mid-distance between the two horizontal lines and mark this with another short horizontal line in the middle.
4. Ask the patient to cross their arms across their chest so that you have access to the waist. Instruct them to stand relaxed and look straight ahead. Try to make sure that they don't deliberately hold themselves in or out.
5. Pass the tape around the waist, making sure it is level and that it is positioned at the mid-distance mark on both sides.
6. Make sure the tape is not pulled too tight. It should rest on the skin but not indent it.
7. Make the measurement at the end of expiration.
8. Measure to the nearest 0.1 cm (1 mm).
9. Make 3 measurements of waist circumference.
10. Record all three measurements and the mean (average) by adding the values together and dividing by 3.

* In case of abnormal findings, assessments of facial edema, peripheral edema, and ascites should be accompanied by clinical photography. All physician assessments for a patient should be performed by the same investigator until at least week 24. In addition, for consistency, a single independent physician blinded to the time point at which the photograph was taken will be performing an evaluation of the clinical photographs obtained.

#### 9.2.3.3. Clinical Outcome Assessments

**Daily e-Diary**

The daily e-diary, developed specifically for this study, will capture frequency of bowel movements as well as stool consistency for each bowel movement. The e-diary will be completed by the patients themselves if 12 years of age and older, and by caregiver otherwise (with input from the patient). When the caregiver is not with their child, bowel movement data will be

collected by the patient (patient ages 8 to 11) or by an alternate caregiver (patients <8 years) such as a nanny, teacher, or daycare provider. Once reunited with their child, the caregiver will be responsible for entering the data on bowel movements in the e-diary.

**Modified Bristol Stool Form Scale**

Stool consistency for patients who have been toilet-trained and who are less than 18 years of age will be assessed using the mBSFS-C. The BSFS was developed as a clinical assessment of intestinal transit time in patients with diseases of the bowel (O'Donnell, 1990) and has been modified for use in children (Lane, 2011). The mBSFS-C categorizes the form of human feces into 5 categories using drawings of different stool forms and consistencies: 1) separate hard lumps, like nuts; 2) sausage-shaped but lumpy; 3) like a sausage or snake, smooth and soft; 4) fluffy pieces with ragged edges, a mushy stool; 5) watery, no solid pieces. The patient or caregiver will be asked to select the picture that best corresponds to each bowel movement. The mBSFS-C has been demonstrated to be reliable and valid for use by children; 8 is the minimum age limit for use of this scale without descriptors being read (Lane, 2011).

**Bristol Stool Form Scale**

Stool consistency for patients who have been toilet-trained and are 18 years of age and older will be assessed using the BSFS. The BSFS was developed as a clinical assessment of intestinal transit time in patients with diseases of the bowel (O'Donnell, 1990). The BSFS categorizes the form of human feces into 7 categories using drawings of different stool forms and consistencies: 1) separate hard lumps; 2) lumpy and sausage-like; 3) like a sausage with cracks on the surface; 4) like a smooth, soft sausage or snake; 5) soft blobs; 6) fluffy, mushy stool; 7) entirely liquid. The patient or caregiver will be asked to select the picture that best corresponds to each bowel movement. The BSFS is widely used to treat and study bowel disorders in clinical and research settings and has demonstrated validity and reliability (Blake, 2016). The BSFS is the measure recommended by the Rome Foundation (Lacy, 2016) and is considered appropriate by the FDA to assess stool consistency in irritable bowel syndrome (IBS)(FDA, 2012).

**Brussels Infant and Toddler Stool Scale**

Stool consistency for patients who are not toilet-trained will be assessed using the BITSS. The BITSS was developed with input from physicians, nurses, and parents to specifically assess stool consistency in infants and young children who use diapers (Vandenplas, 2017). The instrument consists of 7 photographs of different stool forms and consistencies: 1) hard stools; 2) formed stools; 3) loose stools; and 4) watery stools. The caregiver will be asked to select the picture that best corresponds to each bowel movement. BITSS is a reliable assessment of stool consistency for children in diapers and has good agreement with the BSFS.

