RA PHARMACEUTICALS, INC.

STATISTICAL ANALYSIS PLAN

RA101495-01.201: A PHASE 2 MULTICENTER, OPEN-LABEL, UNCONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RA101495 IN SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

RA101495-01.201

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DOCUMENT HISTORY

Version	Author	Description
1.0	Jim MacDougall	• Original Version
2.0	Jim MacDougall	• LDH analysis < 1.5 ×ULN added
3.0	Jim MacDougall	• CH50 removed as an endpoint • ADA removed as an endpoint • Additional text added and/or modified for clarification of analysis methods
4.0	Jim MacDougall	• Removed primary evaluation period for secondary endpoints and LDH < 1.5 ×ULN analysis

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT/APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the drug concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
C5	complement component 5
cm	centimeter
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol 5D questionnaire
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
GGT	gamma-glutamyl transferase
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization
INR	international normalized ratio
ISR	injection site reaction
kg	kilogram
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NCI	National Cancer Institute

PD	pharmacodynamics
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PT	Preferred Term
PTT	partial thromboplastin time
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
sRBC	sheep red blood cell
TEAE	treatment-emergent adverse event
t_{max}	time to corresponding Cmax
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
<LLOQ	below the lower limit of quantification

1 INTRODUCTION

Ra Pharmaceuticals, Inc. is developing RA101495, a subcutaneously–administered cyclic peptide that inhibits the cleavage of complement component 5 (C5), for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

Study RA101495-01.201 is a multicenter, open-label, uncontrolled study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of RA101495 in subjects with PNH.

The study will enroll two separate cohorts based on prior eculizumab treatment history.

- Cohort A (Naïve) will include subjects who have not received eculizumab for treatment of PNH
- Cohort B (Switch) will include subjects who have received treatment with eculizumab for at least 6 months prior to Screening.

The planned enrollment is approximately 8-12 subjects in Cohort A and approximately 6-8 subjects in Cohort B, for a total of up to 20 subjects.

This Statistical Analysis Plan (SAP) describes data-handling and statistical procedures to be used for the analysis and reporting of efficacy and safety data collected under Study RA101495-01.201 (version 1.1 20 October 2016) and presented in the clinical study report (CSR). They are based on those presented in Section 13 of the study protocol. Any post-hoc or exploratory analyses not specified in this SAP will be identified as such when they are presented in the CSR. This SAP has been developed and finalized prior to locking the clinical database.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials” and the most recent ICH-E3 Guideline, entitled “Guidance for Industry: Structure and Content of Clinical Study Reports.”

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

The objectives of the study are

- To assess the safety and tolerability of RA101495 in subjects with PNH
- To assess preliminary efficacy of RA101495 in subjects with PNH

- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of RA101495 in subjects with PNH.

2.2 STUDY DESIGN

Study RA101495-01.201 is a multicenter, open-label, uncontrolled study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of RA101495 in subjects with PNH.

The study will enroll two separate cohorts based on prior eculizumab treatment history.

- Cohort A (Naïve) will include subjects who have not received eculizumab for treatment of PNH
- Cohort B (Switch) will include subjects who have received treatment with eculizumab for at least 6 months prior to Screening.

The planned enrollment is approximately 8-12 subjects in Cohort A and approximately 6-8 subjects in Cohort B, for a total of up to 20 subjects.

Cohort A will commence enrollment prior to Cohort B. Cohort B will not be opened until safety and efficacy data from at least 2 subjects completing the Week 2 visit in Cohort A have been reviewed by the Sponsor and Study Investigators, and evidence of hemolysis suppression is demonstrated.

The study includes an 8-week screening period and a 12-week Treatment Period. During the Treatment Period, subjects will return to the clinic weekly for the first 4 weeks followed by visits every 2 weeks to evaluate safety, tolerability, efficacy, PK and PD. Additional assessments will include immunogenicity, Quality of Life (QOL) questionnaires, biomarker samples, and optional pharmacogenomics. Safety assessments include physical exam, vital signs, electrocardiogram (ECG), clinical laboratory tests, and adverse events (AEs).

At the conclusion of the Treatment Period subjects who complete the study and are demonstrating benefit will have the option to enroll in an extension study to continue receiving treatment with RA101495. Alternatively, they may opt to receive standard-of-care treatment off study, after consultation with their treating physician. If the subject withdraws early from the RA101495-01.201 study for any reason, he/she will not be eligible for the extension study.

From the Week 2 visit onwards, if a subject has not achieved an adequate response (defined as a lactate dehydrogenase [LDH] <1.5 x ULN), and following evaluation of safety and tolerability data by the investigator and the medical monitor, the dose should be escalated to 0.3 mg/kg daily. The dose may also be escalated to 0.3 mg/kg daily at any time in the event of an overt breakthrough hemolysis episode (e.g. hemoglobinuria).

The total duration of study participation for all subjects will include a Screening Period of up to 8 weeks and a 12-week Treatment Period for a total of up to 20 weeks.

2.2.1 Number of Patients

Up to 20 subjects will be enrolled in the study in two cohorts:

- Cohort A (Eculizumab Naïve): approximately 8-12 subjects
- Cohort B (Eculizumab Switch): approximately 6-8 subjects.

2.2.2 Randomization and Blinding Procedures

This is an open-label single-arm uncontrolled study.

2.2.3 Safety Assessments

Safety assessments include physical examination, vital signs, electrocardiogram, *Neisseria meningitidis* testing and prophylactic treatment, adverse events, blood chemistry and hematology, urinalysis, pregnancy test, PNH clone and testing for immunogenicity.

2.2.3.1 Physical Examination

Physical examinations will include the following assessments:

- General inspection
- Weight (kg) and height (height in cm to be collected at screening visit only)
- Examination of the injection site and draining nodes
- Head/ears/eyes/nose/throat examination
- Mucosal examination for icterus
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Assessment for neurological deficits
- Musculoskeletal assessment

Any abnormalities found will be recorded in the eCRF.

2.2.3.2 Vital Signs

Vital signs (heart rate, body temperature, and blood pressure) will be measured in the sitting position after resting for at least 5 minutes.

2.2.3.3 Electrocardiogram

ECGs will be assessed as normal or abnormal by the investigator; any abnormal findings will be described in the eCRF and the investigator will assess clinical significance.

