REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: ORIGNIAL

Clinical Study Protocol Title: **AN OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE EFFICACY AND SAFETY OF REGN3918 IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) WHO ARE COMPLEMENT INHIBITOR-NAIVE OR HAVE NOT RECENTLY RECEIVED COMPLEMENT INHIBITOR THERAPY**

Compound:	REGN3918
Protocol Number:	R3918-PNH-1852
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
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Version/Date:	Original Statistical Analysis Plan / JUL 17, 2019

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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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AH50	Alternative pathway hemolytic activity assay
ALT	Alanine aminotransferase
ASS	Anti-drug antibody analysis set
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CH50	Total Complement hemolytic activity assay
COA	Clinical outcome assessment
CRF	Case report form (electronic or paper)
ECG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
EoS	End of study
eGFR	Estimated glomerular filtration rate
F1+2	D-dimer and N-terminal prothrombin fragments
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
GPI	Glycophosphatidylinositol
HRQoL	Health-related quality of life
HSC	Hematopoietic stem cells
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG4^{P}	Human monoclonal immunoglobulin G4^{P}
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MAC	Membrane attack complex
MAVE	Major adverse vascular event
MMRM	Mixed-effect model for repeated measures

NAS	Neutralizing antibody analysis set
NOAEL	No observable adverse effect level
OLE	Open-label extension
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PRO	Patient reported outcome
PT	Preferred term
Q2W	Every 2 weeks
QLQ-C30	Quality of life questionnaire-core 30
QW	Once weekly
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFPI	Tissue Factor Pathway Inhibitor
t-PA	Tissue plasminogen activator
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
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 prior to first patient first dose as the study is designed as an open-label single-arm trial. 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

Background information on paroxysmal nocturnal hemoglobinuria (PNH) and REGN3918 may be found in the protocol.

The study is a single-arm study and thus patients and the investigator will be aware of treatment allocation. This is deemed acceptable as 1 of the 2 co-primary endpoints of the study is an objective, laboratory-based parameter (i.e., lactate dehydrogenase [LDH]) that is less likely to be biased by knowledge of treatment assignment. The other co-primary endpoint is transfusion avoidance, and the study protocol includes a transfusion algorithm that will standardize the decision to transfuse and thus minimize bias from knowledge of treatment assignment.

The study does not include a placebo control, because there is an approved treatment for PNH (i.e., eculizumab), and not treating patients with active PNH increases the risk of serious or irreversible harm from sequelae of the disease.

In this study, there will be two cohorts, one for dose confirmation (cohort A) and one for dose expansion (cohort B). Cohort A will be comprised of patients whose data will contribute to an initial evaluation at week 8, after 8 weeks of therapy, the purpose of which is the confirmation of the adequacy of the selected dose regimen.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to demonstrate a reduction in intravascular hemolysis by REGN3918 over 26 weeks of treatment (assessed at week 26) in patients with active PNH who are treatment-naive to complement inhibitor therapy or have not recently received complement inhibitor therapy.

1.2.2. Secondary Objectives and Exploratory Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of REGN3918
- To evaluate the effect of REGN3918 on parameters of intravascular hemolysis
- To assess the concentrations of total REGN3918 in serum
- To evaluate the incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3918 over time
- To evaluate the effect of REGN3918 on patient-reported outcomes (PROs) measuring fatigue and health-related quality of life

The exploratory objectives of the study are:

- To explore the effect on clinical thrombosis events
- To explore the effect on renal function and renal injury biomarkers
- To explore the effect of REGN3918 on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To explore the effect of REGN3918 on the level of total C5 protein
- To explore the effect of REGN3918 on PNH clone size
- To explore the effect of REGN3918 on treatment satisfaction and a novel PRO measuring PNH-specific symptoms
- To explore factors contributing to changes in well-being such as fatigue or quality of life in a subset of patients at participating sites (i.e., sub-study)
- To study REGN3918 mechanism of action (including relationship to safety and efficacy), complement pathway biology, PNH, and related complement-mediated diseases
- To collect whole blood DNA and RNA from consented patients in order to explore whether potential differences in patient efficacy and safety are associated with genotype and gene expression, and to further study C5, PNH, or other conditions associated with complement-mediated injury

1.2.3. Modifications from the Statistical Section in the Final Protocol

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

1.2.4. Revision History for SAP Amendments

Not applicable

2. INVESTIGATION PLAN

2.1. Study Design

This is an open-label, single arm, 26-week treatment study in patients with confirmed diagnosis of PNH and active signs and symptoms who either are complement inhibitor naïve or have not received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit, except patients refractory to eculizumab due to the C5 variant R885H/C.

In this study, there will be two cohorts, one for dose confirmation (cohort A) and one for dose expansion (cohort B). Dose confirmation will be made at the interim analysis (Section 7). The inclusion and exclusion criteria and schedule of events are the same for cohort A and cohort B. During the assessment of data from cohort A, recruitment into the study will continue, with patients recruited being assigned subsequently as follows: if a decision is made to expand cohort A, they will be assigned to cohort A. If a decision is made to progress to cohort B, they will be assigned to cohort B.

Patients will be given a single loading dose of REGN3918 30 mg/kg intravenous (IV) on day 1, then a dose not greater than 800 mg subcutaneous (SC) once weekly (QW; ± 1 day) to week 25. Primary analysis is performed at week 26.

Approximately 6 to 12 patients will be enrolled in cohort A, and 24 to 30 in cohort B.

2.2. Sample Size and Power Considerations

This is a single-arm, open-label study, and a formal power calculation for comparison with a control is not intended.

For cohort A, a sample size of 6 is standard in assessing safety and tolerability of a drug dose first tested in patients. Also, it was assessed that sufficient assurance of efficacy with the initial dosing regimen will be provided for a decision to progress from cohort A to cohort B if all 6 cohort A patients achieve an LDH ≤ 1.5 x ULN at week 8 (Section 10.4). Enrollment into cohort A will continue until at least 6 patients have evaluable data (ie, completed week 8 procedures) for the cohort A analysis described in Section 7.

For the overall study (cohort A and cohort B), we used the information from a phase 3 study of ravulizumab compared with eculizumab in active PNH (Lee, 2019) to understand the precision of estimation of the proportions of the primary endpoints to be observed from the current study. The observed proportion of transfusion avoidance was 73.6% in the ravulizumab arm. The proportion of achievement of LDH ≤ 1.5 x ULN has not yet been reported from this study but has been derived from the available information as 95% for ravulizumab. If we assume REGN3918 has ravulizumab-like effects on LDH reduction and transfusion avoidance, i.e. with the same observed proportions from the ravulizumab arm, the following table gives the means and 95% confidence intervals for the proportions of the co-primary endpoints expected to be observed for REGN3918, for the minimal and maximal planned overall sample sizes (cohorts A and B), assuming no change in dosing regimen for cohort B. Patients prematurely withdrawn from the study/study drug in cohort B may not be replaced.