**Pediatric Quality of Life Inventory™ Generic Core Scales**

The PedsQL™ 4.0 Generic Core Scales is a measure assessing health-related quality of life (HRQoL) in children and adolescents. The PedsQL™ Generic Score Scales for patients ages 2 years and above is a 23-item measure that assesses physical functioning, emotional functioning, social functioning, and school/work/studies functioning. Different forms of the PedsQL™ Generic Core Scales allow the instrument to be self-administered in older patients and allow for parent proxy report for younger patients. The items for each of the forms for patients ages 2 to 18 years

are essentially identical, differing primarily in the use of developmentally appropriate language, or first- or third-person tense. The PedsQL™ Generic Core Scales for patients ages 13 to 24 months is a 45-item measure assessing physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning from the perspective of the parent. The instructions for all PedsQL™ Generic Core Scales forms ask how much of a problem each item has been over the past 7 days on a 5-point response scale, ranging from never a problem (0) to almost always a problem (4). The measure will be a self-administered patient-reported outcome (PRO) for patients ages 12 years and older, using the child report (age 12 years), teen report (ages 13 to 17 years), young adult report (ages 18 to 25 years), and adult report (>25 years) forms. For patients 1 to 11 years of age, it will be an observer reporter outcome (ObsRO) measure using different forms for patients 8 to 11 years (parent report for children), 5 to 7 years (parent report for young children), >2 years to 4 years (parent report for toddlers), and 13 to 24 months (parent report for infants). Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate better HRQoL. The total scale score is computed as the sum of all the items over the number of items answered on individual scales. The PedsQL™ Generic Core Scales was developed using focus groups, cognitive interviews, pre-testing, and field-testing measurement development protocols (Varni, 2001) (Varni, 1999) and has demonstrated validity, reliability, ability to detect change, and responsiveness (Desai, 2014) (Varni, 2003) (Varni, 2011) (Varni, 2002) (Varni, 2001). This measure has also been used to evaluate HRQoL in patients with functional and organic gastrointestinal disorders, which tends to be lower compared to healthy controls (Kunz, 2010) (Varni, 2015a).

**Pediatric Quality of Life Inventory™ Gastrointestinal Symptoms Scales**

The PedsQL™ GI Symptoms Scales is a 74-item measure assessing gastrointestinal disease-specific HRQoL in children, adolescents, and adults. The PedsQL™ Gastrointestinal Symptoms Scales is a multidimensional instrument comprising of 14 individual scales which can be administered and scored individually. Only the following 4 scales (23 items) will be administered: stomach pain and hurt (6 items), food and drink limitations (6 items), nausea and vomiting (4 items), and diarrhea (7 items). The format, instructions, Likert response scale, and scoring method for the PedsQL™ Gastrointestinal Symptoms Scales are identical to the PedsQL™ 4.0 Generic Core Scales.

As with the PedsQL™ Generic Core Scales, different forms of the PedsQL™ Gastrointestinal Symptoms Scales allow the instrument to be self-administered in older patients and also allow for parent proxy report for younger patients. There is no PedsQL™ Gastrointestinal Symptoms Scales form to assess gastrointestinal symptoms in patients younger than 2 years of age. The items for each of the forms for patients ages 2 to 25 years are essentially identical, differing primarily in the use of developmentally appropriate language, or first- or third-person tense. The instructions for all PedsQL™ Gastrointestinal Symptoms Scales forms ask how much of a problem each item has been over the past 7 days on a 5-point response scale, ranging from never a problem (0) to almost always a problem (4). The PedsQL™ Gastrointestinal Symptoms Scales will be a self-administered, PRO measure for patients age 12 years (child report), 13 to 18 years (teen report), and 18 years of age and older (young adult report). For patients 2 to 11 years of age, the PedsQL™ Gastrointestinal Symptoms Scales will be an ObsRO measure using different forms for patients 8 to 11 years (parent report for children), 5 to 7 years (parent report for young children), and 2 to 4 years (parent report for toddlers). Items are reverse-scored and linearly transformed to a 0 to

100 scale so that higher scores indicate better HRQoL. The measure was developed by consulting the literature, interviewing pediatric gastroenterologists with clinical experience in treating gastrointestinal disorders, and by conducting focus groups, concept elicitation, and cognitive debriefing (Varni, 2012). The PedsQL™ Gastrointestinal Symptoms Scales has demonstrated validity and reliability (Varni, 2014) (Varni, 2016).