2.2.3.4 *Neisseria meningitidis* Testing

All subjects must have a negative result for *Neisseria meningitidis* colonization via a throat swab prior to study entry.

2.2.3.5 Adverse Event Recording

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following are not considered to be AEs despite requiring hospitalization:

- Pre-existing conditions that, in the opinion of the investigator, did not worsen or progress during study participation
- Routinely scheduled procedures or treatment
- Elective procedures that had been scheduled prior to study participation (i.e. signing of the informed consent form (ICF))

A Serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening (note that this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect

An SAE may also be any other important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events include intensive treatment in an emergency room or

at home for bronchospasm, hyperkalemia, or convulsions that do not result in a formal hospitalization.

Elective hospitalizations scheduled prior to study participation (i.e. signing of the ICF) should not be reported as SAEs.

2.2.3.6 Blood Chemistry and Hematology

Clinical chemistry and hematology analytes to be collected are identified in Table 1 and should be performed as specified in the Time and Events (Table 2).

Table 1: Clinical Chemistry, Hematology, and Coagulation Analytes

Clinical Chemistry	Hematology
alanine aminotransferase (ALT) albumin alkaline phosphatase (ALP) amylase aspartate aminotransferase (AST) bicarbonate bile acids bilirubin (total, direct, and indirect) blood urea nitrogen (BUN) calcium chloride creatinine gamma-glutamyl transferase (GGT) glomerular filtration rate MDRD[a] glucose lactate dehydrogenase (LDH) lipase potassium sodium total protein uric acid	free hemoglobin haptoglobin hematocrit hemoglobin mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) mean corpuscular volume (MCV) platelet count RBC count reticulocyte count and % white blood cell (WBC) count and differential (%) • basophils • eosinophils • lymphocytes • monocytes • neutrophils **Coagulation** international normalized ratio (INR) prothrombin time (PT) fibrinogen activated partial thromboplastin time (APTT) **Other** C-reactive protein (CRP) creatine phosphokinase (CPK)

a: presented in listings only (not summarized).

2.2.3.7 Urinalysis

A urinalysis will be performed to measure pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, RBC casts, bilirubin crystals, uric acid crystals, and cells (squamous epithelial, transitional epithelial, and tubular epithelial). A microscopic examination will be performed, if necessary. Hemoglobinuria will be assessed using a urine colorimetric scoring system (a 0-10 point scale).

The following urinalysis parameters will be summarized: Erythrocytes, specific gravity, and pH. All other urinalysis assessments will be presented in listings.

2.2.3.8 Pregnancy Test

A serum pregnancy test for human chorionic gonadotropin will be performed on female subjects of childbearing potential at Screening.

A urine dipstick pregnancy test (human chorionic gonadotropin) will be performed on female subjects of childbearing potential at Day 1 pre-dose and Day 29, Day 57, and Day 84 (End of Study).

2.2.3.9 PNH Clone

Blood sample for measurement of PNH close size will be collected at Screening (i.e., most recent PNH clone size prior to study entry), Day 29, Day 57, and Day 84 (or End-of-Study Visit). PNH close size will be determined by peripheral blood flow cytometry analysis (RBCs and granulocytes).

2.2.3.10 Immunogenicity

Blood samples for ADAs will be collected prior to dosing on Day 1 and on Day 29, Day 57, and Day 84 (or at the End-of-Study Visit) in all enrolled subjects. Samples will be sent to a central laboratory to determine the presence or absence of antibodies against RA101495 using a validated assay.

Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

2.2.4 Efficacy Assessments

Efficacy assessments include the measurement of serum LDH levels as a measure of intravascular hemolysis. Additional assessments will include laboratory assessments of total bilirubin, total hemoglobin, free hemoglobin, haptoglobin, reticulocytes, and hemoglobinuria.

2.2.5 Exploratory Assessments

Exploratory endpoints include:

- Changes from baseline in QOL questionnaires
  - European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC QLQ-C30)
  - Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)
  - EuroQol 5D (EQ-5D)
- Treatment satisfaction questionnaire

2.2.6 Pharmacodynamic Assessments

The pharmacodynamics (PD) assessments include: sheep red blood cell (sRBC), Wieslab enzyme-linked immunosorbent assay (ELISA), and C5. Blood samples for the PD assessments occur at each study visit (except the screening visit).

Blood samples for RA101495 PD occurs at the following time points in relationship to the first dose of RA101495: pre-dose (within 1 hour before first dose administration) and at 1, 3, and 6 hours post-dose on Day 1.

For subjects who have a dose increase to 0.3 mg/kg, samples for PD should be collected at pre-dose Day 1 of the new dose.

2.2.7 Pharmacokinetic Assessments

Blood samples for RA101495 pharmacokinetics (PK) occurs at the following time points in relationship to the first dose of RA101495: pre-dose (within 1 hour before first dose administration) and at 1, 3, and 6 hours post-dose on Day 1.

For subjects who have a dose increase to 0.3 mg/kg, samples for PK should be collected at pre-dose Day 1 of the new dose.

On other clinic visit days, PK and PD samples should be collected prior to administration of RA101495.

For subjects in Cohort B only, blood samples for PK of eculizumab should be collected at screening, Day 1, Day 15, Day 29, and Day 43 (at 2-week, 4-week, and 6-week) visits. The sample should be collected prior to administration of RA101495.