Table 1: Minimal and Maximal Planned Sample Size

Overall Sample Size (N)	**Observeed Porportion and 95% confidence interval for the proportion**	
	Transfusion avoidance	**LDH ≤ 1.5 x ULN**
Minimum: 30	73.6% (58%, 89%)	95% (87%, 100%)
Maximum: 42	73.6% (60%, 87%)	95% (88%, 100%)

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 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.

3.3. The Pharmacokinetic Analysis Set

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 REGN3918 following the first dose of study drug. Patients will be analyzed according to the treatment actually received.

3.4. The Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all patients who received any study drug and who had at least 1 non-missing ADA result from the REGN3918 ADA assay after the first dose of study drug. Patients will be analyzed according to the treatment actually received.

The neutralizing antibody (NAb) analysis set (NAS) includes all patients who received any study drug and who are positive in the REGN3918 ADA assay or with at least one non-missing result in the REGN3918 NAb assay after first dose of the study drug. Patients who are ADA negative are set to negative in the NAb analysis set. Patients will be analyzed according to the treatment actually received.

3.5. The Exploratory Biomarker Endpoint Analysis Set

The exploratory biomarker endpoint (PD) analysis set 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.

3.6. The Exploratory Clinical Outcome Assessment Analysis Set

The exploratory clinical outcome assessment (COA) analysis set includes all FAS patients who had a baseline and at least 1 non-missing COA measurement following the first dose of study drug.

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)
- Ethnicity (Hispanic/Latino)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height
- PNH signs and symptoms
- Total C5

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®).

In addition, the following historical data will be summarized:

- History in the past 12 months of the following:
  - Transfusions
  - Breakthrough hemolysis
- All available laboratory parameters for measurement of hemolysis in the past 2 years:
  - LDH
  - Hemoglobin
  - Free hemoglobin
  - PNH erythrocytes
  - PNH granulocytes
- Neisseria meningitidis vaccination history
- Aplastic anemia history
- Major adverse vascular event (MAVE) history
- PNH medical history

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 ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO 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 will be summarized, including Meningococcal vaccinations and oral antibiotic prophylaxes will be summarized.

Prio/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.

In addition, erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid will be summarized.

4.4. Rescue Medication/or Prohibited Medication During Study if Applicable

The use of the following concomitant medications is not permitted during the study:

- Alcohol, during the 24 hours prior to each clinic visit when blood is drawn
- Complement inhibitors starting on Day 1

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variables

The co-primary efficacy variables are:

- The proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤ 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive
- The proportion of patients achieving transfusion avoidance defined as no post baseline transfusion of RBCs per protocol through week 26

4.5.2. Secondary Efficacy Variables

The secondary efficacy variables are:

- The rate of breakthrough hemolysis through week 26, where breakthrough hemolysis is defined as the measurement of LDH ≥ 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (i.e., LDH ≤ 1.5 x ULN)
- The proportion of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤ 1.0 x ULN at every scheduled time point between week 4 through week 26, inclusive
- Time (days) to first LDH ≤ 1.5 x ULN
- Percentage of days with LDH ≤ 1.5 x ULN between week 4 and week 26, inclusive
- Change in LDH levels from baseline to week 26
- Percent change in LDH levels from baseline to week 26
- The rate of transfusion with RBCs through week 26
- The number of units of transfusion with RBCs from baseline through week 26
- Change in RBC hemoglobin levels from baseline to week 26
- Change in free hemoglobin levels from baseline to week 26
- Change in total complement hemolytic activity assay (CH50) from baseline to week 26
- Percent change in total complement hemolytic activity assay (CH50) from baseline to week 26
- Change in fatigue (as measured by the FACIT-Fatigue) from baseline to week 26
- Change in health-related quality of life (as measured by the European Organisation for Research and Treatment of Cancer [EORTC]-QLQ-C30) from baseline to week 26
- Change in health-related quality of life (as measured by the EQ-5D-3L) from baseline to week 26

For the second secondary variable (the proportion of patients with normalization), patients for whom one or more of the following apply will be considered as not achieving normalization:

  - Discontinue from study treatment early
  - Have 3 consecutive missing values of the scheduled LDH measurements between week 4 and week 26
  - Have 50% or more missing values of the scheduled LDH measurements between week 4 and week 26, inclusive
  - Experience breakthrough hemolysis event (as defined in the secondary endpoint) while on treatment through week 26

4.5.3. Exploratory Efficacy Variables

The exploratory efficacy variables are:

- Incidence of MAVE through week 26
- Change in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline to week 26
- Treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) at week 26
- Change in PNH symptoms as measured by the de novo PNH symptom-specific questionnaire at week 26
- Change in haptoglobin from baseline to week 26
- Change in bilirubin from baseline to week 26
- Change in reticulocyte count from baseline to week 26
- Change in alternative pathway hemolytic activity assay (AH50) from baseline to week 26
- Percent change in alternative pathway hemolytic activity assay (AH50) from baseline to week 26
- Change in Total C5 from baseline to week 26
- Change in PNH erythrocytes and granulocytes from baseline to week 26

The wearable activity tracker data will not be part of this SAP, and it will not be mentioned further.

4.6. Safety Variables

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 the study. All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, the most 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.

The severity of AEs and of infusion reaction AEs will be graded according to the criteria given in the protocol.

Section 9.4.5 in the protocol gives the criteria for whether laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs.

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. In this study, AESIs are listed below (as provided in the protocol):

- Moderate or severe infusion reactions
- Confirmed Neisseria infection (N. meningitidis or N. gonorrhea)
- Any thrombotic or embolic event, using the Embolic and thrombotic events SMQ, which includes (1) arterial, (2) venous and (3) unspecified and mixed arterial and venous events

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, urinalysis, and other.

Clinical laboratory values will be grouped by function in summary tables. Conventional units may be provided. Laboratory tests are categorized in the protocol as follows:

- Blood chemistry
- Hematology
- Urinalysis
- Other tests

4.6.4. Vital Signs

Temperature, pulse, and blood pressure will be collected.

4.6.5. 12-Lead Electrocardiography (ECG)

Heart rate will be recorded from the ventricular rate. PR, QRS, RR and QT intervals will be recorded, as well as QTcF.

4.6.6. Physical Examination Variables

Physical examination variables include findings that result from evaluations of head and neck, lungs, heart, abdomen, extremities, and skin. Findings may be included in AE and MH tables.