**PedsQL™ Quality of Life Inventory - Family Impact Module**

The PedsQL™ Family Impact Module Scales is a 36-item, self-administered PRO measure assessing the impact of pediatric acute and chronic health conditions on parents and the family. The measure will be administered to parent and non-parent caregivers. Additional instructions for the caregiver to think of the person they care for rather than the child to which the questionnaire refers will be included for non-parent caregivers. The PedsQL™ Family Impact Module assesses the parent's physical functioning, emotional functioning, social functioning, cognitive functioning, communication, and worry as well as family functioning in terms of ability to perform daily activities and maintain family relationships. The instructions ask how much of a problem each item has been for the parent (for physical functioning, emotional functioning, social functioning, cognitive functioning, communication, and worry) or the family (for daily activities and family relationships) over the past 7 days, as a result of their child's health, on a 5-point response scale ranging from never a problem (0) to almost always a problem (4). Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate less negative impact. The total scale score is computed as the sum of all the items over the number of items answered on individual scales. The measure was developed using focus groups, cognitive interviews, and pre-testing measurement development protocols, and informed by prior research and clinical experiences with children with chronic health conditions and their families (Varni, 2004). The PedsQL™ Quality of Life Inventory – Family Impact Module has demonstrated reliability and validity among families caring for a child with complex chronic health conditions such as severe cerebral palsy and birth defects (Varni, 2004).

**Patient/Caregiver Global Impression of Severity**

The PGIS/CareGIS items are self-administered PRO questions for patients ages 12 and above, and self-administered ObsRO questions for patients aged less than 12 years. The PGIS/CareGIS questions will be used to assess the patient's current overall severity of disease and of specific symptoms from the perspective of the patient or caregiver.

**Patient/Caregiver Global Impression of Change**

The PGIC/CareGIC items are self-administered PRO questions for patients ages 12 and above, and self-administered ObsRO questions for patients aged less than 12 years. The PGIC/CareGIC questions will be used to assess the change in overall severity of disease and in specific symptoms compared to the start of the study, from the perspective of the patient or caregiver.

**Clinical Global Impression of Severity**

The CGIS items are self-administered clinical-reported outcome (ClinRO) questions assessing the patient's overall disease activity or symptom severity from the perspective of the treating clinician. Over the course of the study, the treating clinician will rate the patient's current disease activity and symptom severity.

**Clinical Global Impression of Change**

The CGIC items are self-administered ClinRO questions assessing the change in a patient's overall disease activity or symptom severity compared to the start of the study. Over the course of the study, the treating clinician will rate the change in the patient's disease activity and symptom severity.

**Concept Elicitation Interview**

Eligible patients and, when appropriate, their caregivers will participate in a face-to-face concept elicitation interview at screening. Concept elicitation is designed to identify/confirm, describe, and substantiate important and relevant concepts of interest from the perspective of patients and their caregivers. Patients and, when appropriate, their caregivers will be asked questions related to their experience or their child's experience with CD55-deficient PLE in terms of the signs/symptoms of disease, how bothersome each sign/symptom is and which is the most bothersome, as well as the ways in which the disease has impacted his/her life. Each interview will last approximately 60 minutes and will be conducted by a trained internal or external interviewer following a semi-structured interview guide. Further details will be provided in a separate study manual.

**Exit Interview**

At the time point of the primary endpoint, patients and, when appropriate, their caregivers will be interviewed to more fully explore the experiences of trial patients on treatment. Patients and their caregivers, where appropriate, will be asked questions to better understand the change in signs/symptoms (including the sign/symptom identified as most bothersome during the concept elicitation interview), and impact on quality of life. Results from exit interviews will be used to contextualize findings on the clinical outcome assessments (COAs) and other clinical endpoints. Each interview will last approximately 60 minutes and will be conducted by a trained internal or external interviewer following a semi-structured interview guide.

#### 9.2.3.4. Tanner Stages

The Tanner stages will be assessed throughout the study for patients between the ages of 8 and 20 years, in whom pubertal development is not complete (in the assessment of the investigator at specified time points shown in Table 1). If possible, for each adolescent patient, the Tanner stages assessment should be performed by the same investigator or designee trained to assess pubertal development.

### 9.2.4. Safety Procedures

#### 9.2.4.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, and pulse will be collected predose at time points according to Table 1.

Vital signs will be obtained after patient has been sitting quietly for at least approximately 5 minutes. At the first visit, blood pressure should be measured from both arms. The arm with the higher diastolic pressure will be selected for measurement throughout the study.