2.2.8 Schedule of Assessments

The following is the time and events table

Table 2: Time and Events Table

Phase	Screening Period	Treatment Period								
Study Week →	**-8 to 1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12 (End of Study)**
Study Day[a] →	**-56 to -1**	**1 ± 2[b]**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 2**	**43 ± 4**	**57 ± 4**	**71 ± 4**	**84 ± 4**
Study Procedure ↓										
ICF process and signed ICF	X									
Review eligibility criteria	X	X								
Medical history and demographics	X									
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X				X				X
Height and weight[c]	X	X				X				X
Vital signs	X	X				X				X
Electrocardiogram	X	X				X				X
Neisseria throat swab[d]	X									
Neisseria vaccination[d]		X				X				
Ciprofloxacin treatment[d]		X	X	D14						
Blood chemistry[e]	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Coagulation[f]	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
PNH clone size	X					X		X		X

Phase	Screening Period	Treatment Period								
Study Week →	**-8 to 1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12 (End of Study)**
Study Day[a] →	**-56 to -1**	**1 ± 2[b]**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 2**	**43 ± 4**	**57 ± 4**	**71 ± 4**	**84 ± 4**
Pregnancy test[g]	X	X				X		X		X
Adverse events		X	X	X	X	X	X	X	X	X
Assessment of injection site reactions[h]		X	X	X	X	X	X	X	X	X
Pharmacokinetics RA101495[i]		X	X	X	X	X	X	X	X	X
Pharmacokinetics eculizumab[j]	X	X		X		X	X			
Pharmacodynamics RA101495[i]		X	X	X	X	X	X	X	X	X
Anti-drug antibody[k]		X[k]				X		X		X
Quality of life questionnaires										
EORTC-QLQ-C30		X				X		X		X
FACIT-Fatigue		X				X		X		X
EQ-5D		X				X		X		X
Treatment satisfaction assessment										X
Additional biomarker samples[i]		X	X	X	X	X	X	X	X	X
Pharmacogenomic analysis (optional)[l]		X[l]								
Electronic diary training and dispensation, collection at End of Study		X								X
RA101495 administration[m]		X	X	X	X	X	X	X	X	X
RA101495 dispensing and return[n]		X		X		X	X	X	X	X

Abbreviations: EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire; EQ-5D=EuroQol 5D questionnaire; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue Scale; ICF=informed consent form; LDH=lactate dehydrogenase; NA=not applicable; PD=pharmacodynamic; PK=pharmacokinetic.

a. Study visits have a Visit window of ±2 days after the actual planned Visit day for the first 4 weeks, and ±4 days from week 6 to week 12.
b. For Cohort A (Naïve) subjects, the Day 1 Visit may be scheduled at any time after Screening and confirmation of eligibility. For Cohort B (Switch) subjects, the Day 1 Visit should be scheduled to coincide with the next scheduled dose of eculizumab (i.e. 14 ±2 after from the last eculizumab dose). Eculizumab should NOT be administered at the Day 1 Visit or at any time thereafter during the study.
c. Height will be measured only at the Screening Visit.
d. All subjects must have a negative throat swab for *Neisseria meningitidis* infection for eligibility. All subjects in Cohort A must be vaccinated against *Neisseria meningitidis* and should have a booster as indicated by standard of care. All subjects in Cohort A must receive ciprofloxacin to be taken orally on Days 1 to 14. All Cohort B subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster if appropriate) prior to study entry.
e. Including LDH for primary efficacy endpoint
f. Coagulation tests should be performed, according to standard practice, on all subjects taking anticoagulant therapy.
g. For all female subjects of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit and a negative urine pregnancy test must be documented at the Day 1 Visit prior to dosing. All other pregnancy tests will be urine.
h. The injection site should be assessed at each clinic visit through Day 84 (End of Study).
i. Blood samples for PK and PD and additional biomarker sampling at the following time points in relationship to the first dose of RA101495: pre-dose (within 1 hour before first dose administration) and at 1, 3, and 6 hours post-dose on Day 1. For subjects who have a dose increase to 0.3 mg/kg, samples for PK and PD should be collected at pre-dose Day 1 of the new dose, see footnote j. On clinic visit days, PK and PD samples should be collected prior to administration of RA101495.
j. For subjects in Cohort B only, blood samples for PK of eculizumab should be collected at screening, Day 1, Day 15, Day 29, and Day 43. (at 2-week, 4-week, and 6-week) Visits. The sample should be collected prior to administration of RA101495.
k. Blood sample for ADA on Day 1 must be obtained prior to dosing of RA101495.
l. Blood sample for optional pharmacogenomic testing must be obtained on Day 1.
m. On clinic visit days, the study drug RA101495 should be administered after blood samples for PK and PD are collected.
n. Prefilled syringes containing RA101495 will be dispensed every 2 weeks. Subjects will also receive a secure container to dispose of used syringes at each visit and should return the used container containing all used syringes to each study visit. All study drug (syringes) and disposal containers must be returned to the site at the last study visit. Dosing on study visit days will be held until the completion of the PK and PD sample blood collection has been completed.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.1.3 or higher for Windows.

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in patient data listings. Descriptive statistics (n, mean, standard error of the mean, standard deviation, median, minimum, and maximum) will be calculated by treatment group for continuous variables. Confidence intervals will be provided where appropriate. For continuous endpoints, the confidence interval for the mean will be based on the t-distribution (e.g., CLM in the SAS Proc Means procedure).

Frequencies and percentages will be presented by treatment group for categorical and ordinal variables. If there are missing values, the number of missing values will be presented, but without a percentage and the number of non-missing values used as the denominator.

Means, medians, standard deviations, standard error of the mean, and confidence intervals will be reported to one decimal place more than the data reported on the CRF or by the laboratory/vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor. P-values will be reported to 4 decimal places.

3.1.3 Baseline Value and Change from Baseline

Baseline value is defined as the most recent non-missing value obtained immediately prior to administration of first dose (i.e., generally the study day 1 assessment which occurs pre-dose).

However, for Cohort A (Eculizumab Naïve) subject's baseline LDH will be the average of the Study day 1 and Screening period values.

Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each patient (i.e. post-dose – baseline). Percent change from baseline will be calculated as 100×change score/ baseline score.

3.1.4 Screening Values

For the tables and figures, a patient's screening value is defined as the most recent non-missing value with a visit value of "Screening". In the listings, all values which have a visit of "Screening" will be presented.

3.1.5 Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed; observed cases will be used in the analyses.

If a non-numeric clinical laboratory value is reported for an endpoint of the form "< X.XX", "≤ X.XX", ">X.XX", or "≥X.XX" and the endpoint is being summarized as a numeric quantitatively (i.e., assuming the endpoint response is numeric) the numeric value portion of the result being reported will be imputed. As a specific example, for the sRBC lysis endpoint non-numeric values of "<2.00" and ">100.00" may be reported; in these in these instances the values of 2.00 and 100.00, respectively, will be imputed.

Note that this convention will not apply to PK concentration data which is below the lower limit of quantification (i.e., <LLOQ). For PK concentration summary statistics values below the lower limit of quantification will be set to zero, except for the geometric mean, where those values will be set to the lower limit of quantification.

