Clinical Development and Regulatory Affairs
Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	**AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF REGN3918 IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA**
Compound:	REGN3918
Protocol Number:	R3918-PNH-1868
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Version/Date:	Original Statistical Analysis Plan / Jun 4, 2021

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 antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice a day
CH50	Total complement hemolytic activity assay
CRF	Case report form (electronic or paper)
ECG	Electrocardiogram
EOT	End of treatment
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
ICF	Informed consent form
ICH	International Council for Harmonisation
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MAVE	Major adverse vascular event
NAb	Neutralizing antibody
OLE	Open-label extension
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PT	Preferred term
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
ULN	Upper limit of normal
WOCP	Women of childbearing potential

1. OVERVIEW

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 current clinical trial (R3918-PNH-1868) is an open-label extension (OLE), single-arm study with a 2-year open-label treatment period followed by an optional post-end-of-treatment (EOT) period with continued treatment with REGN3918 of variable duration in patients with PNH who have completed 1 of the 2 parent studies (R3918-PNH-1852 [redacted]). In the parent studies, the duration of the treatment period is 26 weeks because it is anticipated that there will be a rapid initiation or maintenance of clinical benefit of REGN3918 on intravascular hemolysis. It is expected, if approved, that REGN3918 would be administered in clinical practice for a duration of years, which is consistent with the current practice for eculizumab and ravulizumab. The longer-term treatment duration provided through this study will enable the evaluation of whether or not the initial clinical benefit anticipated in the parent studies is maintained and will provide further insight into the safety profile.

The study population includes patients coming from the parent study R3918-PNH-1852, which enrolled 24 patients with PNH having active signs and symptoms who are complement inhibitor-naïve or have not recently received complement inhibitor therapy. [redacted] was planned, and would have provided patients for the current study, but it was canceled for business reasons.

Therefore, R3918-PNH-1868 will enroll up to 24 patients from the parent study.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety, tolerability, and effect on intravascular hemolysis (i.e., proportion of patients achieving LDH ≤1.5× upper limit of normal [ULN] over 26 weeks of REGN3918 treatment in patients with PNH).

1.2.2. Secondary Objectives and Exploratory Objectives

The secondary objectives of the study are:

- To evaluate the long-term effect of REGN3918 on intravascular hemolysis
- To assess the concentrations of total REGN3918 in serum
- To evaluate the immunogenicity of REGN3918

The exploratory objectives of the study are:

- To explore the long-term effect on clinical thrombotic events
- To explore the long-term effect on renal function
- To explore the long-term effect of REGN3918 on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To explore the long-term effect of REGN3918 on the concentrations of total C5 protein
- To collect future biomedical research samples from consented patients in order 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 study contains 2 study periods: the 2-year open-label treatment period and the optional post-EOT period (i.e., after completion of the 2-year open-label treatment period).

Patients who have completed the parent study R3918-PNH-1852 will be eligible for screening for this OLE study. The 2-year open-label treatment period will have assessments as described in the protocol occurring approximately quarterly and ending at week 104 (EOT).

The transition of treatment with REGN3918 from the parent study to the OLE study is planned to be uninterrupted. Therefore, the day 1 visit of the 2-year open-label treatment period will occur on the same visit as the EOT study visit in the parent study and overlapping assessments do not need to be repeated in this OLE study. Patients will continue their dose of up to 800 mg QW from the parent study starting at day 1 in the OLE study, with a potential change in dose/dosing interval (on day 1 or subsequently) only for patients in cohort A of the parent study R3918-PNH-1852, if applicable. As part of risk mitigation for this study, it is recommended for patients to receive updated meningococcal vaccination, daily oral antibiotic prophylaxis, and counselling regarding risk of Neisseria gonorrhea, as applicable. In addition, blood transfusions should proceed according to the algorithm in the protocol. Breakthrough hemolysis is defined in the protocol.

Patients who do not enter the optional post-EOT period should be followed for 21 weeks after the end of the 2-year open-label treatment period. Patients should return for monthly visits with assessments corresponding to week 104 (EOT) visit.

