1 TITLE PAGE

RA PHARMACEUTICALS, INC.

RA101495-01.202: 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
Indication Studied:	Paroxysmal Nocturnal Hemoglobinuria
Developmental Phase of Study:	2
EudraCT Number:	2016-003523-34
Company/Sponsor Signatory:	Ra Pharmaceuticals, Inc.
Protocol Version:	Version 1.1
Release Date of Protocol:	20 October 2016

This study will be conducted by Ra Pharmaceuticals, Inc. and affiliates in compliance with the protocol, Good Clinical Practice, and all other applicable regulatory requirements, including the archiving of essential documents.

CONFIDENTIAL

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SPONSOR SIGNATURE PAGE

Protocol Title: A Multicenter, Open-label, Uncontrolled, Extension Study of RA101495 in Subjects with Paroxysmal Nocturnal Hemoglobinuria Who Have Completed a RA101495 Clinical Study

Protocol Date: 20 October 2016

[redacted]

10/20/16

Signature of Ra Pharmaceuticals, Inc. [redacted] Date

Name of Ra Pharmaceuticals, Inc. [redacted]:

[redacted]

Ra Pharmaceuticals, Inc.
87 Cambridge Park Drive
Cambridge, MA 02140

[redacted]

CENTER INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Multicenter, Open-label, Uncontrolled, Extension Study of RA101495 in Subjects with Paroxysmal Nocturnal Hemoglobinuria Who Have Completed a RA101495 Clinical Study

Protocol Version 1.1

Date: 20 October 2016

1. I have received and reviewed the Investigator's Brochure for RA101495.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined in this protocol and in accordance with all applicable regulations and guidelines, including the current International Conference on Harmonisation Good Clinical Practice Guideline.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

_____ _____

Signature of Principal Investigator Date

2 SYNOPSIS

Name of Sponsor Ra Pharmaceuticals, Inc.	**Protocol number** RA101495-01.202	**Investigational product** RA101495
Protocol title	A Multicenter, Open-label, Uncontrolled, Extension Study of RA101495 in Subjects with Paroxysmal Nocturnal Hemoglobinuria Who Have Completed a RA101495 Clinical Study	
Phase of clinical development	2	
Rationale for the study	The purpose of this study is to enable continued access to RA101495 for subjects with paroxysmal nocturnal hemoglobinuria (PNH) after they complete a Ra Pharmaceuticals sponsored clinical study with RA101495. The study will evaluate long-term safety, tolerability, preliminary efficacy, pharmacokinectics (PK), and pharmacodynamics (PD).	
Study objectives	• To provide access to RA101495 for subjects with PNH who have completed a Ra Pharmaceuticals sponsored RA101495 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 in 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.	
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 clinical study. 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 and 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.	

Name of Sponsor Ra Pharmaceuticals, Inc.	**Protocol number** RA101495-01.202	**Investigational product** RA101495
Duration of study participation	The investigational medicinal product (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. In countries where RA101495 is not approved or marketed, but in which sponsored clinical studies have been conducted, subjects may continue to receive RA101495 through a compassionate use pathway.	
Study location and planned number of study centers	All countries and centers participating in a RA101495 PNH clinical study. Planned locations include one or more of the following countries, Australia, Argentina, Canada, Germany, New Zealand, UK, and USA.	
Planned number of subjects	Up to 28 subjects (i.e. all subjects participating in a RA101495 PNH study).	
Study population	To be eligible for this study, subjects must meet **ALL** of the following inclusion criteria: 1. Completion of a qualifying Ra Pharmaceuticals sponsored RA101495 PNH study 2. Evidence of ongoing clinical benefit in the opinion of the Investigator 3. Completion of the informed consent procedure, including signing and dating the informed consent form (ICF) 4. Female subjects of child bearing potential must have had a negative pregnancy test at the completion of the qualifying study prior to first dose of study drug in this extension study 5. Sexually-active female subjects of child-bearing potential (i.e. women who are not post-menopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study. Effective contraception is defined as: o Hormonal contraception (e.g. oral contraceptive, transdermal contraceptive, contraceptive implant, or injectable hormonal contraceptive) for at least 3 months prior to study drug administration, throughout the study, and for 4 weeks after the last dose of study drug. o Double-barrier birth control (e.g. male condom, female condom, diaphragm sponge, or cervical cap together with spermicidal foam/gel/film/suppository) starting at the Screening Visit, throughout the study, and for 4 weeks after the last dose of study drug.	

