16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan (v2.0) 15 October 2021

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Ra Pharmaceuticals Inc (now part of UCB)

STATISTICAL ANALYSIS PLAN

PROTOCOL RA101495-01.202 (UCB study PNH001)

A MULTICENTER, OPEN-LABEL, UNCONTROLLED,
EXTENSION STUDY OF RA101495 IN SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WHO HAVE COMPLETED A RA101495 CLINICAL STUDY

Protocol code:	RA101495-01.202 (UCB study PNH001)
SAP Version:	Final 2.0
SAP Date:	15OCT2021
Author:	[redacted]

DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
Final 1.0	09 April 2021
Final 2.0	15OCT2021

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
1.0	N/A	Initial release	N/A
2.0	2	CRF version updated	New CRF version
	9.4	Reason for treatment discontinuation removed from disposition summary	No separate treatment discontinuation reason was collected in addition to study discontinuation reason
	9.6.4	WHODrug version updated	Newer version used
	9.8.3	AE summary extended	Due to reporting requirements
	9.11	Clarification that no interim analysis was performed	No interim analysis was performed
	10	No analysis of CH50	No data available

APPROVAL SIGNATURES

STUDY TITLE: A MULTICENTER, OPEN-LABEL, UNCONTROLLED,

EXTENSION STUDY OF RA101495 IN SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WHO HAVE COMPLETED A RA101495 CLINICAL STUDY

PROTOCOL NUMBER: RA101495-01.202 (UCB study PNH001)

SAP Final 2.015OCT2021

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1. 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
CH50	Complement Total
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

2. INTRODUCTION

This statistical analysis plan (SAP) covers the analysis and reporting for protocol RA101495-01.202 dated 20 October 2016 and electronic case report form (eCRF) version 44 dated 22 March 2021. The following country-specific amendments are also reflected:

USA: Study Protocol amendment (version 03-FEB-2017)

Germany: Study Protocol amendment (version 03-MAY-2017)

Finland: Study Protocol amendment (version 24-FEB-2017)

UK: Study Protocol amendment (version 07-FEB-2017)

Denmark: Study Protocol amendment (version 11-APR-2017)

3. STUDY OBJECTIVES

3.1 OBJECTIVES

- To provide access to RA101495 for subjects with PNH who have completed a Ra Pharmaceuticals sponsored study, have demonstrated clinical benefit, and who wish to continue receiving RA101495 for treatment of PNH
- To evaluate the long-term safety and tolerability of RA101495 administered to subjects with PNH who have completed a Ra Pharmaceuticals sponsored RA101495 clinical study
- To evaluate the long-term preliminary efficacy of RA101495 administered to subjects with PNH who have completed a Ra Pharmaceuticals sponsored RA101495 clinical study
- To obtain periodic PK and PD data to confirm long-term maintenance of steady-state RA101495 plasma levels and sustained inhibition of hemolysis and complement

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

The design is a multicenter, open-label, extension study for subjects with PNH who have successfully completed a qualifying Ra Pharmaceuticals sponsored RA101495 (zilucoplan) clinical study (RA101495-01.201 or RA101495-01.203). Subjects will continue to receive the final maintenance dose they were receiving in the qualifying study, as long as safety, tolerability, PK and PD data (from the qualifying study or this extension study) continue to demonstrate benefit. If additional data support a change in dose level for an individual subject in this extension study, investigators may increase or decrease the maintenance dose level, based on safety and PD findings, and in consultation with the medical monitor. All subjects will continue to be followed carefully for any evidence of meningococcal and/or other infection.

4.2 STUDY TREATMENT

All eligible subjects will receive open-label RA101495 daily by SC self-injection. The starting

dose in the extension study will be the same as the final maintenance dose the subject was receiving in the qualifying study. The IMP (RA101495) will continue to be provided by the sponsor until RA101495 is approved and available in the territory or the sponsor terminates development of RA101495 for PNH.

4.3 DATA AND SAFETY MONITORING BOARD (DSMB)

No DSMBs are scheduled for this study.

5. SAMPLE SIZE AND POWER CALCULATION

Sample size will be determined by the number of eligible subjects completing a qualifying RA101495 clinical study. No formal statistical sample size estimates were performed.

6. ANALYSIS ENDPOINTS

6.1 EFFICACY ENDPOINTS

Serum LDH levels, total bilirubin, total hemoglobin, free hemoglobin, haptoglobin, reticulocytes, and hemoglobinuria, at each of the scheduled assessment time-points.