#### 9.2.4.2. Physical Examination, Height, and Body Weight

A thorough and complete physical examination will be performed at time points according to Table 1. Each physical examination will include an evaluation of head and neck, lungs, heart, abdomen, extremities, and skin. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history. Additionally, for patients switching from eculizumab, risk assessment of immune complex formation is described in Section 8.5.

Height and body weight will be measured at time points according to Table 1. Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes (should be the same each time). A calibrated scale should be used.

#### 9.2.4.3. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at time points according to Table 1.

Twelve-lead ECGs will be systematically recorded after the patient has been in the supine position for at least 10 minutes.

The ECG will be interpreted locally by the investigator and a consultation with the sponsor may occur. Any new and/or clinically significant changes in ECG parameters should be immediately rechecked for confirmation before making any decision for the concerned patient. Any clinically significant abnormality should be documented as an AE/SAE as applicable.

Heart rate will be recorded from the ventricular rate, and the PR/PQ, QRS, RR, QT intervals, and QTcF will be recorded. The ECG strips or reports will be retained with the source.

#### 9.2.4.4. Laboratory Testing

Samples for laboratory testing will be collected at visits according to Table 1.

Hematology, chemistry (except total C5, CH50 sC5b-9), urinalysis, and pregnancy testing samples may be analyzed by a local/central laboratory.

Other testing will be done by a local, central or specialized laboratory.

Detailed instructions for blood sample collection are provided to study sites.

***Blood Chemistry***

| | | |
|---|---|---|
| Sodium | Total protein, serum albumin | Total bilirubin* |
| Potassium | Creatinine (eGFR) | Total cholesterol** |
| Chloride | Blood urea nitrogen (BUN) / Urea | Triglycerides |
| Calcium | Aspartate aminotransferase (AST) | Uric acid |
| Glucose | Alanine aminotransferase (ALT) | Creatine kinase (CK) |
| Albumin | Alkaline phosphatase | C-reactive protein (CRP) |
| Magnesium | Lactate dehydrogenase (LDH) | |

* If the total bilirubin is above the upper limit of normal, the bilirubin should be fractionated
**(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Fasting lipids and glucose should be obtained at the baseline visit and visits at weeks 12 and 24, if possible.

***Lipid Panel (fasting)***

Total cholesterol (LDL and HDL)

Triglycerides

***Blood Immunoglobin Panel***

Total Ig, IgG, IgM, IgA

***Micronutrient Panel***

Vitamin B12, folate, iron, iron-binding capacity, ferritin

***Hematology Panel***

| | |
|---|---|
| Hemoglobin | Differential: |
| Hematocrit | Neutrophils |
| Red blood cells (RBCs) | Lymphocytes |
| White blood cells (WBCs) | Monocytes |
| Red cell indices | Basophils |
| Platelet count | Eosinophils |
| Reticulocyte count | |

***Coagulation Panel***

PT/aPTT

***Urinalysis***

| | |
|---|---|
| Glucose | |
| Protein | Note: If protein is ++ or more then reflex to urinary protein creatinine ratio |
| Blood | Note: if blood is ++ or more then reflex to microscopy |

***Other Laboratory Tests***

Other laboratory tests may include:

- Complement hemolytic assay (CH50)
- Alpha-1 antitrypsin
- Pregnancy testing: serum human chorionic gonadotropin pregnancy testing or urine pregnancy testing according to local practice
- Sample collection is described separately for drug concentration (Section 9.2.5), ADA (Section 9.2.6), and exploratory biomarkers (Section 9.2.7)

***Abnormal Laboratory Values and Laboratory Adverse Events***

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.2.5.

### 9.2.5. Drug Concentration and Measurements

Samples for drug concentration will be collected prior to drug administration at visits listed in Table 1. The exact sampling time must be recorded, as allowed per local regulation.

Any unused samples may be used for exploratory biomarker research.

### 9.2.6. Anti-Drug Antibody Measurements and Samples

Blood samples for ADA assessment in serum will be collected prior to drug administration at visits listed in Table 1. Samples positive in the ADA assay may be stored and analyzed in the NAb assay at a later time once the NAb assay is available.

Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples may be used for exploratory research, as allowed per local regulation.

### 9.2.7. Pharmacodynamic and Exploratory Biomarker Procedures

Samples will be collected at time points according to Table 1, and tested in a central lab or a specialty lab.