3.2 Analysis Populations

Analysis populations in this study are defined in the sections that follow.

3.2.1 Safety Population

The Safety Population will include all subjects who receive at least one injection of RA101495.

3.2.2 Efficacy Evaluable Population

The Efficacy Evaluable Population will include all subjects in the Safety Population who complete the 12-week Treatment Period.

3.2.3 Per Protocol Population

The Per Protocol Population will include all subjects in the Safety Population who complete the 12-week Treatment Period and have no major protocol violations.

Protocol violations will be assessed as "minor" or "major" during data review meetings that will take place prior to database lock.

3.2.4 Pharmacokinetic Population

The PK Population will include all subjects in the Safety Population who have at least 1 plasma sample obtained for PK assessment.

3.2.5 Pharmacodynamic Population

The PD Population will include all subjects in the Safety Population who have at least 1 plasma sample obtained for PD assessment.

3.3 Analysis Endpoints

3.3.1 Safety Endpoints

Safety assessments will include evaluation of AEs and SAEs (including major adverse vascular event (MAVE criteria), surgery and other procedures, clinical laboratory tests, ECGs, vital signs, and physical examinations. Safety evaluation will also include a determination of anti-drug antibodies (ADA). Laboratory assessments will include PNH clone size.

3.3.1.1 Injection Site Reactions

The investigator will assess the injection sites at each scheduled visit for:

- Pain, tenderness, erythema, and induration severity (Table 3)
- Erythema and induration: maximum linear diameter
- Blisters, ulceration, necrosis: maximum linear diameter and severity
- Lymphadenopathy (absent, mild, moderate, or severe)

Table 3: Grading the Severity of Local Injection Site Reactions

Local Reaction to Injectable Product	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/ redness	2.5 to 5.0 cm	5.1 to 10.0 cm	>10.0 cm	Necrosis or exfoliative dermatitis
Induration/ swelling	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	>10.0 cm or prevents daily activity	Necrosis

The Injection site reactions CRF page has the date of assessment but is not specifically connected to a study visit (even though the assessment is planned to be

done in conjunction with visits). The following algorithm will be used to assign a study visit for each assessment.

Assign Baseline if SVD1SDT<=ADT<=SVD1EDT;
else assign 'Week 1' if SVD8SDT<=ADT<=SVD8EDT;
else assign 'Week 2' if SVD15SDT<=ADT<=SVD15EDT;
else assign 'Week 3' if SVD22SDT<=ADT<=SVD22EDT;
else assign 'Week 4' if SVD29SDT<=ADT<=SVD29EDT;
else assign 'Week 6' if SVD43SDT<=ADT<=SVD43EDT;
else assign 'Week 8' if SVD57SDT<=ADT<=SVD57EDT;
else assign 'Week 10' if SVD71SDT<=ADT<=SVD71EDT;
else assign 'Week 12' if SVD84SDT<=ADT<=SVD84EDT. (So if ADT lies within more than one of the visit periods, assign the first one matching)

Note: Here SVD***x***SDT is the SDTM defined "actual start date" of the visit planned for day ***x***, and SVD***x***EDT the corresponding end date.

3.3.2 Primary Efficacy Endpoint

The primary evaluation period is from Week 6 to Week 12. The primary efficacy endpoint is the change from baseline in serum LDH levels during this period, defined as the mean of the non-missing LDH values of Weeks 6, 8, 10, and 12 minus the baseline LDH value (defined in Section 3.1.3).

Note: This will only include the scheduled assessments, LDH values from unscheduled assessments will only be provided in the listings.

3.3.3 Secondary Efficacy Endpoints

Secondary efficacy variables include the change from baseline values at each of the following scheduled post-baseline assessment time-points:

- total bilirubin
- total hemoglobin,
- free hemoglobin,
- haptoglobin,
- reticulocytes
- hemoglobinuria.

3.3.4 Pharmacodynamic Endpoints

Pharmacodynamic endpoints include:

- Changes from baseline in sRBC lysis for the classical complement pathway
- Changes from baseline in Wieslab ELISA for alternative complement pathway
- Changes from baseline in C5 concentration levels.

3.3.5 Pharmacokinetic Endpoints

Drug exposure in the different cohorts will be evaluated using PK parameters derived from non-compartmental methods. All calculations will be based on actual sampling times. Individual PK parameters will be presented in listings and summarized by cohort using descriptive statistics.

Pharmacokinetic endpoints include:

- Plasma concentrations of RA101495 and its major metabolites (RA103488 and RA102758)
- Maximum plasma concentration (C_{max})
- Time corresponding to C_{max} (t_{max})
- Area under the drug concentration-time curves (AUC_{0-t})
- Plasma concentrations of eculizumab (Cohort B only).

3.3.6 Quality of Life Assessments

Quality of life assessments will be performed according to the Time and Events Table (Table 2). The following QOL questionnaires will be used during this study:

- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale
- EuroQol-5D (EQ-5D).

3.3.6.1 EORTC-QLQ-C30

The EORTC QLQ-C30 consists of 30 questions, which are incorporated into 5 functional domains (physical, role, cognitive, emotional, and social domains; see Table 4); a global health status/global QOL scale; 3 symptom scales (fatigue, pain, and nausea and vomiting scales); 6 single items that assess additional symptoms (e.g. dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea); and the

perceived financial burden of illness treatment (Aaronson, 1993; Aaronson, 1996). Subjects answer questions based on symptoms/status over the preceding week.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items.

Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.
All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

- a high score for a functional scale represents a high / healthy level of functioning
- a high score for the global health status / QoL represents a high QoL,
- a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases:

1) Estimate the average of the items that contribute to the scale; this is the raw score.
2) Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Table 4: Scoring the EORTC QLQ-C30

	Scale	Number of Items	Item Range*	Item Numbers	Functional scales
Global health status / QoL					
Global health status/QoL	QL2	2	6	29, 30	
Functional scales					
Physical functioning	PF2	5	3	1 to 5	F
Role functioning	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	

Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	
* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status/QoL, which are 7-point questions with range = 6,					

For all scales, the Raw Score is the mean of the component items.