6.2 SAFETY ENDPOINTS

Safety assessments will include an evaluation of AEs and SAEs (including major adverse vascular event (MAVE criteria)), clinical laboratory tests, ECGs, vital signs, and physical examinations.

6.3 EXPLORATORY ENDPOINTS

- Quality of life (QOL) questionnaires (e.g. EORTC QLQ-C30 and FACIT-Fatigue)
- Mechanistic biomarkers (e.g. complement function, complement proteins, biomarkers of inflammation, biomarkers for thrombosis, biomarkers of liver function) to be summarized in a separate report.

6.4 PHARMACOKINETIC ENDPOINTS

- Plasma concentrations of RA101495 and its major metabolite(s)

6.5 PHARMACODYNAMIC ENDPOINTS

- CH_{50}
- Sheep RBC (sRBC) lysis for the classical complement pathway
- Wieslab ELISA for alternative complement pathway
- C5 levels

Note: CH_{50} is not analyzed as it is not collected.

7. ANALYSIS POPULATIONS

SAFETY POPULATION

The Safety Population will include all subjects who receive at least 1 injection of RA101495 on or after Day 1 of this extension study (RA101495-01.202).

PHARMACOKINETIC POPULATION

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

PHARMACODYNAMIC POPULATION

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

8. COHORTS

The following cohorts of the study populations will be used for analyses.

Eculizumab Naïve Subjects

This will include all subjects who have not received eculizumab for treatment of PNH (i.e., subjects from study RA101495-01.201 Cohort A (Naïve)).

Eculizumab Switch Subjects

This will include all subjects who have received treatment with eculizumab for at least 6 months prior to Screening. (i.e., subjects from study RA101495-01.201 Cohort B (Switch)).

Inadequate Response to Eculizumab Subjects

This will be a subset of the Eculizumab Switch Subjects coming from the RA101495-01.203 study, including all subjects who had an inadequate response to eculizumab defined as having received eculizumab for at least 6 months plus meeting one or both of the following criteria:

- A documented lactate dehydrogenase (LDH) level ≥ 1.5 x the upper limit of normal (ULN) within 90 days prior to Screening
- Presence of a known C5 mutation conferring resistance to eculizumab.

9. ANALYTICAL PLAN AND STATISTICAL METHODS

9.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

Data will be summarized by eculizumab-naïve, eculizumab switch, and inadequate responder groups with all doses within these groups being pooled.

All clinical study data will be presented in Subject data listings. Descriptive statistics (n, mean, standard error of the mean, standard deviation, median, minimum, and maximum) will be calculated by cohort for continuous variables.

Counts and proportions will be presented by cohort 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.

Assuming that an endpoint is expected to be in a numeric format, all non-numeric values entered as "< X.XX" or "> Y.YY" will be analyzed as X.XX or Y.YY, respectively.

9.2 Definition of Baseline, Study Visits, and Visit Windows

Unless otherwise specified, a subject's baseline will be the value from the Screening/Day 1 value of this study. The Screening Visit will generally coincide with the qualifying study end of study visit. Should the last qualifying study visit be missing, the last available observation in the qualifying study will be used. All screening assessments are expected to be the same as those for the end of qualifying study visit and do not need to be repeated unless clinically indicated. Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each subject (i.e. post-dose – baseline). Percent change from baseline will be calculated as 100×change score/ baseline score.

There will be no windowing of study visits in this study. However, the following rules will be used to assign display values of study visits:

Visit in SDTM	Display in Analysis	Comment
	Baseline	Assigned per SAP above
Day 30	Month 1	
Day 60	Month 2	
Day 90	Month 3	
Day 120	Month 4	
Day 150	Month 5	
Day 180	Month 6	
Day 210	Month 7	
Day 240	Month 8	
Day 270	Month 9	
Day 300	Month 10	

Day 330	Month 11	
Day 360	Month 12	
Day 390	Month 13	
Day 420	Month 14	
3 Month Visit 1	Month 15	
3 Month Visit 1-1	Month 16	
3 Month Visit 1-2	Month 17	
3 Month Visit 2	Month 18	
3 Month Visit 2-1	Month 19	
3 Month Visit 2-2	Month 20	
…		
3 Month Visit x	*Add one month from previous*	
3 Month Visit x-1	*Add one month from previous*	
3 Month Visit x-2	*Add one month from previous*	
…		
3 Month Visit 12	Month 50	
3 Month Visit 12-1	Month 51	
3 Month Visit 12-2	Month 52	
Final Study Visit	Final Study Visit	Combine all subjects' last visit as reported in CRF regardless of study duration.