Biomarker measurements will be performed in specified matrix to determine effects of pozelimab on relevant physiological and pathogenic processes.

The biomarkers studied will be ones believed to be relevant to the understanding of efficacy, pathophysiology of indication target engagement, mechanism of action, and possible toxicities of pozelimab.

Biomarkers studied may include but need not be limited to:

- Thrombosis biomarkers
- Total C5
- sC5b-9
- Others as described in Section 4.5

#### 9.2.7.1. Future Biomedical Research (Optional)

Patients who have a body weight >20 kg and agree to participate in the future biomedical research sub-study will be required to assent/consent to this optional sub-study before collection of the serum and plasma samples. The unused biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of pozelimab, the complement pathway, PLE, and related diseases. Additional samples will be collected for future biomedical research according to the Schedule of Events in Table 1. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the clinical study report.

#### 9.2.7.2. Genomics Sub-Study (Optional)

Patients who agree to participate in the genomics sub-study will be required to assent/consent to this optional sub-study before collection of the samples. This genomics sub-study will not be available in countries where a separate ethics committee (EC) approval is required for such studies, and where such an approval is not in place.

Buccal swab samples for DNA extraction should be collected on day 1 (predose) but can be collected at a later study visit.

DNA samples will be collected for pharmacogenomics analyses. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses with which the sponsor is unable to comply, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical (safety or efficacy) or biomarker response to pozelimab, the complement pathway, PLE, and related complement-mediated diseases, clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of PLE and related complement-mediated diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or PLE and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole exome sequencing, whole genome sequencing, DNA copy number variation, transcriptome sequencing (or other methods for quantitating RNA expression), and methods for quantifying epigenetic modifications may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

Results from the genomic analyses will not be reported in the CSR.

# 10. SAFETY EVALUATION AND REPORTING

## 10.1. Recording and Reporting Adverse Events

### 10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period (see Section 10.1.2). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the follow-up/post treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, serious adverse events (SAEs), AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

### 10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

### 10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Moderate or severe infusion reactions
  - Confirmed *Neisseria* infection
  - Any thrombotic or embolic event
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 21 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor. Also see Section 8.6.2.1.

## 10.2. Definitions

### 10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

### 10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

### 10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 10.1.3).

### 10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours (up to 24 hours) after the infusion is completed.

### 10.2.5. Severity

The severity of AEs will be graded according to the following scale:

**Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

**Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

**Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

***Infusion Reactions***

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

**Mild**: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

**Moderate**: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

**Severe**: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

***Injection Site Reactions***

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

**Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

**Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

**Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

### 10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

## 10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

## 10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (pozelimab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (pozelimab) is assessed against the Reference Safety Information section of the current Investigator's Brochure.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IECs/IRB as appropriate.

# 11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

## 11.1. Statistical Hypothesis

The primary objective of the study is to determine the effect of pozelimab on active CD55-deficient PLE/CHAPLE disease in patients with active disease at baseline. The primary outcome at week 24 is achievement of both of the following:

- Normalization of serum albumin, defined as
  - serum albumin within the normal range at at least 70% of measurements between week 12 and week 24, and
  - no single albumin measurement of <2.5 g/dL between week 12 and week 24, and
  - no requirement for albumin infusion between week 12 and 24
- Improvement at week 24 in clinical outcomes listed in Section 5.1 that were evaluable for improvement at baseline, with no worsening of the others.

The primary endpoint is the proportion of patients achieving the primary outcome.

## 11.2. Justification of Sample Size

The study is regarded as successful if at least 4 of 6 evaluable patients achieve the primary endpoint. Unpublished patient-level data of 14 patients treated with eculizumab (Kurolap, 2017) (Kurolap, 2019) (Ozen, 2017a) were made available to the study sponsor (Ozen unpublished data, Baris-Feldman unpublished data). In the historical control period before initiating eculizumab, 0 of 14 patients met the primary endpoint (90% exact confidence interval (CI): [0.00, 0.19]). If 4 of 6 patients treated with pozelimab achieve the primary endpoint, the 90% exact CI for the probability of achieving the primary endpoint is (0.27, 0.94), with the lower limit of 0.27 clearly greater than the upper limit of 0.19 for the historical control period of the 14 patients. By a Bayesian analysis, a comparison between 4 of 6 pozelimab-treated patients achieving the primary endpoint and 0 of 14 in the historical data by a Beta-Binomial analysis with the Jefferys prior of Beta(0.5, 0.5) would conclude that there is a >99% posterior probability that pozelimab has a greater response rate than untreated patients. There would also be a 90% posterior probability that the response rate with pozelimab is at least 0.37 higher than that of untreated patients. Thus, the study success criterion of observing at least 4 of 6 evaluable patients achieving the primary endpoint provides strong evidence of effectiveness.