For functional scales the score is:

$$\text{Score} = \{1 - (\text{Raw score} - 1)/(\text{range})\} \times 100$$

and for Symptom scales/items and Global health status/QoL:

$$\text{Score} = \{(\text{Raw score} - 1)/(\text{range})\} \times 100.$$

3.3.6.2 FACIT-Fatigue

The FACIT-Fatigue Scale is a 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the preceding week. The level of fatigue is measured on a five point ordinal scale (4 = not at all fatigued to 0 = very much fatigued) [Webster, 2003].

The items and scoring algorithm are given in Table 5.

Table 5: FACIT Fatigue Scale Scoring

Item
I feel fatigued (Reverse Scoring)
I feel weak all over (Reverse Scoring)
I feel listless ("washed out") (Reverse Scoring)
I feel tired (Reverse Scoring)
I have trouble starting things because I am tired (Reverse Scoring)
I have trouble finishing things because I am tired (Reverse Scoring)
I have energy
I am able to do my usual activities
I need to sleep during the day (Reverse Scoring)
I am too tired to eat (Reverse Scoring)
I need help doing my usual activities (Reverse Scoring)
I am frustrated by being too tired to do the things I want to do (Reverse Scoring)
I have to limit my social activity because I am tired (Reverse Scoring)
• Item Response is the "raw score" on the 0 – 4 point scale (0: Not at all – 4: Very Much). • For the items indicated "(Reverse Scoring)" reverse the scoring (Score = 4 – Original Score) (note: reverse scoring occurs for all items except the 'I have energy' and 'I am able to do my usual activities' items) • Overall Fatigue Subscale Score Algorithm: ○ Sum the individual scores

- Multiple the sum by 13
- Divide by the # of non-missing items answered

The higher the score, the better the QOL.

Note that for the analyses, FACIT values coded as "ambiguous" will be mapped to the "missing" category.

3.3.6.3 EQ-5D

The EQ-5D 3 level version [EuroQol, 1990] is a standardized instrument for measuring generic health status. The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has three levels:

Level 1: indicating no problem
Level 2: indicating some problems
Level 3: indicating extreme problems.

For the EQ-5D visual analog scale (VAS) question the patient rates how good or bad their health is today on a 0 – 100 point scale (0 representing worst imaginable health state and 100 representing best imaginable health state).

Note that for the analyses, EQ-5D values coded as "ambiguous" will be mapped to the "missing" category.

3.3.6.4 Treatment Satisfaction Questionnaires

The following treatment satisfaction questionnaire will be administered to Cohort A subjects to assess overall satisfaction with SC administration of the study medication at the end of the 12-week Treatment Period.

"How satisfied are you with the overall method of study medication administration (subcutaneous self-injection)?"

The following more targeted questionnaire will be administered to the Cohort B (Switch) subjects to assess their preference for daily SC self-injection at home compared with biweekly infusions given by a health-care professional in the clinic.

"Overall how satisfied are you with the method of medication administration used in this study (daily subcutaneous self-injection) compared with intravenous eculizumab infusions every 2 weeks?"

Both questions will use the following 5-point Likert response scale:

- Very Dissatisfied=1

- Dissatisfied=2
- Neutral=3
- Satisfied= 4
- Very Satisfied= 5.

3.4 Patients Disposition and Evaluability

3.4.1 Patient Disposition

A disposition of all enrolled subjects will be provided. This will include the number and percentage of patients evaluated for each of the analysis populations (Section 3.2) will be presented by cohort and overall. The number of patients discontinuing from the study and the primary reason for discontinuation will also be summarized.

3.4.2 Protocol Deviations

A listing of protocol deviations will be presented by cohort.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics

Patient demographics and baseline characteristics will be summarized by cohort and overall for the Safety, Efficacy Evaluable, Per Protocol, and Pharmacodynamic Populations.

Descriptive statistics will be provided for age, height, weight, and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared). Frequencies and percentages will be tabulated for sex, race, and ethnicity.

Age will be calculated as (informed consent date – date of birth + 1)/365.25, truncated and displayed as years. BMI will be calculated as weight (kg)/height^2 (m^2), using the weight and height measurements obtained at screening.

Note: If the date of birth day and month are missing impute January 1st, if only the day is missing impute the 1st.

3.5.2 Medical History

Medical history will be collected and summarized by cohort and overall.

3.5.3 PNH Disease History

The following PNH disease history data will be summarized by cohort and overall.

- Age at initial diagnosis (years)

Age at initial diagnosis will be calculated as (date of initial PNH diagnosis – date of birth + 1)/365.25,

Note: If the day and month are missing for date of initial PNH diagnosis, impute July 2nd, if only the day is missing impute the 15th. If the date of birth day and month are missing impute January 1st, if only the day is missing impute the 1st.

- PNH clone size (% RBC, % WBC)
- Complement C5 gene mutation (Present, Absent, unknown)
- Thrombotic event within 6 months prior to screening (yes, no)
- Blood Transfusion within 6 months prior to screening (yes, no)

3.5.4 PNH Treatment History

The following PNH treatment history data will be summarized by cohort and overall.

- Eculizumab treatment history (note: Cohort B only)
  - Age at initial eculizumab treatment

    Age at initial eculizumab treatment will be calculated as (date of initial eculizumab treatment – date of birth + 1)/365.25,

    Note: If the day and month are missing for date of initial eculizumab treatment, impute July 2nd, if only the day is missing impute the 15th. If the date of birth day and month are missing impute January 1st, if only the day is missing impute the 1st.

  - Duration of eculizumab treatment (months)

    Calculated as:

    (stop date of eculizumab treatment – start date of eculizumab treatment+ 1)

    /(365.25/12)

    Note: For stop date and start date, if the day and month are missing impute July 2nd, if only the day is missing impute the 15th. If corresponding duration calculation yields a negative number, impute a value of 1 day = 1/30.4375 months.

  - Eculizumab dose, units and frequency will be provided in the listings.

3.6 Prior and Concomitant Medications

Incidence of prior and concomitant medication will be presented by cohort, therapeutic area, and preferred (generic) drug name.