4.7. Pharmacokinetic Variables

The PK endpoint is concentration of total REGN3918. Target engagement will be assessed by the concentration of total C5. The sampling time points are specified in Section 10.2.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, NAb status, titer, and time point/visit. Samples in this study will be collected at the clinic visits specified in Section 10.2.

4.9. Pharmacodynamic Variables

The following pharmacodynamic biomarkers are included in this study:

- Complement activity as measured by the serum CH50 and AH50 assays
- Complement activation markers: C5a (plasma and urine) and sC5b-9 (plasma)
- PNH clone size: PNH erythrocytes and granulocytes
- Biomarkers of pulmonary hypertension: NT-proBNP
- Biomarkers of thrombosis and inflammation: D-dimer, N-terminal prothrombin fragments (F1+2), Tissue Factor Pathway Inhibitor (TFPI), and IL-6
- A urinary renal injury biomarker panel: clusterin (CLU), Cystatin-C (CysC), Kidney Injury Molecule-1 (KIM-1), Nacetyl-beta-D-glucosaminidase (NAG), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and osteopontin (OPN)

4.10. Clinical Outcome Assessments (COAs)

Patient-reported outcomes (PROs) are a type of clinical outcome assessment (COA) and will be completed according to the schedule in Section 10.2.

COAs include the the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), 2 health-related quality of life (HRQoL) questionnaires (the EORTC-QLQ-C30 and the EQ-5D-3L), the Treatment Satisfaction Questionnaire for Medication (TSQM), and the de novo PNH symptom-specific questionnaire.

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, Q1, Q3, minimum, and maximum.

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

If there is no change in dosing regimen for cohort B, patients of cohort A and cohort B will be pooled for both safety and efficacy analysis. If the dosing regimen is changed, efficacy analyses will be performed separately for cohort A and cohort B.

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 post-treatment 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. Rescue/Prohibited Medications if applicable

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 post-treatment period.

5.5. Patient Disposition

The following displays will be provided:

- The total number of screened patients who met the inclusion criteria regarding the target indication and signed the ICF
- The total number of enrolled patients
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who continued to OLE, and the total number who completed the study but did not continue to OLE
- A listing of patients enrolled but not treated
- A listing of patients prematurely discontinued from treatment, along with 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 period. The time periods of interest are as follows:

- ≥ Day 28
- ≥ Day 56
- ≥ Day 84
- ≥ Day 112
- ≥ Day 140
- ≥ Day 182

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

5.7. Analyses of Efficacy Variables

The co-primary endpoints for the study are the proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤ 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive, and the proportion of patients achieving transfusion avoidance defined as no post-baseline transfusions of RBCs per protocol. The proportions of the co-primary endpoints will be calculated, along with their 95% confidence intervals.

5.7.1. Analysis of Primary Efficacy Variables

For the first co-primary variable (the proportion of patients achieving adequate control of their intravascular hemolysis), patients who have one or more of the following will be considered as not achieving adequate control of their intravascular hemolysis:

- Discontinue from study treatment early
- Have 3 consecutive missing values of the scheduled LDH measurements between week 4 and week 26, inclusive
- Have 50% or more missing values of the scheduled LDH measurements between week 4 and week 26, inclusive
- Experience breakthrough hemolysis event (as defined in the secondary endpoint) while on treatment through week 26

Patients who complete study treatment, have no more than 2 consecutive missing values of the scheduled LDH measurements between week 4 and week 26, have fewer than 50% missing values of the scheduled LDH measurements between week 4 and week 26, and have no breakthrough hemolysis while on treatment will be evaluated based on their non-missing LDH measurements. The proportion of patients achieving adequate control of their intravascular hemolysis will be calculated, along with a 2-sided 95% confidence interval, by a normal approximation as primary analysis and by the exact Clopper Pearson method as a sensitivity analysis.

For the co-primary variable of the proportion of patients achieving transfusion avoidance, the analysis set will consist of all FAS patients. A transfusion will be counted only if the transfusion

follows the predefined transfusion algorithm. The proportion (and 95% confidence interval) of patients achieving transfusion avoidance through week 26 will be calculated by the Kaplan-Meier estimate at week 26. Patients who have no transfusions will be censored at week 26 (completers) or at time of early discontinuation.

Sensitivity analysis of first co-primary endpoint

As a sensitivity analysis to assess the effect of missing LDH values on the primary analysis of the first co-primary endpoint, imputation of missing LDH values from 4 weeks to 26 weeks for all FAS patients will be performed using the multiple imputation method. Missing data will be imputed 100 times to generate 100 complete data sets by using the SAS procedure MI with the following steps:

- Step 1: Intermittent missing data will be imputed, leaving a monotone missing pattern, by the Markov Chain Monte Carlo (MCMC) method in the MI procedure.
- Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern.

The primary analysis of percentage of patients achieving adequate control of their intravascular hemolysis will then be conducted on the 100 complete data sets. The results will be descriptively summarized, including mean, median, standard deviation, Q1, Q3, minimum, and maximum.

Sensitivity analysis of second co-primary endpoint

An analysis of transfusion avoidance will be repeated considering all transfusions, whether or not they were per the predefined transfusion algorithm in the protocol.

Subgroup analysis:

Subgroup analyses will be conducted for the co-primary endpoints by the following subgroup factors:

- Study cohort (A vs B)
- Complement inhibitor experience (naïve vs prior treatment)
- Quartiles of RBC transfusion units in the 6 months before treatment
- Country/region (APAC, EU [South Africa is part of EU], and US)
- Gender
- Baseline LDH levels (≥ median vs < median)
- C5 variants (yes/no)
- Weight (≥ median vs < median)
- Baseline total C5 (≥ median vs < median)

5.7.2. Analysis of Secondary Efficacy Variables

For the secondary variable of the rate of breakthrough hemolysis through week 26, defined as the measurement of LDH ≥ 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (i.e., LDH ≤ 1.5 x ULN), the proportion of patients achieving normalization of their intravascular hemolysis will be calculated, along with a 95% confidence interval, by a normal approximation as primary analysis and by the exact Clopper Pearson method as a sensitivity analysis. Signs and symptoms will be tabulated, as will number of breakthrough hemolyses per patient.

