NCT04209634

STATISTICAL ANALYSIS PLAN
VERSION: 4.0

Clinical Study Protocol Title:	**AN OPEN-LABEL EFFICACY AND SAFETY STUDY OF POZELIMAB IN PATIENTS WITH CD55-DEFICIENT PROTEIN-LOSING ENTEROPATHY (CHAPLE DISEASE).**
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Protocol Number:	R3918-PLE-1878
Clinical Phase:	Phase 2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BID	Twice daily
BITSS	Brussels infant and toddler stool scale
BSFS	Bristol Stool Form Scale
CareGIC	Caregiver global impression of change
CareGIS	Caregiver global impression of severity
CGIC	Clinical global impression of change
CGIS	Clinical global impression of severity
CHAPLE	CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy
COA	Clinical Outcome Assessment
CRF	Case report form (electronic or paper)
CRP	C-reactive protein
ECG	Electrocardiogram
FAS	Full analysis set
FDA	Food and Drug Administration
FPFD	First patient first dose
GI	Gastrointestinal
HBeAg	Hepatitis B e antigen
HBsAG	Hepatitis B surface antigen
HCV RNA	Hepatitis C virus RNA
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
IV	Intravenous

mBSFS-C	modified Bristol Stool Form Scale for Children
MedDRA®	Medical Dictionary for Regulatory Activities
MID	Minimum important difference
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PedsQL™	Pediatric Quality of Life Inventory™
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetic
PLE	Protein-losing enteropathy
PT	Preferred term
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
TFPI	Tissue factor pathway inhibitor
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data. SAP version 1 was finalized prior to first patient first dose, per health authority recommendations, as the study is designed as an open-label single-arm trial. SAP version 2 was finalized after protocol amendment 3 to incorporate changes to the study. SAP version 3, was finalized after protocol amendment 5 to incorporate changes made to the protocol and health authority guidance up to and including 6AUG2020. The current version of the SAP, version 4, was finalized after protocol amendment 6 to incorporate changes made to the protocol. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for this study.

1.1. Background/Rationale for Study Design

CD55-deficient protein losing enteropathy (PLE), also known as CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE), is a life-threatening, ultra-orphan disease of infants, children, adolescents, and young adults with no current approved therapy (Ozen, 2017). R3918-PLE-1878 is an open-label study to evaluate the safety and efficacy of pozelimab in 6 to 20 patients with active CD55-deficient PLE, as an addition to standard-of-care therapies (excluding eculizumab). The hypothesis is that pozelimab treatment will result in normalization of serum albumin and improvement in clinical signs and symptoms in CD55-deficient PLE/CHAPLE disease.

The intent of this study is to generate efficacy and safety data from a clinical study for pozelimab in this indication, and to support licensure for the treatment of CD55-deficient PLE with pozelimab. This study does not include a randomized, concurrent placebo control group. The rationale for this is that there is some prior evidence that therapeutic inhibition of C5, with eculizumab, can resolve serious manifestations of the disease and likely prevent irreversible harm. This evidence comes in the form of two uncontrolled case series of the use of eculizumab in a small number (total 14) of patients (Ozen, 2017) (Kurolap, 2019). Therefore, a trial design involving the withholding of active therapy from some trial subjects, as a control group, is not considered acceptable. These eculizumab data have been used to provide an external control to enable interpretation of the results from our open-label study, as per guidance in 21CFR 314.126. Specifically, the eculizumab data were utilized to determine a quantitative threshold for a treatment effect that would be sufficiently large to distinguish it from variability over the course of disease. We were able to identify a definition of a treatment effect (the normalization of albumin level over a 12-week period, along with improvement in clinical signs and symptoms) that was manifest in no historical cohort patients (over an observation period of several months to years) prior to eculizumab and in all of these patients after eculizumab, within the first six months of treatment. Based on recurring FDA advice provided to us on 19Mar2019, 19Aug2019, 05Sept2019 and 07Apr2021, a second external control has been designed into the R3918-PLE-1878 study. Namely, the collection of data from study patients' charts over six months to several years, prior to baseline. These data are expected to provide further evidence that the improvement in clinical signs and symptoms and in albumin levels after pozelimab treatment is of an effect size that clearly exceeds the variability of the natural course of disease. Taken together, these considerations make a trial

design that uses external controls a scientifically reliable means to assess the effect of pozelimab. Further discussion may be found in Section 3.2.1 of the protocol.

1.2. Revision History for SAP Amendments

Summary of Changes from Version 1 to Version 2	
Change and Rationale for Change	**Sections changed**
Details of most bothersome signs/symptoms analysis, bowel movement frequency and stool consistency, and facial and peripheral edema. Revisions made to address health authority recommendation.	Section 4.5.2 Section 4.10 Section 5.7.1
Additional supportive analyses included for time periods 24-48 weeks and 48-104 weeks to assess maintenance of efficacy. Revisions made to address health authority recommendation.	Section 5.7.2
An additional database lock included at week 12.	Section 7
Summary of Changes from Version 2 to Version 3	
Change and Rationale for Change	**Sections changed**
Edits and additions, due to amendments and interactions with FDA, and for added clarity.	Section 1 Section 1.1
Moved summary of changes to Section 1.2.	Section 1.2
Minor changes to design details, due to amendments and interactions with FDA.	Section 2.1 Section 2.2
Changes to efficacy variables, due to amendments and interactions with FDA.	Section 4.5
Re-arrangement: Moved part of 5.9.2.1 text to 4.8 and added some details. Removed details of NAb assay in the immunogenicity sections.	Section 3.6 Section 4.8 Section 5.9.2 Section 5.9.3

COAs: Additional detail for variable descriptions.	Section 4.10
Additional details and changes to efficacy analyses due to amendments.	Section 5.7
Added statements about COVID-19 data considerations.	Section 6.3
Changes in SOE due to amendments and interactions with FDA.	Section 10.3
History of R3918-PLE-1878 Protocol and Statistical Analysis Plan Amendments added.	Section 10.4
Summary of Changes from Version 3 to Version 4	
Change and Rationale for Change	**Sections changed**
Edits and additions, due to amendments and for added clarity.	Section 1 Section 1.1
Due to extension of study duration, updated endpoints and study design language with previous wording of week 104 to include full 144-week study treatment period	Section 1.3.2 Section 2.1 Section 4.5.2, 4.5.3 Section 4.6 Section 4.10 Section 5.7.2
Treatment duration timepoints updated to match visit schedule study days and 144-week study treatment period	Section 5.6.2
Removal of reference to open label extension	Section 5.8.1
Schedule of events updated to reflect protocol amendment 6	Section 10.2

1.3. Study Objectives

1.3.1. 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 between weeks 12 and 24, and
2. Improvement in the following clinical outcomes that were 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

1.3.2. 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

1.3.3. 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

1.3.4. Modifications from the Statistical Section in the Final Protocol

There are no modifications from the statistical section of the protocol.

2. INVESTIGATION PLAN

2.1. 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 or older (exception will be made for patients under 6 years of age with life-threatening disease).

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.

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 with final dose at week 143), and a follow-up period to week 164.