Prior medications are those that started and stopped before exposure to study medication; concomitant medications are all medications taken during the study

period, including those started before but on going at first dose. Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

3.7 Exposure to Study Treatment

Prefilled syringes containing RA101495 will be dispensed every 2 weeks. Subjects will also receive a secure container to dispose of used syringes at each visit and should return the used container containing all used syringes. All study drug (syringes) and disposal containers must be returned to the site at the last study visit. Dosing on study visit days will be held until the completion of the PK and PD sample blood collection has been completed.

Treatment duration (number of days patient received study medication) will be described using summary statistics by cohort and overall. Treatment duration will be calculated as the Date of last dose – Date of first dose +1.

The number of patients who had a dose escalation and the number of days from baseline where the dose escalation occurred (Date of dose escalation – date of first dose +1) will summarized by cohort and overall.

These analyses will be performed for the Safety Population.

3.8 Safety Analysis

Safety analysis results will be presented using the Safety Population by cohort and overall.

3.8.1 Adverse Events

All adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 18.0 or higher and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Analyses of adverse events will be performed using the safety population.

Treatment emergent adverse events (TEAEs) are defined as follows:

- An AE that occurs after treatment start that was not present at the time of treatment start; or
- An AE that increases in severity after treatment start, if the event was present at the time of treatment start.

The following TEAE summaries will be provided:

- Overall summary of Treatment Emergent Adverse Events
- Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term

- Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity
- Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug
- Incidence of Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term
- Listing of Serious Adverse Events by System Organ Class and Preferred Term.

For these summaries, the number and percentage of patients who experienced at least one of the TEAE as well as the number and percentage of patients who experienced each specific SOC and PT will be presented by cohort. The corresponding number of TEAEs will also be presented.

For the presentation of TEAE incidences, the SOCs will be sorted alphabetically, and within SOC, the preferred term (PT) will be used and presented by decreasing total frequency.

3.8.1.1 Determining Treatment Emergent with Adverse Event Dates

The following rules apply when determining if an AE is treatment-emergent in the scenario where the start date is missing or partially missing. These rules provide an algorithm to "impute" a complete AE start date which will then be used to determine if the AE is treatment emergent.

AE start date missing day and month:

- If the year is the same as the year of the treatment start date, the day and month of the date of treatment start date will be assigned to the missing fields.
- If the year is prior to the year of the treatment start date, December 31 will be assigned to the missing fields.
- If the year is after the year of the date of the treatment start date, January 1 will be assigned to the missing fields.

AE start date missing month only:

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

AE start date missing day only:

- If the month and year are the same as the month and year of the treatment start date, the day of the treatment start date will be assigned to the missing day.

- If either the year is before the year of the date of the treatment start date or if both years are the same but the month is before the month of the treatment start date, the last day of the month will be assigned to the missing day.
- If either the year is after the year of the treatment start date or if both years are the same but the month is after the month of the treatment start date, the first day of the month will be assigned to the missing day.

AE start date completely missing:

- If the AE end date is complete and after the treatment start date, the treatment start date will be assigned to the missing start date.

- If the end date is complete and before the treatment start date, the end date will be assigned to the missing start date

- Otherwise the AE start date will be assigned the treatment start date.

If the end date is complete and the imputed start date as above is after the end date, the start date will be imputed by the end date.

3.8.2 Adverse Events of Special Interest

3.8.2.1 Thrombotic Adverse Events

A separate table for thrombotic AEs will be presented, summarizing TEAEs by PT for each cohort and overall. The events in Table 6 (MAVE criteria, 2007]) will be evaluated in the assessment of thrombotic AEs.

Table 6: Thrombotic Event Description (MAVE Criteria)

MAVE Criteria	AE Preferred Term Mapping
Thrombophlebitis/Deep vein thrombosis	Preferred Term: 10051055 Deep vein thrombosis Preferred Term: 10043570 Thrombophlebitis
Pulmonary embolus	Preferred Term: 10037377 Pulmonary embolism
Myocardial infarction	Preferred Term: 10028596 Myocardial infarction
Transient ischemic attack	Preferred Term: 10044390 Transient ischaemic attack
Renal vein thrombosis	Preferred Term: 10038548 Renal vein thrombosis
Acute peripheral vascular occlusion	Preferred Term: 10053648 Vascular occlusion
Amputation (non-traumatic, non-diabetic)	Preferred Term: 10061627 Amputation
Mesenteric/Visceral vein thrombosis	Preferred Term: 10027402 Mesenteric vein thrombosis Preferred Term: 10077829 Visceral venous thrombosis
Unstable angina	Preferred Term: 10002388 Angina unstable
Mesenteric/Visceral arterial thrombosis	Preferred Term: 10027397 Mesenteric artery thrombosis Lower level term: 10043611 Thrombosis arterial
Hepatic/Portal vein thrombosis	Preferred Term: 10019713 Hepatic vein thrombosis Preferred Term: 10036206 Portal vein thrombosis
Dermal thrombosis	Lower level term: 10042545 Superficial phlebothrombosis
Gangrene (non-traumatic, non-diabetic)	Preferred Term: 10017711 Gangrene Preferred Term: 10009971 Colon gangrene Preferred Term: 10017954 Gastrointestinal gangrene
Cerebral arterial occlusion/cerebrovascular accident	Preferred Term: 10008190 Cerebrovascular accident Preferred Term: 10008089 Cerebral artery occlusion
Cerebral venous occlusion	Preferred Term: 10076895 Cerebral vascular occlusion
Renal arterial thrombosis	Preferred Term: 10038380 Renal artery thrombosis

Abbreviation: MAVE=major adverse vascular event.

3.8.2.2 Injection Site Reactions

Analysis of ISRs will include summaries of the following assessments (defined in Section 3.3.1.1)

- Pain, tenderness, erythema, and induration severity, and lymphadenopathy (categorical variables with grades 1 – 4, and absent).
- Erythema and induration: record the maximum linear diameter
- Blisters, ulceration, necrosis: record the maximum linear diameter and severity

  For both of these assessments, the maximum linear diameter will be summarized.

3.8.3 Clinical Laboratory Evaluation

A list of the clinical chemistry, hematology, and coagulation analytes are listed in Table 1. The exception being PNH clone size which will be summarized in a separate table but included in the hematology listing.

Quantitative laboratory endpoints will be summarized by time point using descriptive statistics.

Urinalysis parameters which do lend themselves to analyses (i.e., "Color") will be presented in the listings only.