Name of Sponsor	Protocol number	Investigational product
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- Intrauterine contraception/device starting at the Screening Visit, throughout the study, and for 4 weeks after the last dose of study drug.
- Total abstinence from sexual intercourse for at least one complete menstrual cycle prior to the Screening Visit, throughout the study, and for 4 weeks after the last dose of study drug
- Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy.

Subjects who meet **ANY** of the following exclusion criteria must be excluded from the study:

1. Platelet count <30,000/µL or absolute neutrophil count (ANC) <500 cells/µL at Screening
2. Calculated glomerular filtration rate of <30 mL/min/1.73m2 based on modification of diet in renal disease (MDRD) equation at Screening
3. Elevation of liver function tests: alanine aminotransferase (ALT) >2xULN or Direct Bilirubin and Alkaline Phosphatase both >2xULN
4. Elevation of amylase or lipase >2xULN
5. History of meningococcal disease
6. Current systemic infection or suspicion of active bacterial infection
7. Pregnant, planning to become pregnant, or nursing female subjects
8. Active malignancy requiring surgery, chemotherapy, or radiation within the prior 12-months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12-months prior to Screening with no detectable recurrence are allowed)
9. History of any significant medical or psychiatric disorder that in the opinion of the investigator would make the subject unsuitable for participation in the study
10. With the exception of RA101495, other treatments with any investigational medicinal product or investigational device within the 30 days prior to Screening or participation in another concurrent clinical trial involving a therapeutic intervention (participation in observational studies and/or registry studies is permitted)
11. Unable or unwilling to comply with the requirements of the study

Name of Sponsor	Protocol number	Investigational product
Ra Pharmaceuticals, Inc.	RA101495-01.202	RA101495

Endpoints and Assessments	**Safety and Tolerability** Safety assessments will include evaluation of AEs and SAEs (including major adverse vascular event (MAVE criteria), clinical laboratory tests, ECGs, vital signs, and physical examinations. Safety evaluations will also include a determination of anti-drug antibodies (ADA). **Efficacy:** Serum LDH levels, total bilirubin, total hemoglobin, free hemoglobin, haptoglobin, reticulocytes, and hemoglobinuria, at each of the scheduled assessment time-points. **Pharmacokinetic:** • Plasma concentrations of RA101495 and its major metabolites • Maximum plasma concentration (C_{max}) • Time corresponding to C_{max} (t_{max}) • Area under the drug concentration-time curves (AUC_{0-t}) **Pharmacodynamic:** • CH_{50} • sheep RBC (sRBC) lysis for classical complement pathway • Wieslab enzyme-linked immunosorbent assay (ELISA) for alternative complement pathway • C5 levels **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)
Statistical considerations	**Study Populations:** The following study populations are defined: • *Safety Population*: All subjects who receive at least 1 injection of RA101495 on or after Day 1 of this extension study (RA101495-01.202) • *Per Protocol Population*: All subjects in the Safety Population who have no major protocol deviations • *PK Population*: All subjects in the Safety Population who have at least 1 plasma sample obtained for PK assessment • *PD Population*: All subjects in the Safety Population who have at least 1 plasma sample obtained for PD assessment **General Considerations**: Data will be summarized within each dose level separately. Where appropriate, data may be pooled across dose levels. A disposition of all consented subjects will be provided and will include a breakdown of subjects who consented, were treated,

Name of Sponsor	Protocol number	Investigational product
Ra Pharmaceuticals, Inc.	RA101495-01.202	RA101495
	discontinued treatment, and were lost to follow-up or withdrew consent. A summary of reasons for screen failures and treatment discontinuations will be provided. A summary of subjects included in each analysis population will be provided. Quantitative variables will be summarized with the mean, standard deviation (SD), median, and range. Categorical variables will be summarized using counts and proportions. **Safety:** Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 18.0 or higher). Incidence rates for treatment-emergent AEs (TEAEs) by maximum severity and SAEs will be summarized. These summaries will be provided regardless of causality and for events that are considered related to treatment with RA101495. Quantitative laboratory endpoints will be summarized by dose level and time point and also by pooling dose levels. 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. Descriptive statistics for vital signs (heart rate, body temperature, and blood pressure) will be presented. 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. **Efficacy:** Efficacy endpoints will be analyzed using descriptive statistics and graphical displays. No formal statistical comparisons are specified. **Pharmacokinetics:** RA101495 and metabolite plasma concentrations will be summarized using descriptive statistics. No formal statistical comparisons are specified. **Pharmacodynamics:** Pharmacodynamics and efficacy endpoints will be summarized using descriptive statistics. No formal statistical comparisons are specified. **Determination of Sample Size:** Sample size will be determined by the number of eligible subjects completing a qualifying RA101495 clinical study. No formal statistical power calculations were performed. **Interim Analysis**: During the study, the Sponsor will conduct periodic interim analyses of the study data, which may include safety, tolerability, PK, PD and efficacy endpoints.	