For the secondary variable of the proportion of patients achieving normalization of their intravascular hemolysis (defined as LDH ≤ 1.0 x ULN at every scheduled time point between week 4 through week 26, inclusive), patients who have one or more of the following will be considered as not achieving adequate control of their intravascular hemolysis:

- Discontinue from study treatment early
- Have 3 consecutive missing values of the scheduled LDH measurements between week 4 and week 26, inclusive
- Have 50% or more missing values of the scheduled LDH measurements between week 4 and week 26, inclusive
- Experience breakthrough hemolysis event (as defined in the secondary endpoint) while on treatment through week 26

Patients who complete study treatment, have no more than 2 consecutive missing values of the scheduled LDH measurements between week 4 and week 26, have fewer than 50% missing values of the scheduled LDH measurements between week 4 and week 26 and have no breakthrough hemolysis will be evaluated based on their non-missing LDH measurements. The proportion of patients achieving normalization of their intravascular hemolysis will be calculated, along with a 95% confidence interval, by a normal approximation as primary analysis and by the exact Clopper Pearson method as a sensitivity analysis.

The same sensitivity analysis described for the first co-primary endpoint will be conducted.

For the secondary variable of the time to first LDH ≤ 1.5 x ULN, a time to first event analysis will be used. The median time and 95% confidence interval will be obtained with a Kaplan-Meier analysis. Patients who have no values of LDH ≤ 1.5 x ULN will be censored at week 26 (completers) or at time of early discontinuation.

For the secondary variable of the percentage of days with LDH ≤ 1.5 x ULN between week 4 and week 26, inclusive, each patient's percentage will be the number of days with LDH ≤ 1.5 x ULN divided by the patient's total treatment duration (total number of days on treatment). The LDH value for each day of the patient's treatment duration will be the most recent LDH measurement up to the day, inclusive. The mean and 95% confidence interval will be presented.

For the secondary variable of the number of units of transfusion of RBCs through week 26, the 26 week total for each patient will be used. A mean and 95% confidence interval will be calculated, based on the assumption of a negative binomial distribution of the number of units of transfusions with RBCs. A transfusion will be counted only if the transfusion follows the predefined transfusion algorithm.

For the secondary variable of the rate of transfusion with RBCs through week 26, the mean and 95% confidence interval will be calculated, based on the assumption of a negative binomial distribution of the number of units of transfusions with RBCs, adjusted for the time on study. A transfusion will be counted only if the transfusion follows the predefined transfusion algorithm.

For the following secondary variables, the analysis set will consist of all FAS patients who have a non-missing baseline measurement of the variable:

- Change in LDH levels from baseline to week 26
- Percent change in LDH levels from baseline to week 26
- Change in RBC hemoglobin levels from baseline to week 26
- Change in free hemoglobin levels from baseline to week 26
- Change in total complement hemolytic activity assay (CH50) from baseline to week 26
- Percent change in total complement hemolytic activity assay (CH50) from baseline to week 26
- Change in fatigue (as measured by the FACIT-Fatigue) from baseline to week 26
- Change inhealth related quality of life (as measured by the EORTC-QLQ-C30) from baseline to week 26 by individual subscales: global health status/quality of life, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, and dyspnea
- Change in (health related quality of life as measured by the EQ-5D-3L) from baseline to week 26

For these variables, means and 95% confidence intervals based on an MMRM analysis will be reported for the last applicable week. The MMRM model will include visit as a fixed term and assume an unstructured covariance matrix. In addition, a sensitivity analysis will be conducted for change and percent change in LDH from baseline to 26 weeks by Last observation carried forward (LOCF) imputation for 26 weeks. The justification for the LOCF imputation is that it is very unlikely for patients to have missing LDH before 4 weeks and a patient's LDH should have reached a stable level by 4 weeks based on eculizumab and ravulizumab trial data, whether it is above or below 1.5 XULN.

5.7.3. Analysis of Exploratory Variables

For the exploratory variable "Incidence of MAVE through week 26," the proportion of patients with at least one MAVE will be presented along with two versions of a 95% confidence interval: normal approximation and exact Clopper-Pearson.

For TSMQ, mean and 95% confidence interval based on an MMRM analysis will be reported for week 26. The MMRM model will include visit as a fixed term and assume an unstructured covariance matrix.

For the following exploratory variables, the analysis set will consist of all FAS patients who have a non-missing baseline measurement of the variable:

- Change in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline to week 26
- Change in PNH symptoms as measured by the de novo PNH symptom-specific questionnaire at week 26
- Change in haptoglobin from baseline to week 26
- Change in bilirubin from baseline to week 26
- Change in reticulocyte count from baseline to week 26
- Change in alternative pathway hemolytic activity assay (AH50) from baseline to week 26
- Percent change in alternative pathway hemolytic activity assay (AH50) from baseline to week 26
- Change in Total C5 from baseline to week 26
- Change in PNH erythrocytes from baseline to week 26
- Change in PNH granulocytes from baseline to week 26

For these variables, means and 95% confidence intervals based on an MMRM analysis will be reported for the last applicable week. The MMRM model will include visit as a fixed term and assume an unstructured covariance matrix.

5.8. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2.

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 overall.

5.8.1. Adverse Events

The verbatim text, the PT, and the primary SOC will be listed in patient listings. 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 for patients who do not participate in the OLE. For those patients who do participate in the OLE, the end of the on-treatment period is from first dose of investigational product until just before the first dose in the OLE study.

Post-treatment AEs are AEs that developed or worsened during the post-treatment period. For patients not entering the OLE, the post-treatment period for AEs is the time after the end of treatment (scheduled week 26 visit) plus 21 weeks. Patients who do participate in the OLE will not have AEs of this category.

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
- TEAEs by relationship to treatment (related, not related), 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 other SAEs will be listed and summarized.

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

Summaries of all TEAEs will include:

- All TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Related TEAEs by severity and SOC and PT
- Time to first occurrence of selected TEAEs
- Serious adverse events: All TEAEs by SOC and PT
- Serious adverse events: Related TEAEs by SOC and PT
- Serious adverse events: All TEAEs by SOC and PT
- Serious adverse events: Related TEAEs by SOC and PT
- Death: All fatal TEAEs by SOC
- Death: Related fatal TEAEs by SOC
- Discontinuation: All TEAEs by SOC and PT
- Discontinuation: Related 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.

Additionally, separate summaries of TEAEs (preferred terms) with frequency ≥1% in any treatment group and TEAEs (preferred terms) with frequency ≥5% in any treatment group will be included in the report.

The summary of TEAEs with frequency ≥5% will also be performed for demographic factors including: gender, age (<65 years, ≥65 years), and race.

5.8.2. Analysis of Adverse Events of Special Interest

Treatment emergent adverse events of special interest will be presented by SMQ and PT (when selection is based on SMQs) and 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/SMQ.

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. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum. The graphs of mean (or median) value of some lab parameter vs. visit will also be plotted.

A listing of all laboratory parameters will include the value, normal range, abnormal flag and treatment-emergent PCSV flag by subject and visit will be provided.