3.8.3.1 Hepatic Laboratory Tests: NCI CTCAE Grading

The liver functions test to be summarized via the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria are provided in Table 7.

Table 7: CTCAE Grading Criteria for Selected Liver Function Tests

Lab Test	Grade/Criteria			
	1	2	3	4
alanine (ALT)	> 1.0 - 3.0 (x ULN)	>3.0 - 5.0 (x ULN)	>5.0 - 20.0 (x ULN)	> 20.0 (x ULN)
alkaline phosphatase (ALP)	>1.0 - 2.5 (x ULN)	>2.5 - 5.0 (x ULN)	>5.0 - 20.0 (x ULN)	> 20.0 (x ULN)
direct bilirubin	> 1.0 – 1.5 (x ULN)	>1.5 – 3.0 (x ULN)	>3.0 - 10.0 (x ULN)	> 10.0 (x ULN)
gamma-glutamyl transferase (GGT)	>1.0 - 2.5 (x ULN)	>2.5 - 5.0 (x ULN)	>5.0 - 20.0 (x ULN)	>20.0 (x ULN)
Grading criteria based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Note: CTCAE ULN grades for direct bilirubin based on CTCAE ULN grades for total ("blood") bilirubin				

3.8.3.2 Pancreatic Enzymes: NCI CTCAE Grading

Amylase and lipase values will be summarized via the NCI CTCAE criteria provided in Table 8.

Table 8: CTCAE Grading Criteria for Selected Pancreatic Enzyme Tests

Lab Test	Grade/Criteria			
	1	2	3	4
amylase	> 1.0 – 1.5 (x ULN)	>1.5 – 2.0 (x ULN)	>2.0 - 5.0 (x ULN)	> 5.0 (x ULN)
lipase	> 1.0 – 1.5 (x ULN)	>1.5 – 2.0 (x ULN)	>2.0 - 5.0 (x ULN)	> 5.0 (x ULN)
Grading criteria based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03				

3.8.4 Anti-drug antibodies

The determination of anti-drug antibodies will not be included in the CSR.

3.8.5 Surgery and Other Procedures

A listing of surgery and other procedures will be provided by cohort and subject.

3.8.6 Vital Signs and Other Physical Findings

Descriptive statistics for vital signs (i.e. heart rate, body temperature, and blood pressure) values and the change from baseline will be presented.

3.8.7 ECG

Descriptive statistics for ECG parameters (i.e., heart rate (HR), PR interval, RR interval, QRS interval, QT interval, QTcB interval, and QTcF interval) at each assessment time point will be presented for the values and change from baseline scores.

QTc intervals will be calculated using both Fridericia's and Bazett's corrections, with the formulae:

Fridericia's correction: $QTc = QT/RR^{0.33}$

Bazett's correction: $QTc = QT/RR^{0.5}$.

Additionally, the ECG interpretation categorized as Normal, Abnormal – Clinically Significant, Abnormal – Not Clinically Significant, Not Evaluable, or Not Done will also be provided for each assessment time point (note: ECG interpretations of "Abnormal – Clinically Significant" would be recorded as AEs).

3.8.8 Physical Examination

The complete set physical examination findings will be provided in listings. Clinically significant physical examination abnormalities will be included and summarized as AEs if appropriate.

3.9 Efficacy Analysis

Efficacy endpoints will be summarized by cohort. No formal statistical comparisons between cohorts will be performed. Tests to assess change from baseline will be applied to endpoints as appropriate.

3.9.1 Primary Efficacy Endpoint Analysis

The primary evaluation period is from Week 6 to Week 12. The primary efficacy endpoint is the change from baseline in serum LDH levels during this period, defined as the mean of the non-missing LDH values of Weeks 6, 8, 10, and 12 minus the baseline LDH value (defined in Section 3.1.3).

The primary efficacy endpoint analysis will be a Wilcoxon signed-rank test on the change from baseline endpoints.

Summary statistics and will be provided for patient's mean LDH value, change from baseline scores, and percent change from baseline scores over the primary evaluation period.

Additionally, summary statistics for the values, change from baseline, percent change from baseline scores, and the two-sided Wilcoxon signed-rank test will be performed at each post-baseline assessment time-point.

3.9.2 Secondary Efficacy Endpoints Analysis

Secondary efficacy endpoints include the change from baseline values at each of the following scheduled post-baseline assessment time-points:

- total bilirubin
- total hemoglobin
- free hemoglobin
- haptoglobin
- reticulocytes
- hemoglobinuria (note: hemoglobinuria will be assessed using a urine colorimetric scoring system).

The change from baseline for each of these endpoints will be assessed by a two-sided Wilcoxon signed-rank test. Additionally the summary statistics will be presented for the values, change, and percent change from baseline scores.

3.9.3 Pharmacodynamic Endpoints Analysis

The pharmacodynamic endpoints include:

- Changes from baseline in sRBC lysis for the classical complement pathway
- Changes from baseline in Wieslab ELISA for alternative complement pathway
- Changes from baseline in C5 concentration levels.

The change from baseline for each of these endpoints will be assessed by a two-sided Wilcoxon signed-rank test. Additionally the summary statistics will be presented for the values, change from baseline, and percent change from baseline scores.

Note: CH50 will not be analyzed.

3.9.4 Pharmacokinetic Endpoints Analysis

The following pharmacokinetic endpoints will be summarized using descriptive statistics:

- Plasma concentrations of RA101495 and its major metabolites (RA103488 and RA102758)

  Note that for the plasma concentration summaries, values assessed after a patient had a RA101495 dose escalation (as discussed in protocol section 10.1.2.1) will be excluded from this table.

- Maximum plasma concentration (C_{max})
- Time corresponding to C_{max} (t_{max})
- Area under the drug concentration-time curves (AUC_{0-t})
- Plasma concentrations of eculizumab (Cohort B only).

3.9.5 Exploratory Endpoints Analysis

3.9.5.1 EORTC QLQ-C30

Summary statistics for each scales/items scores (Section 3.3.6.1) will be presented as well as the corresponding change from baseline scores for each scheduled assessment time-point.