The optional post-EOT period includes continued REGN3918 treatment of variable duration. Patients may continue REGN3918 treatment after they have completed the 2-year open-label treatment period and if they derive clinical benefit and have potential risk upon discontinuation of REGN3918. Eligible patients will be asked to provide separate consent for continuing onto the optional post-EOT period. The optional post-EOT period ends when 1 of the following is met:

- Clinical development of REGN3918 is terminated
- Risk-to-benefit profile of REGN3918 in this patient population is deemed unfavorable
- REGN3918 is approved by the regulatory authority governing the location of the study site

The additional safety information accrued in the post-EOT period will be reported.

It is projected that the first patients enrolled and who continue into the optional post-EOT period will have a study duration of approximately 4 years and the last patients enrolled will have a study duration of at least 2 years. However, the study duration is dependent on the criteria mentioned in the protocol.

At a study level, the end of study is defined as the last visit of the last patient.

At a patient level, the end of study is defined as the end of treatment period (EOT) or, depending on the particular circumstances of the patient, at the end of post-EOT period, which is of variable duration.

2.2. Sample Size and Power Considerations

As this study is a follow-on that plans to include patients from the parent study R3918-PNH-1852, no calculation for sample size was performed. It is expected to enroll up to 24 patients with PNH based on the maximum number of patients who could complete the parent study in the selected/participating countries.

2.3. Study Plan

The Study event table is presented in Appendix 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 (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 REGN3918 following the first dose of study drug.

3.4. The Anti-drug Antibody Analysis Set

The ADA analysis set (AAS) includes all patients who received study drug and had at least one non-missing ADA result following the first dose of study drug.

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.

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
- Months from PNH diagnosis to baseline
- History of PNH signs and symptoms

4.2. Medical History

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

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 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.

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.

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

4.4. Prohibited Medication During Study

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 besides REGN3918 starting on Day 1

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variable

The proportion of patients achieving LDH ≤1.5×ULN over 26 weeks, defined as LDH ≤1.5×ULN at every scheduled time point up to week 26 (inclusive), will be the primary efficacy variable.

4.5.2. Key Secondary Efficacy Variables

The key secondary efficacy variables are:

- The proportion of patients with breakthrough hemolysis over 26 weeks
- The rate and number of units of transfusion over week 26

4.5.3. Other Secondary Efficacy Variables

Other secondary efficacy variables are:

- The proportions of patients with breakthrough hemolysis over 78 weeks and over 104 weeks
- The rates and numbers of units of transfusion with RBCs over 78 weeks and over 104 weeks
- The proportions of patients who are transfusion-free (with RBCs) over over 26 weeks, over 78 weeks, and over 104 weeks
- The proportions of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤1.5×ULN at every scheduled time point up to week 78 (inclusive), and week 104 (inclusive)
- The proportions of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤1.0×ULN at every scheduled time point up to week 26 (inclusive), week 78 (inclusive), and week 104 (inclusive)
- Changes and percent changes in LDH from baseline of the OLE study to week 26, week 78, and week 104
- Changes in RBC hemoglobin levels from baseline of the OLE study to week 26, week 78, and week 104

- Changes in free hemoglobin levels from baseline of the OLE study to week 26, week 78, and week 104
- Concentrations of REGN3918 in serum assessed throughout the study
- Incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3918 throughout the study

4.5.4. Exploratory Efficacy Variables

The exploratory efficacy variables are:

- Changes in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline of the OLE study to week 26, week 78, and week 104
- Changes in haptoglobin from baseline of the OLE study to week 26, week 78, and week 104
- Changes in bilirubin from baseline of the OLE study to week 26, week 78, and week 104
- Changes in reticulocyte count from baseline of the OLE study to week 26, week 78, and week 104
- Changes and percent change in CH50 from baseline of the OLE study to week 26, week 78, and week 104
- Changes in total C5 from baseline of the OLE study to week 26, week 78, and week 104
- Incidences of MAVE over 26 weeks, over 78 weeks, and over 104 weeks

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 will be graded according to the criteria given in the protocol.