All of the 14 eculizumab-treated patients achieved a normalized serum albumin level by 12 weeks of treatment and required no albumin infusions subsequent to treatment initiation (90% exact CI: [0.81, 1.00]) (Kurolap, 2017) (Kurolap, 2019) (Ozen, 2017a). If the true rate of achieving the primary endpoint for patients on pozelimab is 0.81 (the lower limit of the CI for eculizumab), then a sample size of 6 gives a probability of 91% for achieving the study success criterion.

## 11.3. Analysis Sets

### 11.3.1. Efficacy Analysis Set

The full analysis set (FAS) includes all enrolled patients who received any study drug. Efficacy endpoints will be analyzed using the FAS analysis set unless otherwise specified.

### 11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received any study drug. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

### 11.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all patients who received any study drug and who had at least 1 non-missing result for concentration of pozelimab following the first dose of study drug.

### 11.3.4. Immunogenicity Analysis Sets

The ADA analysis set will consist of all patients who received any study drug and who had at least one non-missing ADA result after first dose of the study drug.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA-negative are set to negative in the NAb analysis set).

### 11.3.5. Exploratory Analysis Sets

#### 11.3.5.1. Exploratory Biomarker Endpoint Analysis Set

The PD analysis populations include all patients who received any study drug and who had at least 1 non-missing analyte measurement following the first dose of study drug.

#### 11.3.5.2. Exploratory Clinical Outcome Assessment Analysis Set

The clinical outcome assessment (COA) analysis populations include all patients who received any study drug and who had at least 1 non-missing COA measurement following the first dose of study drug.

## 11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

In addition to summary statistics, data will be plotted whenever needed.

### 11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of enrolled patients
- The total number of patients in each analysis set (eg, provided in Section 11.3)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients enrolled but not treated
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

### 11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

### 11.4.3. Efficacy Analyses

#### 11.4.3.1. Primary Efficacy Analysis

The subset of the FAS with patients having active PLE at baseline will provide the data for the primary efficacy analysis. The percentage of patients achieving normalization of albumin and achieving improvement in the prespecified evaluable clinical outcomes listed in Section 5.1 will be calculated and its 90% CI will be reported.

There are 7 planned albumin measurements between week 12 and week 24, inclusive. Patients will be considered non-evaluable for the primary analysis if there are fewer than 5 available albumin measurements between week 12 and week 24. Albumin measurements outside of the visit windows and/or carried out at local laboratories will be considered as valid measurements. To be considered responders, at least 70% of available measurements must be normal (≥3.5 g/dL). Thus, patients with the minimum of 5 available measurements must have 4 out of 5 normal. Patients with the planned number of 7 measurements must have at least 5 normal. Patients who have more than 7 available measurements (due to unplanned albumin measurement in local labs) must have at least 70% of all available measurements normal. Non-responder imputation for patients with fewer than 5 available albumin measurements between week 12 and week 24 will be carried out as a sensitivity analysis. The mean changes from baseline in albumin over time and the mean number

of albumin infusions per half-year will also be estimated. Patient profiles of albumin over time will be plotted.

There are 4 clinical outcomes that can contribute to the clinical improvement component of the primary endpoint. Patients are evaluable for improvement in each of these based on activity at baseline, as defined in Section 5.1. Patients evaluable for only 1 of the 4 clinical outcomes must show improvement in that clinical outcome and no worsening in the other 3. Patients evaluable for more than 1 clinical outcome must show improvement (as defined) for all of their evaluable outcomes and no worsening in any non-evaluable outcomes.

For facial and peripheral edema, the primary analysis will be performed using the investigating physician's report. Clinical photographs will be rated by a single, central reader blinded to the time point at which the photograph was taken. The correlation of central read to physician's assessment will be described. The central read will be used as a sensitivity analysis on the primary endpoint.