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

All laboratory displays will be done twice, with international units and conventional units.

5.8.4. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be summarized by visit 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.

Listings will be provided with flags indicating treatment-emergent PCSVs.

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).

Listings will be provided with flags indicating PCSVs.

5.9. Analysis of Pharmacokinetic and Immunogenicity Data

5.9.1. Analysis of Pharmacokinetic Data

Summary of concentrations of total REGN3918 and total C5 will be presented by nominal time point (ie, the time points specified in the protocol). Individual data will be presented by actual time. Plots of the concentrations of REGN3918 and total C5 will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification (LLOQ) will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2. Summary statistics of concentrations of total REGN3918 and total C5 may include, but are not limited to arithmetic mean, standard deviation, standard error of the mean, coefficient of variation (in %), minimum, Q1, median, Q3, and maximum.

No formal statistical analysis will be performed.

Descriptive concentration-response (AH50, CH50 and total C5) analysis will be performed as appropriate.

5.9.2. Analysis of Immunogenicity Data

5.9.2.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response catagories:

- Pre-existing immunoreactivity, defined as either an ADA positive response in the REGN3918 ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as a positive response in the REGN3918 ADA assay post first dose when baseline results are negative or missing.
- Treatment-boosted response, defined as a positive response in the REGN3918 ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

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

The following listings will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the REGN3918 ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for treatment-emergent and treatment-boosted ADA response patients.

5.9.2.2. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of patients (%) with NAb positive or negative status in the NAb analysis set will be provided by treatment groups.

5.9.3. Association of Immunogenicity with Exposure, Safety and Efficacy

5.9.3.1. Immunogenicity and Exposure

Association between immunogenicity variables and systemic exposure to REGN3918 will be analyzed. Plots of REGN3918 concentration may be provided for analyzing the potential impact of ADA response status, titer and NAb.

5.9.3.2. Immunogenicity and Safety and Efficacy

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])

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

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

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response.
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- NAb positive patients, that is ADA positive (treatment-emergent & treatment-boost) patients who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive patients:
  - High,
  - Moderate
  - Low

5.10. Analysis of Pharmacodynamic and Biomarker Data

Pharmacodynamic and biomarker variable listed in Section 4.8 may be analyzed and summarized. For each biomarker variable, time profile and percent of change from baseline at each time point will be summarized through 26 week

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

6.3. Data Handling Convention for Missing Data

Rules for handling missing data for primary and secondary efficacy variables are described in Section 4.5.1 and Section 4.5.2.

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.

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

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 Appendix 10.2 (Schedule of Time and Events). The analysis visit windows will be exhaustive 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. No analysis visit windows will be applied for the study scheduled visits. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Day 1 is defined as the first date of study treatment.

Efficacy Analysis Windows

Visit	Targeted Study Days	LDH	Transfusion	Complement Hemolytic	FACIT-Fatigue, EORTC-QLQ-30, PGIS	EQ-5D-3L	PGIC
Screening	<1						
Day 1	1	1	1	1	[1, 7]	[1, 14]	
Day 3	3	[2, 4]	[2, 4]	[2, 4]			
Week 1	8	[5, 11]	[5, 11]	[5, 11]			
Week 2	15	[12, 18]	[12, 18]	[12, 18]	[8, 21]		[12, 21]
Week 3	22	[19, 25]	[19, 25]	[19, 25]			
Week 4	29	[26, 36]	[26, 32]	[26, 42]	[22, 42]	[15, 42]	[22, 42]
Week 5	36		[33, 39]				
Week 6	43	[36, 49]	[40, 46]				
Week 7	50		[47, 53]				
Week 8	57	[50, 63]	[54, 60]	[43, 70]	[43, 70]	[43, 70]	[43, 70]
Week 9	64		[61, 67]				
Week 10	71	[64, 77]	[68, 74]				
Week 11	78		[75, 81]				
Week 12	85	[78, 91]	[82, 88]	[71, 98]	[71, 98]	[71, 98]	[71, 98]
Week 13	92		[89, 95]				
Week 14	99	[92, 105]	[96, 102]				
Week 15	106		[103, 109]				
Week 16	113	[106, 119]	[110, 116]	[99, 126]	[99, 126]	[99, 126]	[99, 126]
Week 17	120		[117, 123]				
Week 18	127	[120, 133]	[124, 130]				
Week 19	134		[131, 137]				
Week 20	141	[134, 147]	[138, 144]	[127, 161]	[127, 161]	[127, 161]	[127, 161]
Week 21	148		[145, 151]				
Week 22	155	[148, 161]	[152, 158]				
Week 23	162		[159, 165]				
Week 24	169	[162, 172]	[166, 172]				
Week 25	176	[173, 179]	[173, 179]				
Week 26	183	[180, 186]	[180, 186]	[162, 186]	[162, 186]	[162, 186]	[162, 186]

Safety Analysis Windows

Visit	Targeted Study Days	Vital Signs	Physical Exam	Body Weight	ECG	Patient Safety Card	Hematology, Blood Chemistries, Pregnancy, Urinalysis	CRP	Direct Antiglobulin
Screening	<1	<1	<1	<1	<1		<1	<1	<1
Day 1	1	1	1	[1,14]		1-92	[1,11]	1	[1, 14]
Day 3	3	[2, 4]	[2, 4]					[2, 4]	
Week 1	8	[5, 11]	[5, 14]					[5, 11]	
Week 2	15	[12, 18]					[12, 21]	[12, 18]	
Week 3	22	[19, 25]						[19, 25]	
Week 4	29	[26, 35]	[15, 42]	[15, 42]			[22, 42]	[26, 42]	[15, 42]
Week 5	36								
Week 6	43	[36, 49]							
Week 7	50								
Week 8	57	[50, 63]	[43, 70]	[43, 70]			[43, 70]	[43, 70]	[43, 70]
Week 9	64								
Week 10	71	[64, 77]							
Week 11	78								
Week 12	85	[78, 91]	[71, 98]	[71, 98]			[71, 98]	[71, 98]	[71, 98]
Week 13	92								
Week 14	99	[92, 105]							
Week 15	106								
Week 16	113	[106, 119]	[99, 126]	[99, 126]			[99, 126]	[99, 126]	[99, 126]
Week 17	120								
Week 18	127	[120, 133]							
Week 19	134								
Week 20	141	[134, 147]	[127, 161]	[127, 161]			[127, 161]	[127, 161]	[127, 161]
Week 21	148								
Week 22	155	[148, 168]							
Week 23	162								
Week 24	169								
Week 25	176								
Week 26	183	[169, 186]	[162, 186]	[162, 186]	[1, 186]	[93, 186]	[162, 186]	[162, 186]	[162, 186]