Section 10.1.1 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):

- 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 rate, and sitting 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 variable is concentration of total REGN3918. The sampling time points are specified in Appendix 10.2.

The total target variable is the concentrations of total C5 at the sampling times specified in Appendix 10.2.

4.8. Immunogenicity Variables

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

4.9. Pharmacodynamic Variables

CH50 is included as a pharmacodynamic biomarker. Change and percent change in CH50 from baseline of the OLE study to week 26, week 78, and week 104 will be assessed.

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. Patients at VHP sites will have more visits than those listed in the Schedule of Events, and these patients will have more visits with laboratories, vital signs and physical examinations. These extra visits will be included in the by-visit tables for those domains.

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.

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. 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 post-treatment period.

5.5. Patient Disposition

The following displays will be provided:

- The total number of screened patients
- 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.

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. SC injection location will also be summarized overall and by the person administering the injection.

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:

- ≥ 13 weeks
- ≥ 26 weeks
- ≥ 39 weeks
- ≥ 52 weeks
- ≥ 65 weeks
- ≥ 78 weeks
- ≥ 91 weeks
- ≥ 104 weeks

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 primary efficacy endpoint is the proportion of patients achieving LDH ≤1.5×ULN over week 26, defined as LDH ≤1.5×ULN at every scheduled time point up to week 26 (inclusive).

For this efficacy endpoint, the analysis set consists of all FAS patients. Patients who fulfill 1 or more of the following will be considered as not meeting the endpoint:

1. Discontinue before week 26
2. Have missing LDH value at week 13 and week 26
3. Have breakthrough hemolysis (as defined in the secondary endpoint and based on investigator judgment) while on treatment in the first 26 weeks

Patients who do not fulfill the above criteria will be evaluated based on their non-missing LDH measurements.

The proportion of patients achieving LDH ≤1.5×ULN over week 26 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 primary endpoint analysis will also be repeated on the subset of patients who were responders in the parent study.

5.7.2. Analysis of Secondary Efficacy Variables

Key Secondary Efficacy Variables:

For the key secondary variable of the rate of breakthrough hemolysis through week 26, the numerator is the number of patients with at least one 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 denominator is the number of patients who achieved initial disease control. This proportion 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.

For the key secondary variable of the number of units of transfusion over 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 key secondary variable of the rate of transfusion with RBCs through week 26 (annualized to transfusions per year), 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: Transfusions with RBCs during the study should proceed according to the following predefined criteria that will trigger a transfusion; however, the actual number of units to be transfused is at the discretion of the investigator:

- Transfuse with RBC(s) if the post-baseline (of the OLE) hemoglobin level is <9 g/dL with symptoms resulting from anemia, or
- Transfuse with RBC(s) if the post-baseline (of the OLE) hemoglobin level is <7 g/dL.

Of note, hemoglobin measurements from local laboratories are allowed.

The key secondary endpoint analyses will also be repeated on the subset of patients who were responders in the parent study.

Other Secondary Efficacy Variables

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

- Percent changes and changes from baseline of the OLE study in LDH levels to week 26, week 78, and week 104
- Changes from baseline of the OLE study RBC hemoglobin levels to week 26, week 78, and week 104
- Changes from baseline of the OLE study in free hemoglobin levels to week 26, week 78, and week 104

For these variables, means and 95% confidence intervals based on 1-sample t-test will be reported for applicable weeks.

For secondary endpoints that are defined by any occurrence of a defined event during a period, the analysis set will consist of all FAS patients. This category of endpoints includes:

- The proportions of patients with breakthrough hemolysis over 78 weeks and over 104 weeks
- The proportions of patients who are transfusion-free (with RBCs) over 26 weeks, over 78 weeks, and over 104 weeks
- The proportions of patients achieving adequate control of their intravascular hemolysis, defined as LDH $\leq$1.5×ULN at every scheduled time point up to week 78 (inclusive), and week 104 (inclusive)
- The proportions of patients achieving normalization of their intravascular hemolysis, defined as LDH $\leq$1.0×ULN at every scheduled time point up to week 26 (inclusive), week 78 (inclusive), and week 104 (inclusive)

For these binary efficacy endpoints, means and 95% confidence intervals, by normal approximation for primary analyses and by the exact Clopper Pearson method for sensitivity analyses, will be calculated.