For the primary endpoint, the definitions of baseline for the component variables are:

- Albumin - The measurement at the baseline visit will be used
- PedsQL GI Symptoms Scales' Stomach Pain and Hurt Subscale - The baseline visit score will be used
- Bowel movement frequency - The daily average from the e-diary from the last 7 days pre-baseline will be used
- Facial edema - The baseline value will be used
- Peripheral edema - The baseline value will be used

#### 11.4.3.2. Secondary Efficacy Analysis

For the responder outcomes for maintenance of effect at week 48 and 144, there are 9 planned albumin measurements between week 12 and week 48 inclusive. Patients will be considered non-evaluable for the secondary analysis if there are fewer than 6 available albumin measurements between week 12 and week 48. Non-responder imputation for patients with fewer than 6 available albumin measurements between week 12 and week 48 will be carried out as a sensitivity analysis. There are 14 planned albumin measurements between week 12 and week 144 inclusive. Patients will be considered non-evaluable for the secondary analysis if there are fewer than 10 available albumin measurements between week 12 and week 144. There are 3 planned albumin measurements between week 24 and week 48 inclusive. Patients will be considered non-evaluable for this secondary analysis if there are fewer than 2 available albumin measurements between week 24 and week 48. There are 5 planned albumin measurements between week 48 and week 96 inclusive. Patients will be considered non-evaluable for this secondary analysis if there are fewer than 3 available albumin measurements between week 48 and week 96. There are 2 planned albumin measurements between week 96 and week 144 inclusive. Patients will be considered non-evaluable for this secondary analysis if there are fewer than 2 available albumin measurements between week 96 and week 144. Albumin measurements outside of the visit windows and/or carried out at local laboratories will be considered as valid measurements. Non-responder imputation for patients with fewer than 10 available albumin measurements between week 12 and week 144 will be carried out as a sensitivity analysis. The mean changes from baseline in albumin

over time and the mean number of albumin infusions per half-year will also be estimated. Patient profiles of albumin over time will be plotted.

Prior to baseline, concept elicitation interviews will seek to identify each patient's most bothersome sign/symptom from the 'core' clinical manifestations. The identification of the most bothersome sign/symptom following the interview and its translation into English may take place after the baseline visit, by expert individuals with no access to post-baseline clinical data. For continuous secondary outcomes, including total protein, total Ig, and weight, patient profiles over time will be tabularly and graphically presented. Changes from baseline in the outcome measures over time will be summarized with mean, 90% CI, and other summary statistics.

For count secondary outcomes, including number of bowel movements per day, frequency of albumin infusions and hospitalization days, counts by day or periods of time will be summarized.

For categorical secondary outcomes, including AEs and physician assessment of disease inactivity, percentages of patients in categories will be summarized.

For time-to-event secondary outcomes, including time to first normalization of serum albumin, survival analysis of data with censoring through time will be conducted.

### 11.4.4. Safety Analysis

#### 11.4.4.1. Adverse Events

***Definitions***

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as either the first dose of study drug to last dose of study drug +21 weeks.
- The posttreatment period is defined as the time after the treatment period.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

***Analysis***

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest-level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

#### 11.4.4.2. Other Safety

***Vital Signs***

Vital signs (temperature, blood pressure, and pulse rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

***Laboratory Tests***

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out-of-laboratory range values.

#### 11.4.4.3. Treatment Exposure

The observation period (defined as the time between the date of first study drug administration and the date of the end of study visit for the patient), rather than the treatment exposure, will be presented.

#### 11.4.4.4. Treatment Compliance

Analysis of treatment compliance will be described in the SAP.

### 11.4.5. Pharmacokinetics

#### 11.4.5.1. Analysis of Drug Concentration Data

The PK endpoint is concentration of total pozelimab in serum over time.

Summary of total drug concentrations and total C5 will be presented by nominal time point (ie, the time points specified in the protocol). Individual data will be presented by actual time. Plots of the concentrations of pozelimab and total C5 will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification (LLOQ) will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2. Summary statistics of concentrations of total pozelimab and total C5 may include, but are not limited to, arithmetic mean, standard deviation, standard error of the mean, coefficient of variation (in %), minimum, Q1, median, Q3, and maximum.

No formal statistical analysis will be performed.