PK and ADA Analysis Windows

Visit	Targeted Study Days	PK	ADA
Screening	<1		
Day 1	1	1	[1, 42]
Day 3	3	[2, 4]	
Week 1	8	[5, 14]	
Week 2	15		
Week 3	22		
Week 4	29	[15, 42]	
Week 5	36		
Week 6	43		
Week 7	50		
Week 8	57	[43, 70]	
Week 9	64		
Week 10	71		
Week 11	78		
Week 12	85	[71, 98]	[43, 133]
Week 13	92		
Week 14	99		
Week 15	106		
Week 16	113	[99, 126]	
Week 17	120		
Week 18	127		
Week 19	134		
Week 20	141	[127, 161]	
Week 21	148		
Week 22	155		
Week 23	162		
Week 24	169		
Week 25	176		
Week 26	183	[162, 186]	[134, 186]

Exploratory Analysis Windows

Visit	Targeted Study Days	Haptoglobin, Reticulocytes, C3, C4, C5a, NT-proBNP, Thromb/Inflamm, Renal Injury	Complement Hemolytic Assay, sC5b-9	Total C5	PNH Eryth, PNH Gran
Screening	<1	<1	<1	<1	<1
Day 1	1	[1, 14]	1	1	[1, 28]
Day 3	3		[2, 4]	[2, 14]	
Week 1	8		[5, 11]		
Week 2	15		[12, 18]		
Week 3	22		[19, 25]		
Week 4	29	[15, 42]	[26, 35]	[15, 42]	
Week 5	36				
Week 6	43				
Week 7	50				
Week 8	57	[43, 70]	[50, 63]	[43, 70]	[29, 84]
Week 9	64				
Week 10	71				
Week 11	78				
Week 12	85	[71, 98]	[71, 98]	[71, 98]	
Week 13	92				
Week 14	99				
Week 15	106				
Week 16	113	[99, 126]	[99, 126]	[99, 126]	[85, 133]
Week 17	120				
Week 18	127				
Week 19	134				
Week 20	141	[127, 161]	[127, 161]	[127, 161]	
Week 21	148				
Week 22	155				
Week 23	162				
Week 24	169				
Week 25	176				
Week 26	183	[162, 186]	[162, 186]	[162, 186]	[134, 186]

Optional Analysis Windows

Visit	Targeted Study Days	Future Biomed	DNA	RNA
Screening	<1			
Day 1	1	[1, 14]	1	[1,4]
Day 3	3			
Week 1	8			[4, 93]
Week 2	15			
Week 3	22			
Week 4	29	[15, 42]		
Week 5	36			
Week 6	43			
Week 7	50			
Week 8	57	[43, 70]		
Week 9	64			
Week 10	71			
Week 11	78			
Week 12	85	[71, 98]		
Week 13	92			
Week 14	99			
Week 15	106			
Week 16	113	[99, 126]		
Week 17	120			
Week 18	127			
Week 19	134			
Week 20	141	[127, 161]		
Week 21	148			
Week 22	155			
Week 23	162			
Week 24	169			
Week 25	176			
Week 26	183	[162, 186]		[94,186]

COA* Analysis Windows

Visit	Targeted Study Days	TSQM
Screening	<1	<1
Day 1	1	
Day 3	3	
Week 1	8	
Week 2	15	
Week 3	22	
Week 4	29	[1, 70]
Week 5	36	
Week 6	43	
Week 7	50	
Week 8	57	
Week 9	64	
Week 10	71	
Week 11	78	
Week 12	85	
Week 13	92	
Week 14	99	
Week 15	106	
Week 16	113	[71, 147]
Week 17	120	
Week 18	127	
Week 19	134	
Week 20	141	
Week 21	148	
Week 22	155	
Week 23	162	
Week 24	169	
Week 25	176	
Week 26	183	[148, 186]

* Note: PNH symptom-specific questionnaire assessed daily (not a weekly questionnaire)

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

There will not be a formal interim analysis of efficacy data.

There will be an interim analysis of the data from cohort A at week 8, the purpose of which is the confirmation of the adequacy of the selected dose regimen.

The interim analysis will be performed by a team from the Sponsor consisting of those from the following functions: Sample Management, Bioanalytical Sciences, Clinical Pharmacology and Quantitative Pharmacology, Regeneron Senior Physicians, Program Director, Precision Medicine, and Biostatistics and Programming. The decision to progress from cohort A to cohort B will be made by the Sponsor in conjunction with the global principal investigator based on the achievement of LDH reduction to ≤ 1.5 x ULN and safety at week 8, as follows:

- If all 6 out of 6 cohort A patients achieve an LDH ≤ 1.5 x ULN at week 8 and the dosing regimen is considered well tolerated, then either the dose regimen will be confirmed and the study will progress to cohort B, or the dosing regimen will be altered, with a lower dose and/or longer dosing interval being tested in an expanded cohort A (up to a further 6 subjects). These revisions would not be considered substantial and therefore would not require a formal protocol amendment.
- If one or more patients fails to achieve LDH ≤ 1.5 x ULN at week 8, then after consideration of all data (including clinical and safety data, REGN3918 PK, CH50, total C5, baseline LDH, and the LDH level achieved), a decision will be made to either:
  - Confirm the dosing regimen and progress to cohort B, or
  - Continue with the selected dosing regimen and expand cohort A up to a maximum of 12 patients, or
  - Increase dose and/or reduce dose interval and re-assess cohort A. This option will require a substantial protocol amendment.

Posterior probabilities of assurance of achieving LDH ≤ 1.5 x ULN conditioned on observed data are provided in tables in Section 10.4, one assuming a non-informative prior and the other assuming an informative prior.

The data to be reviewed for the analysis of cohort A include:

- Laboratory: LDH, blood chemistry, hematology, urinalysis, CH50, drug concentration (PK)
- Clinical data: Transfusion, FACIT-Fatigue, weight, AEs, concomitant medications
- Baseline characteristics: demographics
- Drug administration and patient disposition

8. SOFTWARE

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

9. REFERENCES

1. ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
3. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. Lee JW, Peffault de Latour R, Brodsky RA, Jang JH, Hill A, Röth A, Schreznemeier H, Wilson A, Marantz JL, Maciejewski JP. Effectiveness of eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH) with or without aplastic anemia in the International PNH Registry. *Am J Hematol* 2019; 94(1):E37-E41.