For the rates and numbers of units of transfusion with RBCs over week 78 and week 104, the analysis set consists of all FAS patients. 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. Rates (transfusions per year) will be adjusted for the time on study. A transfusion will be counted only if the transfusion follows the predefined transfusion algorithm.

See Section 5.9 for a description of the analyses of the following secondary efficacy variables:

- Concentrations of REGN3918 in serum assessed throughout the study
- Incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3918 throughout the study

5.8. Analysis of Safety Data

The analysis of safety and tolerability 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 Appendix 10.3 .

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF for the OLE study to before the first dose of study drug of the OLE study.
- The treatment period is defined as the time from the first dose of study drug of the OLE study to the end of the 2-year open-label treatment period, or, in patients who prematurely discontinue/do not enter into the optional post-EOT period, from the first dose of study drug of the OLE study to the last dose of study drug + 21 weeks (i.e., 147 days).
- The post-EOT period of the OLE study is defined as the time after the treatment period of the OLE study.

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.

Treatment-emergent adverse events are defined as those AEs that occur or worsen in severity or become serious during the treatment period or represent the exacerbation of a pre-existing condition during the 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
- 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 severity and SOC and PT
- Serious adverse events: All TEAEs by SOC and PT
- Death: All fatal TEAEs by SOC
- Discontinuation: All TEAEs by SOC and PT
- Non-serious related TEAEs by SOC and PT

Counts will be provided by parent study and overall for each PT within each SOC. Percentages will be calculated using the number of patients from the safety population.

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 (see Section 4.6.2) 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.

Laboratory test results (absolute values and changes from baseline) will be summarized by scheduled assessment time with descriptive statistics.

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

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

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

Unless otherwise specified, laboratory displays will be from the central laboratory.

5.8.4. Analysis of Vital Signs

Vital signs (absolute values and changes from baseline of temperature, pulse, blood pressure) will be summarized by scheduled assessment time with descriptive statistics.

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 at each time point using descriptive statistics.

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

The PK variable is concentration of total REGN3918 in serum over time. The total target variable is the concentrations of total C5 in serum over time.

A summary of total drug concentrations and total C5 will be presented by nominal time point (i.e., 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 (%), minimum, Q1, median, Q3, and maximum.

No formal statistical analysis will be performed.

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 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 weeks 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 ADA-negative patients
- Number (n) and percent (%) of pre-existing patients
- Number (n) and percent (%) of treatment-emergent ADA positive patients by ADA titer categories
  - 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 by ADA titer categories

Listings of all ADA titer levels will be provided for pateints with pre-existing, treatment-boosted and treatment-emergent ADA responses.

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 REGN3918 will be explored. Plots of REGN3918 concentration may be provided for analyzing the potential impact of ADA category and maximum titer on PK.

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-baseline titer for 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 Pharmacodynamic and Biomarker Data

Descriptive statistics will be presented for the following PD and biomarker variables:

- Changes and percent change in CH50 from baseline of the OLE study to week 26, week 78, and week 104
- Changes in total C5 from baseline of the OLE study to week 26, week 78, and week 104 CH50 and C5.

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, for efficacy the baseline assessment is defined as the latest available measurement taken before the first administration of study treatment in the OLE study (which corresponds to the last available measurement from the parent study, usually collected at the parent study's EOT visit), as it is expected that at this time the two different populations from the parent studies should converge with regard to their control of intravascular hemolysis.

For safety assessments, the baseline is defined as the latest available measurement taken before the first administration of OLE treatment. For patients enrolled but not treated, the baseline will be the latest available measurement before enrollment in the OLE.

6.2. 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.