Active PLE is defined as hypoalbuminemia of less than or equal to 3.2 g/dL within the screening period, and at least 7 days (which do not have to be consecutive) of one or more of the following symptoms or signs within the 6 months prior to enrolment: 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 and are recommended to receive daily oral antibiotic prophylaxis and counselling regarding risk of Neisseria gonorrhea, as applicable. Subsequent to the first 2 patients, in addition to the active patient population heretofore described, patients who are well-controlled on eculizumab will be provided an option of switching to pozelimab to avoid IV infusion.

2.2. Success Criteria, Sample Size and Power Considerations

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

The study is regarded as successful if at least 4 of 6 evaluable patients with active PLE achieve the primary endpoint. Patient-level data of 14 patients treated with eculizumab were made available to the study sponsor (Ozen, 2021) (Kurolap, 2019). 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 with active PLE achieving the primary endpoint provides strong evidence of effectiveness.

All of the aforementioned 14 historically 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.

2.3. Study Plan

The study event table is presented in Section 10.2.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following populations will be used for statistical analysis:

3.1. The Full Analysis Set (FAS)

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.

3.2. The Per Protocol Set (PPS)

The per protocol (PPS) includes those patients in the FAS who did not discontinue study drug early and who had no major protocol deviations that potentially affected efficacy.

3.3. The Safety Analysis Set (SAF)

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.

3.4. The Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic (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.

3.5. Anti-drug Antibody Analysis Set (AAS)

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

3.6. Exploratory Biomarker Endpoint Analysis Set

The exploratory biomarker endpoint (PD) analysis population includes all patients who received any study drug and who had at least 1 non-missing analyte measurement following the first dose of study drug.

3.7. Clinical Outcome Assessment Analysis Set

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

- For the bowel movement e-diary, data will be considered missing for a given week if bowel movement or consistency data have not been entered in the diary for >3 days in that week
- For the total score of the PedsQL™ Generic Core Scales and Family Impact Scale as well as the dimensions of the PedsQL™ Generic Core Scales, GI Symptoms Scales, and Family Impact Module, data will be considered missing if more than 50% of the items in the scale or dimension are missing

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Baseline Weight
- Baseline Weight (z-score)
- Baseline Height
- Baseline Height (z-score)
- Baseline Body Mass Index (BMI) calculated from weight and height

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

A detailed chart review will be undertaken on all subjects focusing on the 6 to 12 months prior to baseline, recording evidence of the severity of clinical signs and symptoms, with an emphasis on the core disease features of abdominal pain, diarrhea (bowel movement frequency and loose/watery stool consistency), facial and peripheral edema, nausea and vomiting. In addition, the following historical data will be summarized:

- All available albumin, total protein and total immunoglobulin data from birth
- *Neisseria meningitidis* vaccination history
- Other vaccination history
- All available history of hospitalizations from birth
- All available history of body weight and height from birth
- All available history of albumin infusions and prior thromboembolic events from birth
- Tuberculosis history
- Demonstration of CD55 gene loss of function (and absence of CD55 protein, if necessary)
- All available genetic sequencing data

4.3. Prior/Concomitant Medication and Procedures

Medications will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded to the Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of World Health Organization Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Prior medications are medications taken prior to administration of the first dose of study drug. Concomitant medications are medications taken between the first dose of study drug and the EOS visit.

Prior/concomitant medications, including meningococcal vaccinations and oral antibiotic prophylaxes, will be summarized.

Prior/concomitant procedures will be recorded. Prior procedures are procedures performed prior to administration of the first dose of study drug. Concomitant procedures are procedures performed between the first dose of study drug and the EOS visit.

Eculizumab administration history will be included in a listing.

Historical prednisolone usage and albumin infusions will be collected in detail.

4.4. Prohibited Medication During Study

The following medications are prohibited, with the exception of those listed in Section 8.10.2 of the protocol 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.
- 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.
- No Vitamin B12 supplementation during the first 4 weeks of pozelimab treatment (i.e., cannot be initiated prior to week 4 visit)

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variable

The primary efficacy variable 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 signs/symptoms that were evaluable for improvement at baseline, with no worsening of the others (i.e. 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 (daily average from the e-diary from the last 7 days pre-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 (baseline visit value). 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 (baseline visit value). 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 Symptoms Scales. 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 (baseline visit score). Worsening is defined as a decrease of 25 points or more.

4.5.2. Secondary Efficacy Variables

The secondary efficacy endpoints are:

- 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, frequency of problematic abdominal pain (as described in Section 4.5.1), nausea and 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 Symptoms Scales 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, 48-144 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 frequency of problematic abdominal pain (≥25 point decrease on the Stomach Pain and Hurt subscale of the PedsQL GI Symptoms Scales) or diarrhea subscale of the PedsQL GI Symptoms Scales (≥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 (e.g., 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, 48-144 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 frequency of problematic abdominal pain (≥25-point decrease on the PedsQL GI Symptoms Scales' stomach pain and hurt sub-scale); or frequency of problems with diarrhea (≥25-point decrease on the PedsQL GI Symptoms Scales' diarrhea subscale)
  - 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 (e.g., 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 for patients 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 Symptoms Scales 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 after week 12 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 (e.g., azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation, anti-coagulants (e.g., low-molecular-weight heparin), antibiotics (with the exception of those used for the purpose of Neisserial prophylaxis), anti-platelet agents (e.g., low-dose aspirin)
- Hospitalization days (per 24-week period) 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 to pozelimab in patients over time
- Change and percent change from baseline of total complement activity CH50 over time

4.5.3. Exploratory Efficacy Variables

- 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 of problematic diarrhea and nausea/vomiting as measured by the PedsQL™ GI Symptoms Scales' diarrhea sub-scale and nausea and vomiting sub-scale 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)
- Radiographic features of PLE as captured by unscheduled abdominal imaging assessments taken as part of standard clinical care over time

4.6. Safety Variables

"Incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables from baseline to week 144" is listed in the protocol as a secondary endpoint.

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of study. All adverse events are to be coded to a PT and associated primary SOC according to the Medical Dictionary for Regulatory Activities (MedDRA, the Version 10 or the latest current available version).

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

A Serious Adverse Event is an adverse event (AE) that is classified as serious according to the criteria specified in the protocol.

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.

The severity of AEs that are not infusion reactions, or are not covered in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, 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.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. The following are the AESIs in this study (as provided in the protocol), along with the approach for summarizing them:

- Moderate or severe infusion reactions (use SMQ "Infusion related reactions")
- Confirmed Neisseria infection (use preferred term)
- Any thrombotic or embolic event (use SMQ "Embolic and thrombotic events")

4.6.3. Laboratory Safety Variables

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional units will be provided. The following laboratory tests are given in the table in Section 10.2, with details in the footnotes:

- Blood Chemistry Panel
- Lipid Panel
- Blood Immunoglobulin Panel
- Micronutrient Panel
- Hematology
- Coagulation Panel
- Urinalysis
- Other Laboratory Tests

4.6.4. Vital Signs

Vital signs variables include temperature, sitting blood pressure, and pulse, collected predose at time points according to the table in Section 10.2.

4.6.5. 12-Lead Electrocardiography (ECG)

Twelve-lead ECG parameters include ventricular rate, heart rate and the PR/PQ, QRS, RR, QT, and QTcF intervals.