10. APPENDIX

10.1. Summary of Statistical Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Efficacy analysis	FAS	Confidence intervals, Kaplan-Meier, Exact methods	MMRM with MI	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 Time and Events

Study Period	Screening	Treatment											EoS	Notes
Study Week	up to -4	0		1	2	3	Week 4 to 23 (W4, 8, 12, 16, 20)	Week 4 to 23 (W5, 9, 13, 17, 21)	Week 4 to 23 (W6, 10, 14, 18, 22)	Week 4 to 23 (W7, 11, 15, 19, 23)	24	25	26	
Study Day (W0 to W26 ± 1D)	up to -28	1	3	8	15	22	29, 57, 85, 113, 141	36, 64, 92, 120, 148	43, 71, 99, 127, 155	50, 78, 106, 134, 162	169	176	183	
Visit Location:														
Clinic Visit	X	X	X	X	X	X	X				X		X	Mandatory clinic visit
Clinic, Home Healthcare, or Phone Call Visit[1]								X	X[2]	X		X[2]		Cohort A: Clinic visit mandatory for first visits up to and including week 8. Section 7.2.
Screening:														
Informed Consent	X													Including optional sub-studies
Inclusion/Exclusion	X	X												May re-screen once, as described in Section 8.2.1
Medical History	X	X												Section 8.2.1
Demographics	X													
Prior Concomitant Medications	X													
Historical Lab Parameters for Hemolysis	X													If possible, 2 yr history. Section 8.2.1
Neisseria Meningitidis Vaccination History	X													
TB history and assessment	X													Section 8.2.1
Testing history for hepatitis B and C	X													Testing may be performed by the central lab as needed per local practice. Section 8.2.1
Risk assessment for Neisseria gonorrhea	X													Section 7.8
Height	X													
Enrollment		X												

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Treatment:														
R3918 IV Administration		X												Patients should be observed for at least 30 minutes post-infusion. Section 7.2
R3918 SC Administration				X	X	X	X	X	X	X	X	X		Cohort A: Only W9-25 may be self-administered. Section 7.2
Oral Antibiotics		X	X	X	X	X	X	X	X	X	X	X	X	Per local practice. Section 7.4.2
Meningococcal Vaccine	X	X												Per local practice. Section 7.4.1
IVRS/IWRS Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Diary								X	X	X		X		For self-administration. Section 7.2
Efficacy (central):														
Serum LDH	X	X	X	X	X	X	X		X		X	X	X	Samples not required if blood chem. samples are taken. Section 8.2.3.1
Transfusion Data	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3.2
Complement Hemolytic Assay (serum CH50)	X	X	X	X	X	X	X						X	Day 1, pre-dose and end of the IV infusion. Pre-dose at all other visits. Section 8.2.3.3
FACIT-Fatigue		X			X		X						X	Section 8.2.3.6
EORTC-QLQ-30		X			X		X						X	Section 8.2.3.6
EQ-5D-3L		X					X						X	Section 8.2.3.6
PGIS		X			X		X						X	Section 8.2.3.6
PGIC					X		X						X	Section 8.2.3.6

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Safety:														
Vital Signs	X	X	X	X	X	X	X		X				X	Section 8.2.4.1
Physical Examination	X	X	X	X			X						X	Section 8.2.4.2
Body Weight	X	X					X						X	Section 8.2.4.2
Electrocardiogram	X												X	Section 8.2.4.3
Adverse Events	< ----------x ---------- >													Section 9 If breakthrough hemolysis is suspected, blood samples will be collected for LDH and other assessments. Blood may also be collected in the event of drug hypersensitivity. Section 8.1.3
Concomitant Meds & Tx	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 7.12
Patient Safety Card		X												For Neisseria meningitidis
Laboratory Testing: (Central):														
Hematology	X	X			X		X						X	Includes RBC and free hemoglobin See Section 8.2.4.4 for analytes
Blood Chemistry	X	X			X		X						X	Includes serum lactate dehydrogenase See Section 8.2.4.4 for analytes
Pregnancy Test	X	X			X		X						X	Serum at screening Urine at all other visits
Urinalysis	X	X			X		X						X	See Section 8.2.4.4 for analytes
C-Reactive Protein	X	X	X	X	X	X	X						X	
Direct Antiglobulin Test	X	X					X						X	DAT or Coombs

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
PK and ADA Samples:														
PK Sample		X	X	X			X						X	Day 1, sample pre-dose and end of the IV infusion. Pre-dose at all other visits. Section 8.2.5
ADA Sample		X					X (W12)						X	Pre-dose. Section 8.2.6
Exploratory PD/Biomarkers:														Pre-dose, unless otherwise specified
Haptoglobin	X	X					X						X	Section 8.2.8
Reticulocyte Count	X	X					X						X	
Complement Hemolytic Assay (serum AH50)	X	X	X	X	X	X	X						X	Day 1, sample pre-dose and end of the IV infusion. Pre-dose at all other visits.
Total Complement Levels	X	X					X						X	
Total C5 (plasma)	X	X	X				X						X	Day 1, sample pre-dose and end of the IV infusion. Pre-dose at all other visits.
C5a (plasma and urine)	X	X					X						X	
sC5b-9 (plasma)	X	X	X	X	X	X	X						X	
PNH Erythrocyte Cells	X	X					X (W8, W16)						X	
PNH Granulocyte Cells	X	X					X (W8, W16)						X	
NT-proBNP	X	X					X						X	
Biomarkers of Thrombosis and Inflammation	X	X					X						X	May include D-dimer, F1+2, TFPI, and IL-6
Renal Injury Markers	X	X					X						X	

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Optional Samples:														
Future Biomedical Research Serum/Plasma (optional)		X					X						X	As permitted by local regulatory policies. Section 8.2.9
Whole Blood for DNA Isolation (optional)		X												Section 8.2.9.1
Whole Blood for RNA Isolation (optional)		X		X									X	Section 8.2.9.1
Clinical Outcome Assessments														
PNH Symptom-Specific Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	To be completed daily by patient. Patient will complete daily PNH Symptom-Specific Questionnaire on a device at least 7 days prior to day 1 visit. Section 8.2.7.1 Cohort A: Optional Cohort B: Mandatory when available
TSQM							X (W4, W16)						X	Section 8.2.7.1 Cohort A: Optional Cohort B: Mandatory when available
Wearable Device		< ---------- W0 to W12 ---------- >												Should be worn according to the schedule set out in the study manual Section 8.2.7.2

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV For Studies in healthy subjects only	Comments
Clinical chemistry		
ALT	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	> 1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008
Total Bilirubin	> 1.5 ULN > 2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Concept paper on DILI – FDA draft Guidance Oct 2008 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)	Conjugated bilirubin dosed on a case-by-case basis
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 To be counted within the same treatment phase, whatever the interval between measurement