### 11.4.6. Analysis of Immunogenicity Data

Anti-drug antibodies will be characterized by the type and level of the observed response. Samples positive in the ADA assay will be further characterized for NAbs and ADA titers.

Anti-drug antibodies response categories and titer categories that will be assessed are as follows:

- Preexisting immunoreactivity: defined as a positive ADA assay response at baseline with all ADA results negative after the first dose of study drug, or a positive assay response at baseline with all ADA assay responses less than 9-fold over baseline titer levels after the first dose of study drug
- Treatment-emergent response: defined as any positive ADA assay response after the first dose of study drug when the baseline results are negative or missing
- Treatment-boosted response: defined as any positive ADA assay response after the first dose of study drug that is 9-fold over baseline titer levels when baseline is positive in the ADA assay

Treatment-emergent ADA responses may be further characterized into persistent, transient and indeterminate responses.

Titer value category (titer range):

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤10,000)
- High (tier >10,000)

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers, and NAb positivity presented by patient and time point will be provided. Incidence of treatment-emergent, persistent and NAb responses will be assessed as absolute occurrence (N) and percent of patients (%), grouped by ADA titer level.

Plots of drug concentrations will be examined and the influence of ADA responses on individual PK profiles evaluated. Assessment of impact of ADA responses on safety and efficacy may be provided.

### 11.4.7. Analysis of Exploratory Pharmacodynamic and Biomarker Data

Analysis of biomarker data is defined in the SAP.

### 11.4.8. Analysis of Exploratory Clinical Outcome Assessment Data

Analysis of COA data is defined in the SAP.

## 11.5. Interim Analysis

There will not be a formal interim analysis of the efficacy data for an early stopping of the study.

## 11.6. Timing of Analyses

Database locks and analyses prior to the final database lock are planned for the following times for the stated purposes:

- First database lock for reporting on the primary efficacy endpoint takes place at 24 weeks from the first dose in the sixth active patient (may be more patients depending on the rate of patient accrual)
- Second database lock and reporting of longer-term effects takes place at 1 year from first dose in the last patient
- Third database lock and reporting of longer-term effects takes place at 2 years from first dose in the last patient

## 11.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

# 12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

## 12.1. Data Management and Electronic Systems

### 12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The case report form (CRF) data for this study will be collected with an electronic data capture (EDC) tool.

### 12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- eCOA system – capture COA

## 12.2. Study Monitoring

### 12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH E6 R2). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current, approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

### 12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

## 12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

## 12.4. Study Documentation

### 12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRFs/eCRFs that will be provided to the sponsor.

### 12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

# 13. ETHICAL AND REGULATORY CONSIDERATIONS

## 13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

## 13.2. Informed Consent

### 13.2.1. Adult Patients

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

### 13.2.2. Pediatric Patients

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient and his/her parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents'/guardians' consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk-benefit assessment, the ICF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the patient to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient's parent(s) or legal guardian(s).

## 13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

## 13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

## 13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

# 14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

# 15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

## 15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

## 15.2. Close-Out of a Site

The sponsor and the investigator have the right to close out a site prematurely.

***Investigator's Decision***

The investigator must notify the sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

***Sponsor's Decision***

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time.
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines.
- The total number of patients required for the study are enrolled earlier than expected.

In all cases, the appropriate IRB/EC and health authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

# 16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

# 17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

# 18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

# 19. REFERENCES

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# 20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: An Open-Label Efficacy and Safety Study of Pozelimab in Patients with CD55-Deficient Protein-Losing Enteropathy (CHAPLE Disease) and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the Sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

# SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

**(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)**

*To the best of my knowledge, this report accurately describes the conduct of the study.*

Study Title: AN OPEN-LABEL EFFICACY AND SAFETY STUDY OF POZELIMAB IN PATIENTS WITH CD55-DEFICIENT PROTEIN-LOSING ENTEROPATHY (CHAPLE DISEASE).

Protocol Number: R3918-PLE-1878

Protocol Version: R3918-PLE-1878 Amendment 6

*See appended electronic signature page*

Sponsor's Responsible Medical/Study Director

*See appended electronic signature page*

Sponsor's Responsible Regulatory Liaison

*See appended electronic signature page*

Sponsor's Responsible Clinical Study Team Lead

*See appended electronic signature page*

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00158650 v1.0

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| Approval/eSignature | [redacted]2022 23:23:51 GMT+0000 |
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