4.6.6. Physical Examination Variables

Physical examination variables include results of evaluations of head and neck, lungs, heart, abdomen, extremities, and skin, as well as height and body weight.

4.7. Pharmacokinetic Variables

The PK variable is the concentration of total pozelimab, total C5, and time shown in Section 10.2.

4.8. Immunogenicity Variables

The immunogenicity variables are anti-drug antibody (ADA) status, titer at nominal time point/visit. Samples in this study will be collected at the clinic visits specified in Section 10.2. PK sample at Week 4 may be analyzed for ADA in patients positive for ADA at week 12 or the first time point analyzed, provided there is sufficient volume.

4.9. Exploratory Biomarker Endpoint Variables

Exploratory variables may include but are not limited to:

- Markers of thrombosis: D-dimer, and N terminal prothrombin fragments [F1+2)]
- 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.

4.10. Clinical Outcome Assessments (COAs)

The following clinical outcome assessments (COAs) will be included:

- The number of bowel movements per day, based on a one-week average, captured by e-diary from baseline to week 24 will be assessed through daily completion of an e-diary.

  Notes: The daily e-diary, developed specifically for this study, will capture frequency of bowel movements over a 24-hour period. The e-diary will be completed by the patient 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. The number of bowel movements per day will be calculated each week of the study. It will be based on a one-week average and calculated as the sum of the number of bowel movements in a given week divided by the number of days with non-missing bowel movement frequency data. If more than 3 days of bowel movement data is missing in a given week, bowel movement frequency data will be considered missing for that week. Bowel movement frequency data will be summarized overall and by respondent type.

- The number of days/week with ≥1 bowel movement with loose/watery stool consistency as measured by the Bristol Stool Form Scale (BSFS) for patients who are 18 years of age and older, modified Bristol Stool Form Scale for Children (mBSFS-C) for patients who are toilet-trained and less than 18 years of age, or the BITTS for patients who are not toilet-trained, and captured by e-diary from baseline to week 24.

  Notes: The consistency of each bowel movement will be captured using the daily e-diary which will be completed by the patient if aged 12 years of age and older or completed by the caregiver if the patient is less than 12 years of age (with input from the patient). Stool consistency will be evaluated using the BITTS for patients who are not toilet-trained, the mBSFS-C for patients <18 years of age, and the BSFS for patients ages 18 years of age and older. The BITTS, mBSFS-C, and BSFS each have a unique set of images and text-based descriptors as response options. The BITTS consists of 7 photographs of different stool forms and consistencies: 1) hard stools (3 images); 2) formed stools (1 image); 3) loose stools (2 images); and 4) watery

stools (1 image). The mBSFS-C categorizes the form of stool into 5 categories using drawings with written descriptors: 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 BSFS categorizes the form of human feces into 7 categories using drawings and written descriptions: 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. Loose/watery stool consistency will be defined as the three images of loose or watery stools on the BITTS, the images and descriptors for categories 4 or 5 on the mBSFS-C, and the images and descriptors for categories 6 or 7 on the BSFS. The number of days/week with ≥1 loose/watery bowel movement, calculated each week of the study as the sum of the number of days with ≥1 loose/watery bowel movement in a given week divided by the number of days with non-missing stool consistency data and then multiplied by 7, will be presented. If more than 3 days of stool consistency data are missing in a given week, stool consistency data will be considered missing for that week. Stool consistency data will be summarized overall and by respondent type.

- Frequency of problematic abdominal signs and symptoms, as assessed by the PedsQL™ GI Symptoms Scales' stomach pain and hurt sub-scale, food and drink limits sub-scale and diarrhea subscale from baseline to week 144.

  Notes: The Stomach Pain and Hurt, the Food and Drink Limits, and the Diarrhea subscales of the PedsQL™ GI Symptom Scale ask the patient (if age >=12 years) or caregiver (if patient <12 years) to rate how much of a problem each item concept has been over the past 7 days on a 5-point response scale, ranging from never (0) to almost always (4). Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate less frequency of problems with abdominal signs and symptoms. To reverse score, the 0-4 scale items will be transformed to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0. The mean score is estimated as the sum of the items over the number of items answered. If more than 50% of the items in the scale are missing, the Scale Score will not be calculated. Scores on the PedsQL(TM) subscales will be summarized overall and by respondent type.

- 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

  Notes: In the PedsQL Generic Core Scales, the patient (if age >=12 years) or caregiver (if patient age <12 years) rates how much of a problem each item concept has been over the past 7 days on a 5-point response scale, ranging from never (0) to almost always (4). For patients >2 years of age there are 8 items assessing physical functioning, 5 items assessing emotional functioning, 5 items assessing social functioning, and 5 items assessing school/work functioning. For patients 13 months to

24 months, there are 9 items assessing physical functioning, 10 items assessing physical symptoms, 12 items assessing emotional functioning, 5 items assessing social functioning, and 9 items assessing cognitive functioning. Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate better HRQoL. To reverse score, the 0-4 scale items are transformed to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0. The mean score for the physical functioning and work/school functioning subscales for patients ages 2 years of age and older will be estimated as the sum of the items over the number of items answered in that scale. For patients ages 13 to 24 months, the Physical Health Summary Score will be calculated as the sum of the items in the physical functioning and physical symptoms scales divided by the number of items answered in those scales. If more than 50% of the items in the scale are missing, the scale scores will not be calculated. The total score will be calculated as the sum of all the items over the number of items answered on all the scales. The PedsQL(TM) Generic Core Scales Total and Physical Health Summary Scores will be reported separately for patients 13 to 24 months. Total and subscale scores for patients >2 years will be summarized overall and by respondent type.

- GI signs and symptoms (Diarrhea sub-scale and Nausea and vomiting sub-scale) as measured by the (PedsQL™ GI Symptoms Scales from baseline over time.

  Notes: The Diarrhea as well as the Nausea and Vomiting subscales of the PedsQL™ GI Symptom Scale have 7 and 4 items, respectively, in which the patient (if age >=12 years) or caregiver (if patient age <12 years) rates how much of a problem each item concept has been over the past 7 days on a 5-point response scale, ranging from never (0) to almost always (4). Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate less frequency of problems with abdominal signs and symptoms. To reverse score, the 0-4 scale items will be transformed to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0. The mean score is estimated as the sum of the items over the number of items answered. If more than 50% of the items in the scale are missing, the Scale Score will not be calculated. The subscale scores will be summarized overall and by respondent type.

- Caregiver well-being and burden as measured by the PedsQL™ Family Impact Module from baseline over time.

  Notes: In the PedsQL™(TM) Family Impact Module, the caregiver rates how much of a problem each item concept has been for the caregiver (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 scale ranging from never (0) to almost always (4). There are 6 items assessing physical functioning, 5 items assessing emotional functioning, 5 items assessing social functioning, 5 items assessing cognitive functioning, 3 assessing communication, 5 assessing worry, 3 assessing daily activities, and 5 assessing family relationships. Items are reverse-scored and linearly transformed to a 0 to 100 scale so that higher scores indicate better HRQoL for the caregiver and family of patients. To reverse score, the 0-4 scale items are transformed to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0. The mean score for the physical functioning and work/school functioning subscales will be estimated as the sum of the items over the number of items answered in that scale. If more than 50% of the items in the scale are missing, the scale scores will not be calculated. The Parent Health-Related Quality of Life Summary Score (20 items) is the sum of the items divided by the number of items in the physical functioning, emotional functioning, social functioning, and cognitive functioning scales. The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered in the Daily Activities and Family Relationship scales. The total score and the Parent Health-Related Quality of Life Summary Score will be reported.