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4 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definitions
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT/APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the drug concentration-time curve
BUN	blood urea nitrogen
C5	complement component 5
Cmax	maximum plasma concentration
CPK	creatine phosphokinase
CRO	clinical research organization
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
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
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPI	glycosylphosphatidylinositol
GPI-AP	glycosylphosphatidylinositol-anchored proteins
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board

Abbreviation	Definitions
ISR	injection site reaction
IV	intravenous
LDH	lactate dehydrogenase
LFT	Liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple-dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
NCI	National Cancer Institute
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PTT	partial thromboplastin time
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SOP	Standard operating procedure
TEAE	treatment-emergent adverse event
t_{max}	time to corresponding C_{max}
ULN	upper limit of normal
URI	upper respiratory infection
VAS	visual analogue scale
WBC	white blood cell

5 TIME AND EVENTS TABLE

Assessments to be performed during the study are shown in Table 1.

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.

6 INTRODUCTION

Ra Pharmaceuticals, Inc. is developing RA101495, a subcutaneously–administered 15-amino acid cyclic peptide that inhibits the cleavage of complement component 5 (C5), for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

6.1 STUDY RATIONALE

The RA101495-01.202 study is an extension study to Ra Pharmaceuticals' sponsored qualifying studies evaluating RA101495 in subjects with PNH. Subjects who successfully complete participation in these qualifying studies, with evidence of continued clinical benefit in the opinion of the treating investigator, will have the option to continue to receive treatment with RA101495. While on this study, the subject will continue to be monitored for safety, tolerability, preliminary efficacy, PK, and PD. Subjects may continue to receive RA101495 provided by the sponsor until RA101495 is approved and available or the sponsor terminates the development of RA101495 for PNH. In countries where the study is conducted, but RA101495 is neither approved nor marketed, then study subjects may continue to receive RA101495 through a compassionate use pathway.

Please refer to the Investigational Brochure for additional information on the chemistry, toxicology, pharmacology, and safety of RA101495, based on studies conducted in animals and the Phase 1 healthy volunteer study.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 OBJECTIVES

The objectives of the study are:

- To provide access to RA101495 for subjects with PNH who have 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

7.1.1 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. Safety evaluation will also include a determination of anti-drug antibodies (ADA).

7.1.2 EFFICACY ENDPOINTS

Efficacy:

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

7.1.3 PHARMACOKINETIC:

- Plasma concentrations of RA101495 and its major metabolite(s)
- Maximum plasma concentration (C_{max})
- Time corresponding to C_{max} (t_{max})
- Area under the drug concentration-time curves (AUC_{0-t})

7.1.4 PHARMACODYNAMIC

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

7.1.5 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)

8 STUDY DESIGN

8.1 OVERVIEW OF 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 clinical study. 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.

8.1.1 SCREENING PERIOD

The Screening Visit should coincide with the qualifying study end of 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. 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.

8.1.2 TREATMENT PERIOD

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. In countries where RA101495 is not approved or marketed, but in which sponsored clinical studies have been conducted, subjects may continue to receive RA101495 through a compassionate use pathway.

8.2 SUBJECT REGISTRATION PROCEDURES

8.2.1 SCREENING AND ENROLLMENT

Written informed consent must be obtained before ANY study-related or enrollment procedures are performed.