9.3 HANDLING OF MISSING DATA

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

9.4 SUBJECT DISPOSITION

A disposition of all consented subjects will be provided. This will include a breakdown of subjects who consented, were treated, and were discontinued from the study. The primary reason for discontinuation from the study will be summarized. Additionally, a summary of subjects included in the analysis populations outlined in Section 7 will be included.

Listings of all the disposition data, including date of IC signed, date and reason of discontinuation, and protocol version will be created.

9.5 PROTOCOL DEVIATIONS

Major Protocol deviations will be summarized. Protocol deviations will be presented in a listing that will include all deviations that lead to a subject being withdrawn from the per-protocol population.

9.6 SUBJECT CHARACTERISTICS

9.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Subject demographics and baseline characteristics will be summarized for the safety population.

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, ethnicity, and country.

Age will be calculated as (informed consent date in the RA10495-01.202 study – date of birth + 1)/365.25, truncated and displayed as years. Should either or both the month and day of birth be missing, the date will be set to June 1st.

BMI will be calculated as weight (kg)/height^2 (m^2), using the weight and height measurements obtained at screening.

Inches will be converted to centimeters with 2.54 cm being equal to 1 in.

9.6.2 MEDICAL HISTORY

Medical history will be summarized with data that was collected at the screening visit of the subject's qualifying study will be coded using MedDRA version 19.1 or higher. The summary in this section will be run for the safety Population. The number of Subjects with prior and concurrent conditions by preferred term will be output.

9.6.3 PNH DISEASE AND TREATMENT HISTORY

Separate listings for PNH disease history and PNH treatment will be created.

9.6.4 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant medications ongoing from the qualifying study will be documented. All medications will be documented using WHODrug Global Format B3 September 2020 or higher. Concomitant medications include any prescription or over-the-counter medication that is ongoing on Day 1 or that is initiated following the first dose of study drug on Day 1. A medication will be classified as a prior medication if its start date is earlier than the date of first study drug administration and is not ongoing at the first dose.

Incidence of prior and concomitant medications will be presented by therapeutic area, and preferred (generic) drug name for the safety population

9.7 EFFICACY ENDPOINTS AND ANALYSIS

9.7.1 ANALYSIS OF EFFICACY ENDPOINTS

Efficacy endpoints will be summarized at each scheduled assessment time point using descriptive statistics for the observed and change from baseline values for safety population.

Efficacy assessments include:

- LDH levels
- Total bilirubin
- Total hemoglobin
- Free hemoglobin
- Haptoglobin
- Reticulocytes
- Hemoglobinuria using a urine colorimetric system.

9.8 SAFETY ENDPOINTS AND ANALYSIS

Safety analysis results will be presented using the safety Population.

9.8.1 EXPOSURE TO STUDY TREATMENT

Subjects were required to self administer RA101495 as a SC injection once daily (every 24 hours at approximately the same time each day). On Day 1, the last dose administered on the final day of the qualifying study was considered the first dose on the extension study and was not be repeated. On days of the scheduled study visit at the investigator site, the dose was to be administered after the blood work was completed at the investigator site

Dose-levels will be summarized from the start of this study. The number of subjects with an increase in dose and decrease in dose (relative to the dose at the start of the study) will be summarized.

9.8.2 CLINICAL LABORATORY EVALUATION

Data listings will be produced for all collected laboratory data including hematology, chemistry, and coagulation and urinalysis. Laboratory values outside laboratory's normal ranges will be flagged as H (high, above normal) or L (low, below normal) in laboratory data listings.

(A) CLINICAL CHEMISTRY, HEMATOLOGY, AND COAGULATION ANALYTES

Hematology, Serum Chemistry, Coagulation, C-reactive protein, and Creatine phosphokinase analyte, and Liver Function Test (see Table 3) values and change from baseline will be tabulated using descriptive statistics at each planned visit. The data will be presented in separate listings.