- Clinician global impression of change (CGIC) over time to week 144.

  Notes: The CGIC is a question which asks the treating physician to rate the change in the severity of disease over the course of the study on a 7-point response scale ranging from much worse (-3) to no change (0) to much better (3).

- Clinician global impression of severity (CGIS) from baseline to week 144.

  Notes: The CGIS is a question which asks the treating physician to rate the severity of signs and symptoms of disease on a 5-point response scale ranging from no sign/symptoms (0) to very severe (4).

- Patient/caregiver global impression of change (PGIC/CareGIC) over time to week 144.

  Notes: The PGIC consists of 6 questions and the CareGIC consists of 5 questions which assess from the perspective of the patient (if age >=12 years) or caregiver (if age <12 years), respectively, the change in overall disease severity, diarrhea, stomach pain (PGIC only), impact of disease on school/work, impact of disease on physical functioning, and impact of disease on food and drink limitations since the patient started the study medication. Patients or caregivers will rate the change of the sign/symptom or impact on a 7-point response scale ranging from much worse (-3) to

no change (0) to much better (3). Responses on the PGIC and CareGIC scores will be reported overall and stratified by respondent type.

- Patient/caregiver global impression of severity (PGIS/CareGIS) from baseline to week 144.

  Notes: The PGIS consist of 6 questions which assess, from the perspective of the patient (if age >=12 years), overall disease severity, diarrhea, stomach pain, impact of disease on school/work, impact of disease on physical functioning, and impact of disease on food and drink limitations. Patients will rate the severity of the sign/symptom or impact on a 5-point response scale ranging from absent (0) to very severe (4) for overall disease severity and sign/symptoms or from not at all (0) to very much (4) for the disease impacts. The CareGIS consist of 5 questions which assess, from the perspective of the caregiver (if patient age <12 years), overall disease severity, diarrhea, impact of disease on school/work, impact of disease on physical functioning, and impact of disease on food and drink limitations. Caregivers will rate the severity of the sign or impact on a 5-point response scale ranging from absent (0) to very severe (4) for overall disease severity and signs or from not at all (0) to very much (4) for the disease impacts. PGIS and CareGIS will be reported overall and stratified by respondent type.

- If appropriate to age and stage of sexual maturation, the Tanner pubertal stage

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For longitudinal data, changes and/or percentage changes will be summarized as appropriate.

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Continuous data will be summarized using the number of patients with data, mean, median, standard deviation, Q1, Q3, minimum and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

5.2. Medical History

Medical history will be descriptively summarized overall for the study in safety population.

All reported patient medical history will be presented by primary SOC and PT. The tables will be presented by SOC sorted alphabetically and decreasing patient frequency of PT. In addition, all medical history of specific interest, as described in Section 4.2, will be summarized by patient incidence and percentage.

5.3. Prior/concomitant Medications

All prior medications, dictionary coded by WHODD, will be descriptively summarized for the study, for patients in the safety set. Summaries will present patient counts (and percentages) for all prior medications, by decreasing frequency of the overall incidence of ATC followed by therapeutic class. In the case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication but may be counted again for a different category if the same medication falls under multiple categories.

All concomitant medications during the treatment period, dictionary coded by WHODD, will be descriptively summarized for patients in the safety set. In the case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, and hence may be counted again for a different category if the same medication falls under multiple categories.

For the follow-up period, medications will be dictionary coded by WHODD and will be descriptively summarized as described for the treatment period. Summaries will present patient counts (and percentages).

5.4. Prohibited Medications

A listing of prohibited medications, found in Section 4.4, will be provided for the patients in the safety analysis set for the treatment period and follow-up period.

5.5. Patient Disposition

The following displays will be provided:

- The total number of screened patients: signed the ICF
- The total number of enrolled patients
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Compliance with protocol-defined investigational product will be calculated as follows:

> Treatment Compliance = (Number of investigational product doses taken during study period)/(Number of investigational product doses prescribed to be taken during period) x 100%,

where temporary dose discontinuation is ignored. IV and SC doses will be analyzed separately and combined for this compliance analysis.

The percentage of patients who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized.

5.6.2. Exposure to Investigational Product

Exposure to investigational product will be examined for each patient.

The total number of complete and incomplete injections administered will be summarized for infusions and SCs combined and also separately. SC injection location will also be summarized.

In addition, duration of treatment will be calculated as: [last dose day] – [first dose day] + 1. The number of patients exposed to the investigational product will be presented by specific time periods. Time periods of interest are as follows:

- ≥ Day 29
- ≥ Day 57
- ≥ Day 85
- ≥ Day 169
- ≥ Day 337
- ≥ Day 1,002

In addition, frequencies and percentages of SC injections by location will be presented.

5.7. Analyses of Efficacy Variables

5.7.1. Analysis of Primary Efficacy Variable

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 (defined in Section 4.5.1) and achieving improvement in the prespecified clinical outcomes listed in Section 4.5.1 will be calculated and its 90% exact CI will be reported.

There are 7 planned albumin measurements between week 12 and week 24 inclusive. Patients will be considered not evaluable for the primary analysis if there are fewer than 5 available albumin measurements between week 12 and week 24. Albumin measurements will be carried out at local laboratories and those within the 12 week visit to 24 visit range but outside of the visit windows will be considered as valid measurements. To be considered responders, at least 70% of available measurements, although not necessarily consecutive, 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) must have at least 70% of all available measurements normal. The mean changes from baseline in albumin over time will also be estimated and 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 4.5.1. Patients evaluable for only 1 of the 4 clinical outcomes must show improvement as defined in Section 4.5.1 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 physicians report. Clinical photographs will be rated by a single, central reader blinded to the timepoint 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; if missing, the screening measurement 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 visit value will be used
- Peripheral edema - The baseline visit value will be used

For the clinical outcome assessments, the rules for missing post-baseline data are as follows:

- Facial edema and peripheral edema: A measure is required at Week 20 and/or Week 24 (and the last observed measure will be used)
- Bowel movement frequency: At least one valid week of measurements (defined as at least 4 of 7 days with measurements) is required in Weeks 20 through 24 (and the last week of observation will be used)
- Stomach Pain and Hurt sub-scale: A valid score at Week 24, or a calculable score at a non-scheduled assessment in weeks 20 through 24, is required

A patient is not evaluable for the primary endpoint if any of these rules for missing data fail to be met.