At the Screening Visit, subjects will be assigned a unique subject number that will also link to their qualifying study. Screening assessments are expected to be the same as the end of qualifying study visit and are listed below. These tests would be repeated only if clinically indicated (note that it is expected that the end of qualifying study visit and the Screening Visit for the extension study occur on the same day and these assessments are performed only once to satisfy the requirements of both study protocols):

- Documentation of successful completion of qualifying study

- Review and record AEs ongoing at entry into this study (see Section 12.3)
- Review and documentation of prior and concomitant medications
- Physical examination, including height and weight
- Vital signs (heart rate, body temperature, and blood pressure) in the sitting position after resting at least 5 minutes
- 12-lead electrocardiogram in a supine position (lying down) for at least 5 minutes prior to, and during, the recording (every 12 months or as clinically indicated)
- Blood samples for clinical chemistry (including LDH), hematology, coagulation, and PNH clone size
- Urine sample for urinalysis
- Documentation of a negative pregnancy test for females of childbearing potential
- Completion of quality of life questionnaires

The inclusion and exclusion criteria will be reviewed to determine subject eligibility for study drug dosing on Day 1. 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.

8.2.2 TREATMENT GROUP ASSIGNMENT

All subjects will receive RA101495.

8.2.3 BLINDING

This study is open-label.

8.2.4 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCT

If a subject prematurely discontinues treatment with the investigational medicinal product (IMP), RA101495, at any time, the subject should return to clinic for a Final Study Visit. The following procedures will be completed at this visit:

- Review and documentation of concomitant medications
- Physical examination, including weight
- Vital signs (heart rate, body temperature, blood pressure) in the sitting position after resting for at least 5 minutes
- 12-lead ECG in a supine position (lying down) for at least 5 minutes prior to, and during, the recording
- Blood samples for clinical chemistry, hematology, coagulation, and PNH clone size
- Urine sample for urinalysis
- Urine pregnancy for females of childbearing potential only

- Completion of QOL questionnaires
- Record AEs
- Return of all used and unused study drug syringes to site

Following discontinuation from the study, standard-of-care treatment may be initiated as recommended by the treating physician.

8.2.5 WITHDRAWAL FROM THE STUDY

Subjects who are withdrawn from the study must promptly discontinue treatment with RA101495, and make every effort to return to the clinic to complete the Final Study Visit study, as described in Section 8.2.4. All unused study drug must be returned to the clinic as described in Section 10.2.

In the event an investigator discontinues the study at his center, a subject may transfer to another investigator participating in this study.

8.3 EARLY STUDY TERMINATION

The Sponsor may terminate this study early, either in its entirety, or at one or more study sites, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at the site for reasonable cause, after providing written notice to the Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

Nonclinical toxicology data supporting chronic dosing in this study is provided by an ongoing 39-week study in primates. The duration of dosing in that study and review of in-life data is designed to exceed the duration of treatment of subjects enrolled into this extension study. If the chronic toxicology study is halted or terminated, a review of the available data will be conducted to assess risk to subjects on this extension study. As appropriate based on this review the Sponsor will notify the investigator and appropriate measures will be taken to ensure the safety of subjects.

8.4 FINAL STUDY VISIT

The end-of-study is defined as the date of the last subject 's last visit.

9 SELECTION OF STUDY POPULATION

9.1 INCLUSION CRITERIA

To be eligible for this study, subjects must meet all of the following inclusion criteria:

1. Completion of a qualifying RaPharmaceuticals sponsored RA101495 PNH study

2. Evidence of ongoing clinical benefit in the opinon of the investigator

3. Completion of the informed consent procedure, including signing and dating the informed consent form (ICF)

4. Female subjects of child bearing potential must have had a negative pregnancy test at the completion of the qualifying study prior to first dose of study drug in this extension study

5. Sexually-active active female subjects of child-bearing potential (i.e. women who are not post-menopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study. Effective contraception is defined as:

    - Hormonal contraception (e.g. oral contraceptive, transdermal contraceptive, contraceptive implant, or injectable hormonal contraceptive) for at least 3 months prior to study drug administration, throughout the study, and for 4 weeks after the last dose of study drug.
    - Double-barrier birth control (e.g. male condom, female condom, diaphragm sponge, or cervical cap together with spermicidal foam/gel/film/suppository) starting at the Screening visit, throughout the study, and for 4 weeks after the last dose of study drug.
    - Intrauterine contraception/device starting at the Screening visit, throughout the study, and for 4 weeks after the last dose of study drug.
    - Total abstinence from sexual intercourse for at least one complete menstrual cycle prior to the Screening visit, throughout the study, and for 4 weeks after the last dose of study drug
    - Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy

9.2 EXCLUSION CRITERIA

Subjects who meet any of the following exclusion criteria must be excluded from the study:

1. Platelet count <30,000/µL or absolute neutrophil count (ANC) <500 cells/µL at Screening

2. Caluculated glomerular filtration rate of <30 mL/min/1.73m2 based on modification of diet in renal disease (MDRD) equation at Screening