Parameter	PCSV For Studies in healthy subjects only	Comments
CPK	> 3 ULN >10 ULN	FDA Feb 2005 Am J Cardiol April 2006 Categories are cumulative First row is mandatory. Rows following one mentioning zero can be deleted.
Creatinine	≥ 150 µmol/L (adults) ≥ 90 µmol/L (6-12 year-old) ≥ 30% from baseline ≥ 100% from baseline	Benichou C., 1994
Creatinine Clearance (Cockcroft's formula)	< 30 ml/min (severe renal impairment) ≥30 - < 50 ml/min (moderate renal impairment) ≥50 - ≤ 80 ml/min (mild renal impairment)	Use is optional. FDA criteria May 1998
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed. 2008
Sodium	≤129 mmol/L ≥ 160 mmol/L	
Potassium	< 3 mmol/L ≥ 5.5 mmol/L	FDA Feb 2005
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)	Threshold for therapeutic intervention
Triglycerides	≥ 4.6 mmol/L (4 g/L)	Threshold for therapeutic intervention
Glucose Hypoglycaemia Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 7 mmol/L (fasted); ≥ 11.1 mmol/L (unfasted)	 ADA May 2005 ADA Jan 2008
CRP	> 2 ULN or >10 mg/L, if ULN not provided	FDA Sept 2005

Parameter	PCSV For Studies in healthy subjects only	Comments
Hematology		
WBC	< 3.0 Giga/L (3000/mm3) < 2.0 Giga/L (2000/mm3) (Black)	Increase-in WBC: not relevant To be interpreted only if no differential count available.
Neutrophils	< 1.5 Giga/L (1500/mm3) < 1.0 Giga/L (1000/mm3) Black	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria
Eosinophils	> 0.5 Giga/L (500/mm^3) or > ULN if ULN ≥ 0.5 Giga/L	Gallin 1989, Harrisson 13th Ed, 1994.
Hemoglobin	At least 20 g/L (1.24 mmol/L) decrease versus baseline	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥ 30 g/L, ≥ 40 g/L, ≥ 50 g/L)
Platelets	< 100 Giga/L (100 000/mm^3)	International Consensus meeting on drug-induced blood cytopenias, 1991.
Vital signs		
HR	≤ 40 bpm and decrease from baseline ≥ 20 bpm ≥ 100 bpm and increase from baseline ≥ 20 bpm	Proposed change: To be are applied for all positions (including missing) except STANDING
SBP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 140 mmHg and increase from baseline ≥ 20 mmHg	Proposed change: To be are applied for all positions (including missing) except STANDING
DBP	Young and elderly subjects ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 90 mmHg and increase from baseline ≥ 10 mmHg	Proposed change: To be are applied for all positions (including missing) except STANDING
Orthostatic Hypotension	SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg	

Parameter	PCSV For Studies in healthy subjects only	Comments
Weight	≥ 5 % increase versus baseline ≥5% decrease versus baseline	FDA Feb 2007
ECG parameters		CPMP 1997 guideline
HR	≤ 40 bpm and decrease from baseline ≥ 20 bpm ≥ 100 bpm and increase from baseline ≥ 20 bpm	
PR	≥ 220 ms	
QRS	≥ 120 ms	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Males Females Borderline 431-450 ms 451-470 ms Prolonged* > 450 ms > 470 ms QTc ≥500 ms ≥ 500 ms <u>Increase versus baseline</u> (Males and Females) Borderline Δ 30-60 ms Prolonged * Δ > 60 ms	To be applied to any kind of QT correction formula *QTc prolonged and ΔQTc > 60 ms are the PCSA to be identified in individual subjects/patients listings.

10.4. Posterior Probability of Assurance for LDH Normalization

Probability of assurance based on a non-informative prior:

Interim Posterior Probability (IPP): Pr(Pr(LDH ≤ 1.5x ULN)>0.9)											
Interim	Observed number of patients with LDH > 1.5x ULN										
n	0	1	2	3	4	5	6	7	8	9	10
1	0.40	0.01									
2	0.51	0.05	<0.01								
3	0.59	0.10	<0.01	<0.01							
4	0.66	0.15	0.02	<0.01	<0.01						
5	0.71	0.20	0.03	<0.01	<0.01	<0.01					
6	0.75	0.25	0.05	<0.01	<0.01	<0.01	<0.01				
7	0.79	0.30	0.07	0.01	<0.01	<0.01	<0.01	<0.01			
8	0.81	0.35	0.09	0.01	<0.01	<0.01	<0.01	<0.01	<0.01		
9	0.84	0.39	0.12	0.02	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	
10	0.86	0.44	0.14	0.03	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
11	0.88	0.48	0.17	0.04	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
12	0.89	0.52	0.20	0.06	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Note: Pr(LDH ≤ 1.5x ULN)>0.9 is the intended assurance level, and IPP is the probability of obtaining that assurance level based on observed data. A Jeffery's non-informative prior Beta(0.5, 0.5) is used.											

Probability of assurance based on an informative prior:

Interim Posterior Probability (IPP): Pr(Pr(LDH ≤ 1.5x ULN)>0.9)											
Interim	Observed number of patients with LDH > 1.5x ULN										
n	0	1	2	3	4	5	6	7	8	9	10
1	0.86	0.44									
2	0.88	0.48	0.17								
3	0.89	0.52	0.20	0.06							
4	0.91	0.56	0.24	0.07	0.01						
5	0.92	0.59	0.27	0.09	0.02	<0.01					
6	0.93	0.62	0.30	0.10	0.03	<0.01	<0.01				
7	0.94	0.65	0.33	0.12	0.04	<0.01	<0.01	<0.01			
8	0.94	0.68	0.36	0.15	0.04	0.01	<0.01	<0.01	<0.01		
9	0.95	0.71	0.40	0.17	0.05	0.01	<0.01	<0.01	<0.01	<0.01	
10	0.96	0.73	0.43	0.19	0.07	0.02	<0.01	<0.01	<0.01	<0.01	<0.01
11	0.96	0.76	0.46	0.21	0.08	0.02	<0.01	<0.01	<0.01	<0.01	<0.01
12	0.97	0.78	0.49	0.24	0.09	0.03	<0.01	<0.01	<0.01	<0.01	<0.01
Note: Pr(LDH ≤ 1.5x ULN)>0.9 is the intended assurance level, and IPP is the probability of obtaining that assurance level based on observed data. An informative prior Beta(0.5, 9.5) is used, which represents a prior effective sample size of 0.5+9.5=10 and reflects a probability of 0.05 of failing to show LDH ≤ 1.5x ULN											

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ESig Approval	[redacted]19 19:12:57 GMT+0000
ESig Approval	[redacted]000
ESig Approval	[redacted]-2019 15:39:50 GMT+0000

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