Regardless of assessability status with respect to missing data for albumin and the above clinical measures, a patient will be considered a non-responder if at least one of the following holds:

- The patient discontinues due to lack of efficacy
- The patient discontinues due to an adverse event
- The patient fails to achieve an albumin measure in the normal range at any visit
- The patient experiences no clinical improvement as defined in Section 4.5.1 at any visit

Sensitivity and subset analyses for the primary endpoint:

- Repeat of the primary analysis using non-responder imputation for patients with fewer than 5 available albumin measurements between week 12 and week 24; in this analysis, patients with fewer than 5 albumin measurements will be included in the analysis as non-responders
- Repeat of the primary analysis in which patients with baseline albumin >2.9 g/dL are non-evaluable, unless no such patients are recruited
- Repeat of the primary analysis, using the central reads of facial and peripheral edema, rather than the investigators' reads
- Per protocol analysis of the primary efficacy endpoint

Supportive analyses for the primary endpoint:

- Responder analysis based on improvement in clinical outcomes only

5.7.2. Analysis of Secondary Efficacy Variables

For the composite responder efficacy variables 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 6 planned albumin measurements between week 48 and week 144 inclusive. Patients will be considered non-evaluable for this secondary analysis if there are fewer than 4 available albumin measurements between week 48 and week 144. Within the range of weeks of interest, 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.

In addition, a repeat of the primary analysis, defining albumin normalization as having all available measurements in the normal range, will be performed.

For the above responder efficacy variables, the estimate and 90% exact confidence interval for the proportion responding will be presented.

The baseline measure for analyses of secondary efficacy variables will be the measure at the baseline visit (or the screening visit's value if the baseline value is missing), with the following exceptions:

- Week 12, 24 and 48 clinical outcomes are used as baseline for measures of maintenance of effect
- The bowel movement frequency efficacy variable will be assessed using the diarrhea sub-scale of the PedsQL™ GI Symptoms Scales

For continuous secondary outcomes, patient profiles over time will be tabularly and graphically presented. Changes (and/or percentage changes, as appropriate) from baseline in these outcome measures over time will be summarized with mean and 90% CI. There are 3 basic types of endpoints that are considered continuous: (1) Labs or other measurements, (2) Single item scales with 5 to 7 levels, and (3) Scales based in multiple items, each with several levels.

Labs or other measurements:

- Assessment of abdominal ascites (assessed by measurement of abdominal circumference) from baseline to week 24
- 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 stool to blood ratio, and change from baseline to week 12 and week 24
- Body weight and height, (expressed as z-scores) over time; plots of raw values over time separately will be given for individual patients
- Absolute value and percent change from baseline of total complement CH50 assay over time

(2) Single item scales:

- 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

(3) Scales based on multiple items:

- Change in abdominal symptoms, as assessed by the PedsQL™ GI Symptoms Scales stomach pain and hurt sub-scale, food and drink limits, and diarrhea sub-scales 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

For count secondary outcomes, counts per day or per other period of time will be summarized:

- Number of hospitalization days per 24-week period in the following time periods: -24 weeks to baseline, baseline to 24 weeks, 24 to 48 weeks, 48 to 72 weeks and 72 to 96 weeks.
- The number of bowel movements per day, based on a one-week average, captured by e-diary from baseline to week 24
- Frequency of albumin infusions expressed as number per 24-week period in the following time periods: -24 weeks to baseline, baseline to 24 weeks, 24 to 48 weeks, 48 to 72 weeks and 72 to 96 weeks.
- Cumulative dose of corticosteroids (in hydrocortisone equivalents) divided into the following time periods: -24 weeks to baseline, baseline to 24 weeks, 24 to 48 weeks, 48 to 72 weeks and 72 to 96 weeks.
- IV or SC immunoglobulin, biologic immunomodulators (anti-TNF, vedolizumab), small molecule immunomodulators (e.g., azathioprine, mesalazine), micronutrients, enteral or parenteral supplementation, anti-coagulants (e.g., low-molecular-weight heparin), antibiotics (with the exception of those used for the purpose of Neisserial prophylaxis), anti-platelet agents (e.g., low-dose aspirin) will be listed.
- Stool consistency is measured by the Bristol Stool Form Scale (BSFS) for patients who are 18 years of age and older, modified Bristol Stool Form Scale for Children (mBSFS-C)for patients who are toilet-trained and less than 18 years of age, or the BITTS for patients who are not toilet-trained, and captured by e-diary from baseline to week 24. The number of days/week with ≥1 loose/watery bowel movement, calculated each week of the study as the sum of the number of days with ≥1 loose/watery bowel movement in a given week divided by the number of days with non-missing stool consistency data, multiplied by 7, will be presented.

For time-to-event secondary outcomes, including time to first normalization of serum albumin and other tests listed above, times for patients will be summarized using Kaplan-Meier methods.

For the assessment of response for the most bothersome symptom, a patient will be considered a responder if he/she meets the a priori pre-defined threshold for response as defined in Section 4.5.2 for his/her most bothersome symptom.

5.7.3. Analysis of Exploratory Efficacy Variables

If the Tanner pubertal stages are performed, the information will be presented in a listing. All other exploratory efficacy variables will be summarized in the same manner as the continuous secondary efficacy variables.

With a few exceptions, the baseline measure for analysis of exploratory efficacy variables will be the measure at the baseline visit (or the screening visit's value if the baseline value is missing). Exceptions: There is no baseline measure for CGIC or PGIC/CareGIC.

5.8. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.3.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG).

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Section 10.3.

The summary of safety results will be presented for each treatment group.

5.8.1. Adverse Events

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

Day 1 is the first day of investigational product dosing, Day –1 is the day before, and there is no Day 0.

Pre-treatment AEs are defined as AEs that developed or worsened during the pre-treatment period. The pre-treatment period is defined as the time between when the patient gives informed consent and just before the start of investigational product dosing.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period. The on-treatment period is defined as the time from first dose of investigational product up to 21 weeks after the last dose of investigational product.

Post-treatment AEs are AEs that developed or worsened during the post-treatment period.

The focus of adverse event summaries in the clinical study report will be on TEAEs.

For details on handling missing data and partial dates, see Section 6.

Summaries of all TEAEs 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 4.6.1), presented by SOC and PT
- Treatment related TEAEs, presented by SOC and PT
- Treatment-emergent AESIs (defined by experiencing a prespecified PT or prespecified grouping of PTs, or by being put in a grouping specified in the CRF)

Deaths and all SAEs will be summarized.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be summarized.

Summaries of all TEAEs will include:

- All TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Serious adverse events: All TEAEs by SOC and PT
- Death: All fatal TEAEs by SOC and PT
- Discontinuation: All TEAEs by SOC and PT
- Non-serious related TEAEs by SOC and PT

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the safety population in each treatment group.

Primary SOCs will be sorted according to the order described in the Guideline on summary of product characteristics (December 1999, European commission), with the total overall classes coming first and labeled "Any class". Within each primary SOC, PTs will be sorted by decreasing frequency of investigational product.

A second type of table with counts of each primary SOC in decreasing order of frequency will be provided. A third type of table with counts of each PT in decreasing order of frequency will also be provided.

5.8.2. Analysis of Adverse Events of Special Interest

Treatment emergent adverse events of special interest (listed in Section 4.6.2) will be presented by SOC and PT (when selection is based on the e-CRF tick box). The summaries will be sorted by decreasing incidence of PT within each SOC.

5.8.3. Clinical Laboratory Measurements

A treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal at Screening and Baseline but abnormal after treatment with investigational product, or a laboratory value that was abnormal at Baseline and exacerbates after treatment with investigational product. "Exacerbations" will be identified by the Medical Monitor using clinical judgment.