6.2.1. 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. 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 (described in Section 5.8) 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.

No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

6.2.2. PCSV

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

6.2.3. 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.

6.3. Analysis Visit Windows

Data analyzed by visit (including efficacy, laboratory, vital sign, and ECG data) will be summarized by the study scheduled visits described in Appendix 10.2 (Schedule of Time and Events). Except for efficacy variables, the analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit and end of treatment (EOT) have the potential to be summarized. 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. Windows are given in Table 1.

Table 1: General Analysis Windows

Visit	Targeted Study Day	Window
Day 1	1	1
Week 13	92	[47, 137]
Week 26	183	[138, 228]
Week 39	274	[229, 319]
Week 52	365	[320, 410]
Week 65	456	[411, 501]
Week 78	547	[502, 592]
Week 91	638	[593, 683]
Week 104	729	[684, 773]

For efficacy variables, the analysis windows are the target dates ± 14 days for all visits starting with the Week 13 visit. These windows are given in Table 2.

Table 2: Efficacy Analysis Windows

Visit	Targeted Study Day	Window
Week 13	92	[78, 106]
Week 26	183	[169, 197]
Week 39	274	[260, 288]
Week 52	365	[351, 379]
Week 65	456	[442, 470]
Week 78	547	[533, 561]
Week 91	638	[624, 652]
Week 104	729	[715, 743]

6.4. 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.

An interim data lock(s) for regulatory submissions of REGN3918 or publication purposes may be conducted. Safety data such as adverse event, laboratory parameters, vital signs, and ECG may be included in the analysis.

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, Exact methods, 1-sample t-test	MI and subgroup analyses for primary	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	2-Year Open-Label Treatment Period[1]									Optional Post-EOT Period[2]
Study Week	Day 1/ Week 0[5]	Week								Every 6 months after EOT until End of Post-EOT period
		13	26	39	52	65	78	91	EOT (104)	
Visit Window (weeks)		±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	± 2 w
Clinic Visit	X	X	X	X	X	X	X	X	X	X
Screening/Baseline:										
Inclusion/Exclusion criteria	X									
Informed consent	X									X[2]
Demographics	X									
Medical history	X									
Height	X									
Risk assessment for Neisseria gonorrhea[3]	X									
Enrollment via IVRS/IWRS	X									
Treatment:										
REGN3918 administration[4]	- ----------X[4]----------									X
Oral antibiotics	- ----------X----------									X
Meningococcal vaccine (as needed)	- ----------X----------									X
Patient diary (if applicable, compliance check)[5]	X	X	X	X	X	X	X	X	X	X

Study Period	2-Year Open-Label Treatment Period[1]									Optional Post-EOT Period[2]
Study Week	Day 1/ Week 0[5]	Week								Every 6 months after EOT until End of Post-EOT period
		13	26	39	52	65	78	91	EOT (104)	
Visit Window (weeks)		±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	± 2 w
Clinic Visit	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Serum LDH[6]	X	X	X	X	X	X	X	X	X	X
Transfusion record update	X	X	X	X	X	X	X	X	X	
RBC hemoglobin[7]	X	X	X	X	X	X	X	X	X	
Free hemoglobin[7]	X	X	X	X	X	X	X	X	X	
Safety:										
Body weight	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X		X		X		X	X
Electrocardiogram	X				X				X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Patient safety card for *Neisseria meningitidis*	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:										
Hematology[7]	X	X	X	X	X	X	X	X	X	X
Blood chemistry[6]	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCP only)	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Titers to *Neisseria meningitidis* (only if indicated as per local practice)[8]	X	X	X	X	X	X	X	X	X	X