Table 3: Clinical Chemistry, Hematology, and Coagulation Analytes

Clinical Chemistry	Hematology
alanine aminotransferase (ALT)	
albumin	
alkaline phosphatase (ALP)	hematocrit
amylase	hemoglobin
aspartate aminotransferase (AST)	mean corpuscular hemoglobin (MCH)
bicarbonate	mean corpuscular hemoglobin concentration (MCHC)
bile acids	mean corpuscular volume (MCV)
bilirubin (direct, and indirect)	platelet count
blood urea nitrogen (BUN)	RBC count
calcium	white blood cell (WBC) count and differential (%)
chloride	**Coagulation**
creatinine	international normalized ratio (INR)/prothrombin time (PT)
gamma-glutamyl transferase (GGT)	fibrinogen
glucose	partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT)
lipase	**Other**
potassium	C-reactive protein (CRP)
sodium	creatine phosphokinase (CPK)
total protein	
uric acid	

(B) URINALYSIS

Urinalysis will be performed for measurement of pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, and cells.

Urinalysis values will be tabulated using descriptive statistics at each planned visit.

(C) PREGNANCY TEST

A urine dipstick pregnancy test (human chorionic gonadotropin) will be performed on female subjects of childbearing potential. These results will be listed.

(D) PNH CLONE

PNH clone size will be determined by peripheral blood flow cytometry analysis (RBCs and

granulocytes) and is performed every 3 months. These results will be summarized and listed.

9.8.3 ADVERSE EVENTS

Adverse events will be coded using MedDRA (version 19.1 or higher). All events will be summarized and presented by Incidence rates for treatment-emergent adverse events (TEAEs) by maximum severity and SAEs will be summarized. These summaries will be provided regardless of causality and for events that are considered possibly related to treatment with RA101495.

TEAEs are defined as follows:

- An AE that occurs after a subject's initial treatment RA101495 start for this study (RA101495-01.202) that was not present at the time of treatment start; or
- An AE that increases in severity after treatment start in this study, if the event was present at the time of treatment start.

TEAEs will be summarized for each cohort.

AEs occurring before the first dose of study drug in this study will be summarized separately and included in the overall AE analysis as appropriate.

The following TEAE summaries will be provided and, where applicable, summarized by system organ class, and preferred term:

- Overall summary of Treatment Emergent Adverse Events
- Incidence of Treatment Emergent Adverse Events
- Incidence of Non-serious Treatment Emergent Adverse Events
- Incidence of Treatment Emergent Adverse Events by Maximum Severity
- Incidence of Treatment Emergent Adverse Events by Relationship to Study Drug
- Incidence of Treatment Emergent Adverse Events Leading to Study Discontinuation
- Incidence of Serious Treatment Emergent Adverse Events.
- Incidence of Treatment Emergent Adverse Events above Reporting Frequency Threshold of 5%
- Incidence of Non-Serious Treatment Emergent Adverse Events above Reporting Frequency Threshold of 5%

- Incidence of TEAEs Leading to Death
- Incidence of treatment-related TEAEs Leading to Death*
- Incidence of treatment-related serious TEAEs *
- Incidence of treatment-related TEAEs leading to study drug discontinuation*
- Incidence of Grade 3 or greater TEAEs*
- Incidence of treatment-related Grade 3 or greater TEAEs*

(*: only in overall summary)

For these summaries, the number and percentage of subjects who experienced at least one of the TEAE as well as (where applicable) the number and percentage of subjects who experienced each specific SOC and PT will be presented. The corresponding number of TEAEs will also be presented, where applicable.

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.

(A) 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.

<u>AE start date missing day and month:</u>

- 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.

<u>AE start date missing month only:</u>

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

<u>AE start date missing day only:</u>

- 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.

(B) ADVERSE EVENTS OF SPECIAL INTEREST

(I) THROMBOTIC ADVERSE EVENTS

A separate table for thrombotic TEAEs will be presented, summarizing TEAEs by SOC and PT. The events in Table 1 (Hillmen, 2007]) will be evaluated in the assessment of thrombotic TEAEs.

Table 1: 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.

(II) HEPATIC ADVERSE EVENTS

Hepatic TEAEs and will be summarized separately by SOC, PT, and cohort. Liver function tests will be summarized by changes from baseline and graded in severity using the NCI CTCAE (Version 4.03) criteria.

These AEs will defined using MedDRA SMQs as:

Drug related hepatic disorders – comprehensive search (SMQ)(20000006) excluding liver neoplasms, malignant and unspecified (SMQ)(20000011) and liver neoplasms, benign (SMQ)(20000012).