Baseline clinical laboratory analytes and change from Baseline in clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics.

For categorical urinalysis variables, counts and percentages will be presented.

5.8.4. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics. The graphs of mean (or median) value of some vital sign parameter vs. visit will also be plotted.

5.8.5. Analysis of 12-Lead ECG

ECG parameters (PR interval, QT interval, QTcF interval, QRS interval, and heart rate [from ventricular rate]) will be summarized by visit and change from Baseline to each scheduled and collected assessment time.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal).

5.9. Analysis of Pharmacokinetic and Immunogenicity Data

5.9.1. Analysis of Pharmacokinetic Data

Descriptive statistics of concentrations of total pozelimab and total C5 will be presented. Mean concentrations of each analyte will be tabulated by visit and treatment group, with concentrations below the LLOQ set to zero.

Plots of the mean concentrations will be presented by nominal sampling time. Plots of the individual concentrations will be presented by actual sampling time. In the linear-scaled plots, concentrations below the LLOQ will be set to zero; in the log-scaled plots, concentrations below the LLOQ will be imputed as LLOQ/2.

5.9.2. Analysis of Immunogenicity Data

5.9.2.1. Analysis of ADA Data

Immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category and maximum titer observed in patients in the ADA analysis set.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay.

Treatment-emergent is further sub-categorized as:

- Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
- Transient - Not persistent or indeterminate, regardless of any missing samples
- Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

The maximum titer of each patient is classified as:

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

The following analysis will be provided:

- Number (n) and percent (%) of pre-existing patients
- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients

A listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.9.3. Association of Immunogenicity with Exposure, Safety and Efficacy

5.9.3.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to pozelimab will be explored by treatment. Plots of individual pozelimab concentration time profiles may be provided to examine the potential impact of ADA category and maximum titer on these profiles.

5.9.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-first dose titer in treatment-emergent or treatment-boosted ADA positive patients:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

5.10. Analysis of Pharmacodynamics and Biomarkers

For the thrombosis and complement activation biomarker variables described in Section 4.9, descriptive statistics (means and mean changes) will be presented by visit. Where applicable, plots of means and mean changes will be presented by visit.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product. If the scheduled Baseline Day 1 measurements are not available, screening assessments may be used; when scores are used, this rule applies to scores, not individual variables.

6.2. Data Handling Convention for Efficacy Variables

In Section 4.10, COAs are discussed. The rules for number of missing items necessary for a scale to be missing are given, as well as the number of days in a week with no counts necessary for a weekly count to be missing.

In Section 5.7.1, the primary analysis and sensitivity and supportive analyses are discussed. The rules for number of missing measures necessary for a patient to be non-evaluable or a non-responder, depending on the analysis, are given.

In Section 5.7.2, similar rules are given for secondary efficacy responder analyses.

6.3. Data Handling Convention for Missing Data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

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. For analysis purposes, these data will be treated the same as data collected under normal circumstances.

6.3.1. Adverse events

If the severity of a TEAE is missing, it will be classified as “severe” in the frequency tables by severity of TEAE. If the measurement of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, in order to simplify the programming flow, the imputation is proposed to align with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

6.3.2. PCSV

Patients who had post-baseline PCSV, but missing baseline value will be regarded as having treatment emergent PCSV.

6.3.3. Date of first / last study drug administration

Date of first study drug administration is the first non-missing start date of dosing filled in the CRF "Investigational Product" module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.4. Visit Windows

Data analyzed by visit (including efficacy, laboratory data, visit sign, ECG) will be summarized by the study scheduled visits described in Section 10.2 (Schedule of Time and Events). Analysis visit windows will be constructed using ranges applied to the number of days in study (study days) when the measure is collected, with the general rule of windows being half-way between consecutive visits' target days. There will be no gaps, so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. Analysis visit windows will not be applied to study scheduled visits.

6.5. Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries, except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. INTERIM ANALYSIS

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

- The first database lock takes place at 12 weeks from the first dose in the fourth active patient, for an FDA meeting
- The second database lock for reporting on the primary efficacy endpoint takes place at 24 weeks from the first dose in the eighth active patient
- The third database lock and reporting of longer-term effects takes place at 1 year from first dose in the last patient
- The fourth database lock and reporting of longer-term effects takes place at 2 years from first dose in the last patient

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

9. REFERENCES

ICH. E9 Statistical Principles for Clinical Trials (ICH Harmoised Tripartite Guideline). 1998; International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Kurolap A, Eshach-Adiv O, Hershkovitz T, Paperna T, Mory A, Oz-Levi D, et al. Loss of CD55 in Eculizumab-Responsive Protein-Losing Enteropathy. N Engl J Med 2017; 377(1):87-89.

Kurolap A, Eshach Adiv O, Hershkovitz T, Tabib A, Karbian N, Paperna T, et al. Eculizumab Is Safe and Effective as a Long-term Treatment for Protein-losing Enteropathy Due to CD55 Deficiency. J Pediatr Gastroenterol Nutr 2019; 68(3):325-333.

Ozen A, Comrie WA, Ardy RC, Dominguez Conde C, Dalgic B, Beser OF, et al. CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis. N Engl J Med 2017; 377(1):52-61.

Ozen A, Kasap N, Vujkovic-Cvijin I, Apps R, Cheung F, Karakoc-Aydiner E, et al. Broadly effective metabolic and immune recovery with C5 inhibition in CHAPLE disease. Nat Immunol 2021; 22(2):128-139.

10. APPENDIX

10.1. Summary of Statistical Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Efficacy analysis	FAS	Confidence intervals	No	Yes	Yes
Adverse Events	SAF	Descriptive Statistics	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Events

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

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
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
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

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
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

10.2.1. 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 Protocol 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 Protocol Section 8.3.1 for details.
7. Risk assessment for *Neisseria gonorrhea* is described in Protocol 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 Protocol Section 9.2.3.3.
10. Meningococcal vaccination is required and daily oral antibiotic prophylaxis is recommended as described in Protocol 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 Protocol 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 Protocol Section 9.2.4.4 Laboratory Testing.
21. See Blood Immunoglobulin Panel in Protocol 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 Protocol Section 9.2.1.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical chemistry		
ALT	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	FDA DILI Guidance July 2009
AST	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	FDA DILI Guidance July 2009
Alkaline Phosphatase	> 1.5 ULN	FDA DILI Guidance July 2009
Total Bilirubin	≥1.3 ULN (Under 18 yrs) > 1.5 ULN (18 yrs +) > 2 ULN (18 yrs +)	FDA DILI Guidance July 2009
ALT and Total Bilirubin	ALT ≥ 3 ULN and Total Bilirubin ≥ 2 ULN (under 18 yrs) ALT > 3 ULN and Total Bilirubin > 2 ULN (18 yrs +)	FDA DILI Guidance July 2009
CPK	> 3 ULN >10 ULN	FDA Feb 2005 Am J Cardiol April 2006 Categories are cumulative First row is mandatory.
Creatinine	≥ 30% increase from baseline ≥ 60% increase from baseline	Benichou C., 1994