Study Period	2-Year Open-Label Treatment Period[1]								Optional Post-EOT Period[2]
Study Week	Day 1/ Week 0[5]	Week							Every 6 months after EOT until End of Post-EOT period
		13	26	39	52	65	78	91	EOT (104)	
Visit Window (weeks)		±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	± 2 w
Clinic Visit	X	X	X	X	X	X	X	X	X	X
PK, ADA and Biomarker Samples:										
PK sample of REGN3918	X	X	X	X	X	X	X	X	X	
Total C5 (plasma)	X	X	X	X	X	X	X	X	X	
Complement hemolytic assay (serum CH50)	X	X	X	X	X	X	X	X	X	
Haptoglobin	X	X	X	X	X	X	X	X	X	
Bilirubin[6]	X	X	X	X	X	X	X	X	X	
Reticulocyte count[7]	X	X	X	X	X	X	X	X	X	
ADA sample for REGN3918	X		X		X		X		X	X[9]
Optional Research:										
Future biomedical research (optional)	X	X	X		X				X	
Whole blood for DNA isolation (optional)[10]	X									

Footnotes for the Schedule of Events Table

1. After completion of the 2-year open-label treatment period, patients who do not enter into the optional post-EOT period should be followed for 21 weeks. Patients should return for monthly clinic visits with assessments corresponding to week 104 (EOT) visit.

2. The optional post-EOT period includes continued REGN3918 treatment of variable duration. Patients may continue REGN3918 treatment after they have completed the 2-year open-label treatment period and if they derive clinical benefit and have potential risk to discontinue REGN3918. The optional post-EOT period ends when 1 of the following is reached: clinical development of REGN3918 is terminated, risk-to-benefit profile of REGN3918 in this patient population is deemed unfavorable, or REGN3918 is approved by the regulatory authority governing the location of the study site. Patients will be asked to provide separate consent for continuing onto the optional post-EOT period.

3. Risk assessment for Neisseria gonorrhea is described in the protocol.

4. Study drug administration will occur QW throughout the entire study, starting from the day 1 visit until and including the end-of-treatment visit (for the 2-year open-label treatment period) and for the optional post-EOT period (if applicable). Administration of study drug may be done at the clinical site, by a healthcare professional at the patient's home, or by self-administration/administration by the patient or designated person, respectively. These various options for administration will depend on the preference of the investigator and patient, the availability of clinical supply, and the home healthcare visiting professional, and presentation of the study drug that may change during the course of the study. If the presentation of the study drug becomes available for self-administration /administration by patient or designated person, then sufficient injection training at the scheduled administration(s) with REGN3918 will be provided prior to undertaking study drug administration. Study drug kits will be dispensed at the clinical site visit or, as applicable, transported to the patient by a healthcare professional or by a DTP service provider.

   The recommended daily oral antibiotic prophylaxis will commence on the day of dosing and will consist of penicillin V 500 mg BID, or Erythromycin 500 mg BID in the case of penicillin allergy (to be determined by the investigator). See the protocol for details.

5. A patient diary will be provided to collect information that may include AEs, study drug administration, concomitant medications, vital signs, etc. depending on availability of a home healthcare visiting professional and other considerations. For self-administration/administration by a designated person, a compliance check with the patient diary will be undertaken at clinic visits.

6. On visits where chemistry overlaps with serum LDH and/or bilirubin assessments, the chemistry testing will include these assessments.

7. On visits where hematology overlaps with RBC hemoglobin, free hemoglobin, and/or reticulocyte count assessments, the hematology testing will include these assessments.

8. Revaccinate patients at any time throughout the study. If the patient has had titers measured for *Neisseria meningitidis* and they demonstrate inadequate level of immunity, then revaccination should be done.

9. ADA samples will be collected every 12 months after EOT and until the end of post-EOT period. Samples will be used for detecting the presence of ADA only; NAb positivity will only be assessed for treatment-emergent ADA-positive samples.

10. Whole blood sample for DNA should be collected on day 1 (predose) but can be collected at a later study visit. Patients who had consented to DNA testing in the parent study and had provided a sample for analysis do not need to provide separate consent/sample for the OLE study.

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
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.

Parameter	PCSV For Studies in healthy subjects only	Comments
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
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.

Parameter	PCSV For Studies in healthy subjects only	Comments
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	
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	

Parameter	PCSV **For Studies in healthy subjects only**	Comments
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.

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