3. Elevation of liver function tests (LFT): alanine aminotransferase (ALT) >2xULN or Direct Bilirubin and Alkaline Phosphatase (ALP) both >2xULN

4. Elevation of amylase or lipase 2xULN

5. History of meningococcal disease

6. Current systemic infection or suspicion of active bacterial infection

7. Pregnant, planning to become pregnant, or nursing female subjects

8. Active malignancy requiring surgery, chemotherapy, or radiation within the prior 12-months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12-months prior to Screening with no detectable recurrence are allowed)

9. History of any significant medical or psychiatric disorder that in the opinion of the investigator would make the subject unsuitable for participation in the study

10. With the exception of RA101495, other treatments with with any investigational medicinal product or investigational device within the 30 days prior to Screening or participation in another concurrent clinical trial involving a therapeutic intervention (participation in observational studies and/or registry studies is permitted)

11. Unable or unwilling to comply with the requirements of the study

9.3 REMOVAL AND REPLACEMENT OF SUBJECTS IN THE STUDY

9.3.1 PREMATURE DISCONTINUATION

Every reasonable effort should be made to encourage retention of subjects in the study, maximize compliance with study drug, and facilitate attendance at all scheduled study visits.

All subjects have the right to refuse further participation in the study at any time and for any reason. A subject's participation must, therefore, be terminated immediately upon his/her request.

The investigator will make every attempt to ascertain the reason(s) for discontinuation and to document this in detail in the source documentation and the appropriate sections of the electronic case report form (eCRF). Subjects may be withdrawn from the study due to any of the following reasons:

- Subject withdraws consent
- Subject is non-compliant, defined as refusal or inability to adhere to the study procedures
- Unacceptable or intolerable treatment-related AEs
- Use of any other investigational treatment
- Any illness or circumstance (e.g. incarceration) that would substantially impact the study procedures or outcome measures
- At the request of the Sponsor, regulatory agencies, or independent ethics committee (IEC)/institutional review board (IRB)

- Loss to follow-up

9.3.2 REPLACEMENT OF SUBJECTS

Subjects who discontinue their participation will not be replaced.

10 INVESTIGATIONAL MEDICINAL PRODUCTS AND TREATMENTS

10.1 STUDY TREATMENT ADMINISTRATION

10.1.1 IDENTITY OF INVESTIGATIONAL PRODUCTS AND TREATMENT

[redacted]

Subjects will be instructed to self-inject SC doses daily. The dose (dose volume) for each injection will depend on the dose at the end of the qualifying study and subject's bodyweight (see Section 10.1.3 and Section 10.1.4).

10.1.2 TREATMENT GROUPS

All subjects will receive RA101495 at the same dose level at the time they completed the qualifying study.

10.1.3 DOSING SCHEDULE

Subjects will be 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 last day of the qualifying study is considered the first dose on the extension study and should not be repeated. On days of the scheduled study visit at the investigator site, the dose must be administered after the blood work is completed at the investigator site.

10.1.4 DOSE OR DOSING SCHEDULE MODIFICATIONS

Doses of RA101495 will be determined by a target dose and weight, accomplished using a fixed dose by weight brackets. These brackets are grouped by body weight category such that each subject will receive the no less than the target minimum dose to avoid sub-therapeutic dosing. For the 0.1 mg/kg dose, subjects will receive, at a minimum, a fixed dose of 0.1 mg/kg (range [redacted]); for the 0.3 mg/kg dose, subjects will receive a minimum dose of 0.3 mg/kg (range [redacted]). Table 2 summarizes dose presentations for RA101495 0.1 mg/kg and 0.3 mg/kg doses.

Dose adjustments are allowed throughout this extension study for reasons of safety and control of hemolysis and should be discussed with the medical monitor.

Table 2 Dose Presentations by Weight Brackets

Target Dose (mg/kg)	Dose Presentation			Weight Range (kg)	Dose Range (mg/kg)
	Fill Volume		Dose		
	Number	mL	mg		
0.1	1	[redacted]	[redacted]	43 to ≤ 61	[redacted]
0.1	2	[redacted]	[redacted]	>61 to ≤88	[redacted]
0.1	3	[redacted]	[redacted]	>88 to ≤109	[redacted]
0.3	4	[redacted]	[redacted]	43 to ≤56	[redacted]
0.3	5	[redacted]	[redacted]	>56 to ≤77	[redacted]
0.3	6	[redacted]	[redacted]	>77 to ≤109	[redacted]

10.1.4.1 MISSED DOSE

If a subject misses one dose (i.e. 1 day) of RA101495, the subject should take the next planned dose as scheduled, and contact the investigator as soon as possible. If a subject misses 2 or more doses, the subject must notify the investigator immediately.