Parameter	PCSV	Comments
Sodium	≤129 mmol/L (Under 18 yrs) ≥ 150 mmol/L (Under 18 yrs) ≤129 mmol/L (18 yrs +) ≥ 160 mmol/L (18 yrs +)	Must also be outside the normal range.
Potassium	≤3.5 mmol/L or 3.5 mEq/L (Under 2 yrs) ≥6.0 mmol/L or 6.0 mEq/L (Under 2 yrs) ≤3.5 mmol/L or 3.5 mEq/L (2 to 17 yrs) ≥5.5 mmol/L or 5.5 mEq/L (2 to 17 yrs) < 3 mmol/L (18 yrs +) ≥ 5.5 mmol/L (18 yrs +)	FDA Feb 2005 Must also be outside the normal range.
Total Cholesterol	≥6.20 mmol/L (Under 18 yrs) >7.74 mmol/L (18 yrs +)	Must also be outside the normal range.
Triglycerides	≥ 4.0 mmol/L	Must also be outside the normal range.
Glucose	Hypoglycaemia <2.7 mmol/L or 50 mg/dL (Under 18 yrs) Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted) (Under 18 yrs) ≤3.9 mmol/L and <LLN (18 yrs +) ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA May 2005, Jan 2008 Must also be outside the normal range.
CRP	>10 mg/L	FDA Sept 2005

Parameter	PCSV	Comments
Hematology		
WBC	<4.0 GIGA/L or 4,000 /mm3 (Under 2 yrs) >20.0 GIGA/L or 20,000 /mm3 (Under 2 yrs) <3.0 GIGA/L or 3,000 /mm3 (2 to 5 yrs) >16.0 GIGA/L or 16,000 /mm3 (2 to 5 yrs) <5.0 GIGA/L or 5,000 /mm3 (6 to 11 yrs) >17.0 GIGA/L or 17,000 /mm3 (6 to 11 yrs) <4.5 GIGA/L or 5,000 /mm3 (12 to 17 yrs) >13.5 GIGA/L or 17,000 /mm3 (12 to 17 yrs) < 3.0 Giga/L (3000/mm3) (Non-Black 18 yrs +) < 2.0 Giga/L (2000/mm3) (Black 18 yrs +) ≥ 16.0 Giga/L (18 yrs +)	Must also be outside the normal range.
Neutrophils	<1.2 GIGA/L or 1,200 /mm3 (Under 2 yrs) > 1 ULN (Under 2 yrs) <1.2 GIGA/L or 1,200 /mm3 (2 to 17 yrs) > 1 ULN (2 to 17 yrs) < 1.5 Giga/L (1,500/mm3) (Non-Black 18 yrs +) < 1.0 Giga/L (1,000/mm3) (Black 18 yrs +)	Must also be outside the normal range.
Eosinophils	>0.5 GIGA/L or 500 /mm3 Or >ULN if ULN >0.5 GIGA/L or 500 /mm3 (Under 18 yrs) >0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) (18 yrs +)	Harrisson 17th Ed, 2008.

Parameter	PCSV	Comments
Hemoglobin	< 1.40 mmol/L or 9.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL (Under 2 yrs) < 1.55 mmol/L or10.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL (2 to 17 yrs) ≤115 g/L (Male 18 yrs +) ≤95 g/L (Female 18 yrs +) ≥185 g/L (Male 18 yrs +) ≥165 g/L (Female 18 yrs +) Decrease from Baseline ≥20 g/L (18 yrs +)	Must also be outside the normal range.
Platelets	<100 GIGA/L or 100,000 /mm3 (Under 18 yrs) > 700 GIGA/L or 700,000 /mm3 (Under 18 yrs) < 100 Giga/L (100,000/mm^3) > 700 Giga/L (100,000/mm^3)	Must also be outside the normal range.
Vital Signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	
SBP	≤70 mmHg and decrease from baseline ≥20 mmHg (Under 2 yrs) ≥98 mmHg and increase from baseline ≥20 mmHg (Under 2 yrs) ≤70 mmHg and decrease from baseline ≥20 mmHg (2 to 5 yrs) ≥101 mmHg and increase from baseline ≥20 mmHg (2 to 5 yrs) ≤80 mmHg and decrease from baseline ≥20 mmHg (6 to 11 yrs) ≥108 mmHg and increase from baseline ≥20 mmHg (6 to 11 yrs) ≤90 mmHg and decrease from baseline ≥20 mmHg (12 to 17 yrs) ≥119 mmHg and increase from baseline ≥20 mmHg (12 to 17 yrs) ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg (18 yrs +) ≥ 160 mmHg and increase from baseline ≥ 20 mmHg (18 yrs +)	

Parameter	PCSV	Comments
DBP	≤34 mmHg and decrease from baseline ≥10 mmHg (under 2 yrs) ≥54mHg and increase from baseline ≥10 mmHg (Under 2 yrs) ≤34 mmHg and decrease from baseline ≥10 mmHg (2 to 5 yrs) ≥59mHg and increase from baseline ≥10 mmHg (2 to 5 yrs) ≤48 mmHg and decrease from baseline ≥10 mmHg (6 to 11 yrs) ≥72mHg and increase from baseline ≥10 mmHg (6 to 11 yrs) ≤54 mmHg and decrease from baseline ≥10 mmHg (12 to 17 yrs) ≥78 mmHg and increase from baseline ≥10 mmHg (12 to 17 yrs) ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg (18 yrs +) ≥ 110 mmHg and increase from baseline ≥ 10 mmHg (18 yrs +)	
Weight	≥ 5% decrease versus baseline	FDA Feb 2007
ECG parameters		Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
HR	≤80 bpm and decrease from baseline ≥20 bpm (Under 2 yrs) ≥175 bpm and increase from baseline ≥20 bpm (Under 2 yrs) ≤75 bpm and decrease from baseline ≥20 bpm (2 to 5 yrs) ≥140 bpm and increase from baseline ≥20 bpm (2 to 5 yrs) ≤ 50 bpm and decrease from baseline ≥ 20 bpm (Age 6 to 11 yrs) ≥ 120 bpm and increase from baseline ≥ 20 bpm (Age 6 to 11 yrs) ≤50 bpm and decrease from baseline ≥20 bpm (12 to 17) ≥120 bpm and increase from baseline ≥20 bpm (12 to 17) ≤50 bpm and decrease from baseline ≥20 bpm (18 yrs +) ≥120 bpm and increase from baseline≥20 bpm (18 yrs +)	

Parameter	PCSV	Comments
PR	≥ 140 ms (Under 2 yrs) ≥ 160 ms (2 to 5 yrs) ≥ 170 ms (6 to 11 yrs) ≥ 180 ms (12 to 17 yrs) >200 ms and increase from baseline ≥25% (18 yrs +) >220 ms and increase from baseline ≥25%(18 yrs +) >240 ms and increase from baseline ≥25% (18 yrs +)	
QRS	≥85 ms (Under 2 yrs) ≥95 ms (2 to 5 yrs) ≥ 100 ms (6 to 11 yrs) ≥ 110 ms (12 to 17 yrs) >110 ms and increase from baseline ≥25% (18 yrs +) >120 ms and increase from baseline ≥25% (18 yrs +)	

Parameter	PCSV	Comments
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms (Under 12 yrs) Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms (12 to 17 yrs) >450 ms >480 ms >500 ms AND Increase from baseline [30-60] ms Increase from baseline >60 ms (18 yrs +)	To be applied to QTcF correction formulas

10.4. History of R3918-PLE-1878 Protocol and Statistical Analysis Plan Amendments

The original Statistical Analysis Plan (SAP) was submitted to the FDA on 03Jan2020 prior to the first patient being screened in the R3918-PLE-1878 study on 24Feb2020. The study had been designated as safe to proceed on 5Sep2019 following an Investigation New Drug (IND) application submission.