Global health status

- Global health status/QoL

Functional scales

- Physical functioning
- Role functioning
- Emotional functioning
- Cognitive functioning
- Social functioning

Symptom scales/items

- Fatigue
- Nausea and vomiting
- Pain
- Dyspnoea
- Insomnia
- Appetite loss
- Constipation
- Diarrhoea

- Financial difficulties.

The change from baseline for the EORTC QLQ-C30 scales will be assessed by a two-sided Wilcoxon signed-rank test.

3.9.5.2 FACIT-Fatigue

The overall FACIT-Fatigue score and the individual 13 item scores (Section 3.3.6.2) will be summarized as well as the corresponding change from baseline scores for each scheduled assessment time-point. Shift tables displaying the individual item values from baseline to each post-baseline visit will also be presented.

The change from baseline for the FACIT-Fatigue overall and individual item scores will be assessed by a two-sided Wilcoxon signed-rank test.

3.9.5.3 EQ-5D

The five EQ-5D scale scores (score values range 1 – 3) and the VAS score (Section 3.3.6.3) will be summarized as well as the corresponding change from baseline scores for each scheduled assessment time-point. Shift tables displaying the individual dimension values from baseline to each post-baseline visit will also be presented.

The change from baseline for the EQ-5D VAS score will be assessed by a two-sided Wilcoxon signed-rank test. For this change from baseline analysis the item response categories (e.g., 1, 2, and 3) will be summarized as a continuous variable.

3.9.5.4 Treatment Satisfaction Questionnaires

For both treatment satisfaction questions (Section 3.3.6.4) the number and percentage for each response category will be summarized.

Both treatment satisfaction will be assessed by a two-sided Wilcoxon signed-rank test testing against a score of neutral. This is equivalent to subtracting 3 from each of the scores and testing against a score of 0 (i.e., the default for a Wilcoxon signed-rank test).

3.10 Interim Analysis

During this open-label study, the Sponsor will review safety and efficacy data as it becomes available during the Treatment Period. Following completion of the 12-week visit, data will be cleaned and locked at the individual subject level, and will be available for final analysis by the Sponsor on a rolling basis. Completion and final data lock of Cohort A may occur before, and independent of, Cohort B, or vice versa.

3.11 Sample Size Considerations

For Cohort A (Naïve) a sample size of 8 subjects yields approximately 95% power to reject the null hypothesis that the median LDH change from baseline is 0 for the

primary efficacy endpoint. This assumes a mean decrease in LDH from 2200 U/L at baseline to 327 U/L during the primary evaluation period (Weeks 6 -12) with corresponding standard deviations of 1034 U/L and 443 U/L, and a within-subject correlation estimate of 0. This yields a change from baseline mean of 1873 U/L and standard deviation of 1125 U/L. The power is based on a 2-sided Wilcoxon signed-rank test at the 0.05 significance level.

For Cohort B (Switch) a sample size of 6 subjects will yield a standard error of approximately 114 for an LDH mean change from baseline estimate. This assumes a standard deviation of 443 for the baseline and post-baseline endpoints and a within-subject correlation estimate of 0.8, which yields change from baseline standard deviation of 280 U/L.

The LDH mean and standard deviation estimates are based on the results summarized by Hillmen [2006].

3.12 Replacement of Subjects

Enrolled subjects who prematurely discontinue study treatment for any reason prior to the Day 84 Visit may be replaced, at the discretion of the Sponsor.

4 References

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Webster K, Cella D, and Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 2003; 1:79-85.

5 List of Tables, Figures, and Listings

Table shells will be provided in a separate document.

Table Number	Table Title
14.1.1	Patient Disposition
14.1.2.1	Medical History; Safety Population
14.1.2.2	PNH Disease History; Safety Population
14.1.2.3	PNH Treatment History; Safety Population
14.1.3.1	Prior Medications; Safety Population
14.1.3.2	Concomitant Medications; Safety Population
14.1.4	Exposure to Study Treatment; Safety Population
14.1.5.1	Demographics; Safety Population
14.1.5.2	Demographics; Efficacy Evaluable Population
14.1.5.3	Demographics; Per Protocol Population
14.1.5.4	Demographics; Pharmacodynamic Population
14.2.1.1	Summary of LDH Values; Safety Population
14.2.1.2	Summary of LDH Values; Efficacy Evaluable Population
14.2.1.3	Summary of LDH Values; Per Protocol Population
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14.2.2.1	Summary of Total Bilirubin Values; Safety Population
14.2.2.2	Summary of Total Bilirubin Values; Efficacy Evaluable Population
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14.2.3.1	Summary of Total Hemoglobin Values; Safety Population
14.2.3.2	Summary of Total Hemoglobin Values; Efficacy Evaluable Population
14.2.3.3	Summary of Total Hemoglobin Values; Per Protocol Population
14.2.3.4	Summary of Total Hemoglobin Values; Pharmacodynamic Population
14.2.4.1	Summary of Free Hemoglobin Values; Safety Population
14.2.4.2	Summary of Free Hemoglobin Values; Efficacy Evaluable Population
14.2.4.3	Summary of Free Hemoglobin Values; Per Protocol Population
14.2.4.4	Summary of Free Hemoglobin Values; Pharmacodynamic Population
14.2.5.1	Summary of Haptoglobin Values; Safety Population

Table Number	Table Title
14.2.5.2	Summary of Haptoglobin Values; Efficacy Evaluable Population
14.2.5.3	Summary of Haptoglobin Values; Per Protocol Population
14.2.5.4	Summary of Haptoglobin Values; Pharmacodynamic Population
14.2.6.1	Summary of Reticulocyte Values; Safety Population
14.2.6.2	Summary of Reticulocyte Values; Efficacy Evaluable Population
14.2.6.3	Summary of Reticulocyte Values; Per Protocol Population
14.2.6.4	Summary of Reticulocyte Values; Pharmacodynamic Population
14.2.7.1	Summary of Hemoglobinuria Values; Safety Population
14.2.7.2	Summary of Hemoglobinuria Values; Efficacy Evaluable Population
14.2.7.3	Summary of Hemoglobinuria Values; Per Protocol Population
14.2.7.4	Summary of Hemoglobinuria Values; Pharmacodynamic Population
14.2.8	Summary of sRBC Values; Pharmacodynamic Population
14.2.9	Summary of Wieslab ELISA Values; Pharmacodynamic Population
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