(III) PANCREATIC ENZYME ELEVATION

Pancreatic enzyme elevation will be reported as incidence of baseline and post baseline grades per NCI CTCAE (Version 4.03) criteria for increased amylase (Preferred Term “Amylase

increased") and increased lipase (Preferred Term "Lipase increased").

(IV) INJECTION SITE REACTION ADVERSE EVENTS

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

- Pain, tenderness, erythema, and induration severity (Table 2)
- Erythema and induration: maximum linear diameter
- Blisters, ulceration, necrosis: maximum linear diameter and severity
- Lymphadenopathy (absent, mild, moderate, or severe)

Table 2: 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). Study visit will be assigned algorithmically based on the visit start and end dates and the actual ISR assessment date.

ISRs will be further analysed by SOC and PT for high level terms “injection site reactions”, and “administration site reactions”.

(C) TEAE WITH SOC "INFECTIONS AND INFESTATIONS"

TEAEs related to infection will be summarized separately by system organ class, preferred term, and cohort. These are defined as those with “infections and infestations” as their system organ class.

9.8.4 IMMUNOGENICITY

No analysis of immunogenicity will be performed.

9.8.5 ELECTROCARDIOGRAM

Descriptive statistics for ECG parameters (i.e. heart rate (HR), PR interval, RR interval, QRS interval, QT interval, and QTcB intervals, and QTcF intervals) at each assessment timepoint will

be presented. The interpretation of ECG will be summarized at each visit.

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: $QTc = QT/RR^{0.5}$.

9.8.6 VITAL SIGNS AND OTHER SAFETY PARAMETERS

Descriptive statistics for the actual value at each timepoint and the change from baseline to each post baseline timepoint in systolic and diastolic BP, heart rate, and body temperature will be tabulated by cohort and overall.

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

Grade 3 and 4 of increased lipase and amylase levels over baseline levels will be tabulated.

9.9 EXPLORATORY ENDPOINTS

All exploratory analyses will be done for the safety population.

9.9.1 EORTC QLQ-C30

Summary statistics for each scales/items scores 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 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:

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

Due to the potential for non-normal data, the change from baseline for the EORTC QLQ-C30 scales will be assessed by a two-sided Wilcoxon signed-rank test.

9.9.2 FACIT-FATIGUE

The overall FACIT-Fatigue score and the individual 13 item scores 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 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.

[redacted]

9.9.3 MECHANISTIC BIOMARKERS

A separate analysis plan will be prepared for mechanistic biomarkers.

9.10 OTHER ENDPOINTS AND ANALYSIS

9.10.1 PHARMACOKINETICS

All following pharmacokinetic endpoints will be summarized using descriptive statistics.

- Plasma concentrations of RA101495 and its major metabolites

9.10.2 PHARMACODYNAMIC

Pharmacodynamic endpoints will be summarized at each scheduled assessment time point using descriptive statistics for the observed and change from baseline values.

Note: CH_{50} is not analyzed as it is not collected.

9.11 INTERIM ANALYSIS

A formal interim analysis was not performed.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

1. Due to the small number of subjects increasing doses, all analysis is done on the pooled cohorts instead of by dose level.

2. Due to some injections being done away from the clinic, total number of injections will not be summarized.

3. No analyses will be done on maximum plasma concentration, time to maximum concentration, or area under the drug-concentration time curves.

4. Due to the small number of subjects in the study, no analysis will be done on the per-protocol population. Similarly no hypothesis testing will be done on study endpoints.

5. Pancreatic enzyme elevation will not be summarized as AEs, but using the incidence of NCI CTCAE grades for amylase and lipase.

6. TEAEs for infections will not be restricted to Neisseria meningitidis.

7. No analysis will be done on subject-years of exposure.

8. No analysis of immunogenicity (ADA) will be performed.

9. No analysis of CH50 will be performed.

10. No interim analysis was performed.
    .

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the *protocol number* will be presented. On the next line a *table/listing number* followed by the *title* of the table/listing and p*opulation* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under to the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002 or other appropriate formats.

The list of tables, listings, and figures is given in section below. Shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

12. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.

Aaronson NK, Cull A, Kaasa S, et al. The European Organization for Research and Treatment of Cancer (EORTC) modular approach to quality of life assessment in oncology: an update. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd Ed. New York, NY: Lippincott Williams & Wilkins. 1996:179-189.