Five amendments to the study R3918-PLE-1878 protocol and one amendment to the SAP have been submitted to the FDA, based on feedback received from the Agency. A second amendment to the SAP (the current document, Version 3.0) consistent with the final protocol amendment has been authored and will be submitted to the Agency. All protocol amendments have not required an amendment to the SAP.

This Appendix provides a brief summary of sequence of protocol and SAP amendments as related primarily to key study design requirements from the Agency.

On 02Jan2019, the Sponsor approved a protocol for the R3918-PLE-1878 study, for discussion with the Agency at a pre-IND meeting on 19Mar2019. The FDA advised the Sponsor to ensure that sufficient historical data are collected on each trial patient in order to be able to interpret changes from baseline in the context of disease variability prior to baseline and to show that treatment effect size is clearly greater than that due to disease variability. Additionally, the Agency request the Sponsor to make several changes to the protocol. In accordance with this advice, Amendment 1 of the protocol was approved by the Sponsor on 08May2019, with the following changes, as requested by the Agency:

- Primary endpoint altered from normalization of albumin, to a combination of normalization of albumin along with improvement of one or more amongst a core set of signs and symptoms (bowel movement frequency, abdominal pain, peripheral and facial edema). However, clear threshold definitions of activity, improvement and worsening were not provided in the amended protocol.
- Primary analysis to include only patients active at baseline, and not well-controlled patients switching from eculizumab, and a minimum of 6 active patients from 4.

In response to this amendment, further advice was received from the Agency on 19Aug2019. The Agency reiterated its advice to ensure that sufficient historical data should be collected on each trial patient. The Agency further advised the Sponsorto construct a primary clinical endpoint that ensures relevance to core symptoms of disease, as perceived by patient and caregiver, if necessary, by individualization. Furthermore, the Sponsor is to establish clear clinically meaningful threshold definitions for evaluable disease activity for improvement and worsening. Following this advice from the Agency, Amendment 2 of the protocol was approved on16Dec2019, with the following changes:

- Provision of clear threshold definitions of activity, improvement and worsening for the four core domains of signs and symptoms.
- Adoption of an individualized endpoint of response of ‘most bothersome symptom’ based on concept elicitation interview during screening, as a key secondary endpoint.

On 5Sep2019, following an IND application submission, the Agency granted a Study May Proceed letter, along with further advice (in addition to advice on 19Aug2019). The Agency advised the Sponsor to increase the stringency of the primary albumin responder definition (to "between Weeks 13 to 24, patients will have serum albumin within the normal range (≥3.5 g/dL) for at least 8 of the 12 weeks, no value <2.5 g/dL, and will not require albumin infusion for any threshold"). Further, the Sponsor is to decrease the tolerance for missing values between weeks 12 and 24. Furthermore, the Agency requested details regarding how baseline clinical scores would be captured. Clear success criteria for the study were to be include in a protocol amendment and a SAP. The Agency indicated that the success criteria should be based on the upper limit of the 90% confidence interval (CI) for the historical controls. The Agency reiterated the importance of pre-baseline data, specifying key laboratory parameters graphically plotted over time (from the time of initial presentation until study enrollment), a summary of the key signs/symptoms that were reported at each clinical visit during that time (focusing on the items selected for inclusion in the endpoint, such as abdominal pain, diarrhea, and edema) as examples of useful pre-baseline data. Finally, the Agency advised that the edema rating scales have more detailed severity descriptors for each point on the scale.

On 3Jan2020, the original SAP was provided to the Agency, containing clear success criteria based on the lower limit of the 90% CI for the treated patients being larger than the upper limit of the CI for the historical controls. On 24Feb2020, the first subject was enrolled, in Istanbul, Turkey.

On 17Mar2020, the Sponsor approved Amendment 3, the purpose of which was to permit the enrollment of children under 6 in the early part of the trial, if disease is life-threatening, and to permit albumin infusions during the screening period for life-threatening disease.

Also, on 17Mar2020, the Sponsor received further Agency advice, in response to the SAP. The Agency recommended to limit enrollment of active patients to those with albumin below 2.9 g/dL (not 3.2 g/dL as in the protocol). The Sponsor has not modified the protocol in this regard because all patients recruited in the trial have met the Agency requirement of albumin less than 2.9 g/dL at baseline. The Agency advised that all patients to be included in the primary analysis should show sufficiently severe symptoms (meeting the criteria for active disease) that fulfill the "evaluable" criteria for at least one of the four core symptoms as defined in the primary endpoint. Furthermore, the Agency requested that the threshold for meaningful change on the PedsQL scales be increased from 6 points to 25 points, since the latter reflects a one-category change on the raw scales. Accordingly, Amendment 1 of the SAP was finalized on 15Apr2020 and submitted to the Agency.

On 09Jun2020, protocol amendment 4 was approved by the Sponsor. This amendment allowed for flexibility in data collection in light of the SARS-CoV-2 pandemic. This amendment also provided revised threshold definitions for nausea and vomiting and for stool consistency scales.

On 26Aug2020, after review of protocol amendment 4 and the SAP amendment 1, follow-up advice was received from the Agency. This advice reiterated that all patients to be included in the primary analysis should show sufficiently severe symptoms and the threshold for meaningful change on the PedsQL scales be increased. As a result, on 18Feb2021, Amendment 5 was approved by the Sponsor. In this amendment, to meet the Agency's requests, patients without evaluable disease activity in any of the four core symptoms comprising the primary endpoint are

excluded from the primary analysis (note: all of the 9 active patients recruited into the trial as of 24May2021 have evaluable disease activity in at least one of the four core symptom areas). Secondly, the threshold for meaningful change on the PedsQL GI Symptoms Scales' problematic frequency of abdominal pain, nausea and vomiting, and diarrhea sub-scales was increased from 6 to 25 points. These latest changes are reflected in this current SAP (amendment 2, version 3).

On 07Apr2021, a discussion was held with the Agency regarding potential for Breakthrough Designation. Data from the first 4 subjects recruited in R3918-PLE-1878, with at least 6 weeks of post baseline data, were provided. External control data were provided in the form of albumin levels on these subjects preceding baseline for a period of 793 to 2210 days. As observed for the historical patient cohort, none of the subjects achieved a normalization of albumin for 12 weeks (or even for more than 3 days) over this pre-baseline period. In contrast, the pozelimab treatment period saw an on-going normalization of albumin in all 4 patients lasting between 5 and 21 weeks. The Agency reiterated its advice to collect pre-baseline data (6-12 months prior enrollment), from chart review, on the core signs and symptoms of disease, to be able to interpret post dosing changes in the context of pre-dosing variability.

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