10.2 STUDY TREATMENT MANAGEMENT

10.2.1 PREPARATION AND DISPENSING

Pre-filled syringes will be dispensed to each subject monthly. Frequency of dispensing of IMP may be adjusted during the study.

Subjects will be provided training and detailed instructions regarding administration of RA101495 using the pre-filled syringes and the injection device in a separate manual.

10.2.2 STUDY DRUG SUPPLY, STORAGE, AND HANDLING

[redacted]

The IMP should be stored at 2 °C to 8°C at the study site. Once dispensed to subjects, the IMP may be stored at controlled room temperature (20°C to 25°C [68°F to 77°F]) protected from sources of heat, light and damage. Storage of IMP outside of room temperatures should be avoided.

Subjects will be instructed to self-inject SC doses daily every 24 hours at approximately the same time each day.

All subjects will receive a study drug kit that will include RA101495 (prefilled syringes), a syringe disposal container, alcohol wipes, and adhesive dressings.

10.2.3 DISPOSAL, RETURN, OR RETENTION OF UNUSED DRUG

At all visits, subjects will also receive a secure container to dispose of used syringes while at home. At each visit and the subject should bring the used container containing all used syringes to be returned to the site. The unused study drug (unused syringes) should be retained by the subject and be used first in the immediate weeks following each visit.

10.2.4 DRUG ACCOUNTABILITY AND COMPLIANCE

All study drug (syringes) and disposal containers must be returned to the site at the last study visit.

Compliance will be assessed at each study visit.

11 STUDY ASSESSMENTS

Please refer to Table 1 Time and Events for the timing of assessments.

11.1 SUBJECT AND BASELINE DISEASE CHARACTERISTICS

11.1.1 DEMOGRAPHIC DATA

The following demographic data collected from the qualitfying study will be linked to the extension sudy: date of birth, gender, ethnicity, and race.

11.1.2 DISEASE AND PRIOR TREATMENT HISTORY

The data regarding the diagnosis of PNH will have been recorded in the qualifying study; these data will be linked to the extension protocol.

11.1.3 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant medications ongoing from the qualifying study will be documented. 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.

Findings will be recorded on the subject's source documents and entered on the appropriate eCRF. Any changes to concomitant medications during the Treatment Period will be recorded in the eCRF.

11.2 SAFETY ASSESSMENTS

11.2.1 MEDICAL AND SURGICAL HISTORY

Relevant medical history will be documented in the qualifying study.

Adverse events ongoing from the qualifying study should be reviewed and recorded on the specific AE eCRF page for such ongoing events at the time of the last study visit of the qualifying study.

If during the course of the study, a subject requires surgery with general anesthesia for any reason, continuation of study drug in the perioperative period is recommended, and should be discussed with the medical monitor. The event leading to surgery should be recorded as an AE per Section 12.3.

11.2.2 PHYSICAL EXAMINATION

Physical examinations will include the following assessments:

- General inspection
- Weight (kilograms)
- 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.

11.2.3 VITAL SIGNS

Vital signs signs (heart rate, body temperature, and blood pressure) will be measured in the sitting position after resting for at least 5 minutes. If blood samples are scheduled at the same time, vital signs should be measured before the blood draw. Blood pressure may be measured manually or by automated device, preferably in the non-dominant arm. The same measurement technique should be used throughout the study for all subjects. Temperature will be measured with an electronic device.

11.2.4 ELECTROCARDIOGRAM

Subjects should be in a supine position (lying down) for at least 5 minutes prior to and during the 12-lead ECG recording. ECGs will be assessed as normal or abnormal by the investigator. Any abnormal findings will be recorded in the eCRF and clinical significance will be assessed by the investigator and if a finding is deemed clinically significant it should recorded as an adverse event. The ECG recording strip will be signed and dated by the investigator and stored in the medical records.

ECGs should be performed prior to blood draws when both assessments are completed. Assessments should be completed once every 12 months, at the Final Study Visit, and as clinically indicated (Table 1).