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.

13. APPENDIX I: LIST OF TABLES, LISTINGS, AND FIGURES

Table 14.3.2.4 Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug Safety Population

Table 14.3.2.5 Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class, and Preferred Term Safety Population

Table 14.3.2.6 Serious Treatment Emergent Adverse Events by System Organ Class, and Preferred Term Safety Population

Table 14.3.2.7 Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term above Reporting Frequency Threshold of 5% Safety Population

Table 14.3.2.8 Incidence of Non-Serious Treatment Emergent Adverse Events by System Organ Class, Preferred Term above Reporting Frequency Threshold of 5% Safety Population

Table 14.3.2.9 Incidence of Treatment-related Treatment Emergent Adverse Events by System Organ Class and Preferred Term Safety Population

Incidence of Treatment-related Grade 3 or greater Treatment Emergent Adverse Events by System Organ Class and Preferred Term Safety Population

Table 14.3.3.1 Thrombotic Treatment Emergent Adverse Events by System Organ Class, and Preferred Term Safety Population

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Table 14.3.4.3 Summary of Coagulation Laboratory Values Safety Population

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Table 14.3.4.6 Summary of Liver Function Test Values Safety Population

Table 14.3.4.7 Increased Amylase and Lipase Test Values Safety Population

Table 14.3.4.8 Summary of PNH Clone Size Values Safety Population

Table 14.3.5 Summary of Vital Signs by Visit Safety Population

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Listing 16.2.18 Deaths Safety Population

14. APPENDIX II. SCHEDULE OF ASSESSMENTS

Table 1 Table Time and Events

Study Month	Screening [a] /Day 1[a,b]	1	2	3	6	9	12	Then Every 3 Months	Then Every 12 Months only	Final Study Visit
Study Day→	1	30 ± 7	60 ± 7	90 ± 7	180 ± 7	270 ± 7	360 ± 7	- (± 7)	- (± 7)	-
Study Procedure ↓										
Signature of ICF [a]	X									
Review eligibility criteria	X									
Prior and Concomitant medications	X	X	X	X	X	X	X	X		X
Physical examination	X[b]	X	X	X	X	X	X	X		X
Vital signs	X[b]	X	X	X	X	X	X	X		X
ECG	X[b]						X		X	X
Blood chemistry	X[b]	X	X	X	X	X	X	X		X
Hematology	X[b]	X	X	X	X	X	X	X		X
Coagulation[c]	X[b]	X	X	X	X	X	X	X		X
Urinalysis	X[b]	X	X	X	X	X	X	X		X
PNH Clone size	X[b]			X	X	X	X	X		X
Pregnancy test	X[b]	X	X	X	X	X	X	X		X
Quality of life assessments	X[b]	X	X	X	X	X	X	X		X
Adverse event monitoring (including injection site reactions)	X[b]	X	X	X	X	X	X	X		X
Pharmacokinetics[d]	X	X	X	X	X	X	X			
Pharmacodynamics[d]	X	X	X	X	X	X	X			
Additional Biomarkers[d]	X	X	X	X	X	X	X			
Anti-drug antibodies	X	X	X	X	X	X	X	X		X
RA101495 dispensing and return[e]	X	X	X	X	X	X	X	X		X
RA101495 administration[f]	X[g]	X	X	X	X	X	X	X		

a. The Screening Visit should coincide with the qualifying study end of study visit and include signing of the informed consent. The informed consent should be provided to the subject prior to the qualifying study end of study visit to facilitate a proper informed consent process.
b. All screening assessments are expected to be the same as those for the end of qualifying study visit and do not need to be repeated unless clinically indicated. Record AEs ongoing from qualifying study on Day 1 on the specific AE eCRF for ongoing AEs from the qualifying study.
c. Coagulation tests should be performed as per standard practice on any subject taking anticoagulant therapy in addition to specified assessments in the study.
d. PK/PD/Biomarkers sampling prior to dose on day of visit (dose held that morning and administered in clinic after blood samples are obtained).
e. Study drug dispensing and return is monthly. Frequency of dispensing of IMP may be adjusted during the study.
f. Study drug administration should be administered in clinic after PK and PD collection on clinic visit days for the first 12 months.
g. On Day 1, the last dose administered on the last day of the qualifying study is considered the first dose on the extension study and should not be repeated.