11.2.5 ADVERSE EVENT RECORDING

Guidance on the identification, monitoring, and reporting of AEs are provided in Section 12.

11.2.6 LABORATORY SAFETY ASSESSMENTS

11.2.6.1 BLOOD CHEMISTRY, HEMATOLOGY, AND COAGULATION

Clinical chemistry and hematology analytes to be collected are identified in Table 3 and performed as specified in the Table 1. All coagulation tests should be performed as per standard practice on any subject taking anticoagulant therapy in addition to specified assessments in this schedule of events.

Table 3 Clinical Chemistry, Hematology, and Coagulation Analytes

Clinical Chemistry	Hematology
alanine aminotransferase (ALT)	free hemoglobin
albumin	haptoglobin
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 (total, direct, and indirect)	platelet count
blood urea nitrogen (BUN)	RBC count
calcium	reticulocyte count
chloride	white blood cell (WBC) count and differential (%)
creatinine	**Coagulation**
gamma-glutamyl transferase (GGT)	international normalized ratio (INR)/prothrombin time (PT)
glucose	fibrinogen
lactate dehydrogenase (LDH)	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	

11.2.6.2 URINALYSIS

A urinalysis will be performed to measure pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, and cells. A microscopic examination will be performed, if necessary, occult blood, and cells. A microscopic examination will be performed, if necessary. Hemoglobinuria will be assessed using a urine colorimetric scoring system.

11.2.6.3 PREGNANCY TEST

A urine dipstick pregnancy test (human chorionic gonadotropin) will be performed on female subjects of childbearing potential as per the Table 1,Time and Events.

11.2.7 PNH CLONE

PNH clone size will be determined by peripheral blood flow cytometry analysis (RBCs and granulocytes) and is performed every 3 months as per Table 1, Time and Events.

11.3 IMMUNOGENICITY

Blood samples for ADAs will be collected on all study visit days and the final study day. 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.

11.4 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.

11.5 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Blood samples for the measurement of plasma concentrations of RA101495 and metabolites will be collected on all subjects.

Blood samples for pharmacodynamic assessments will be collected an all subjects and include measurements of:

- CH50
- sRBC lysis for classical complement pathway
- Wieslab ELISA for alternative complement pathway
- C5 levels

Blood samples for PK and PD will be collected per the timepoints in Table 1 Time and Events.

All samples will be sent to a central laboratory for analysis. Detailed instructions regarding PK and PD sample collection, processing, and shipping will be provided in a separate laboratory manual.

11.6 EXPLORATORY ASSESSMENTS

11.6.1 QUALITY OF LIFE ASSESSMENT

Quality of Life assessments will be performed according to the Time and Events Table, Table 1. These will include:

- 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-F) Scale

11.6.1.1 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); 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.

11.6.1.2 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 past week. The level of fatigue is measured on a four point Likert scale (4 = not at all fatigued to 0 = very much fatigued) [Webster, 2003].

11.6.2 BIOMARKERS

Blood samples will be collected at designated time points in Table 1, Time and Events. After the first year, blood samples for biomarker analysis should be collected whenever possible when there is an AE of thrombosis, pancreatic or hepatic event. All biomarkers will be analyzed by biological or biochemical assays at an accredited laboratory. Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

The study of biomarkers related to complement function, thrombosis, inflammation, and liver function will provide further insight in to the clinical efficacy and tolerability to RA101495 in PNH subject s. Complement protein levels and complement activity will be tested to evaluate response to RA101495 and understand subject characteristics related to variations in response to drug. Markers of thrombosis and inflammation will be tested to assess correlation with complement function and clinical response to RA101495 and to identify markers that may correlate with thrombotic risk in PNH subjects. Additionally, markers for liver function will be assessed to evaluate tolerability of RA101495. A list of analytes will be created through review of the literature, ongoing clinical studies, and ongoing exploratory work and may be finalized after completion of the study.

The completion of these investigations may be conditional based on the results of this or other clinical studies, and samples may be selected for analysis on the basis of clinical outcome. The results of the biomarker investigations will be reported separately from the main clinical study report.

12 SAFETY REQUIREMENTS

12.1 DEFINITIONS

12.1.1 ADVERSE EVENT

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 ICF)

12.1.2 SERIOUS ADVERSE EVENT

An SAE is any untoward medical occurrence that:

- results in death
- is life-threatening 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 an SAE.

12.1.3 ADVERSE EVENTS OF SPECIAL INTEREST

12.1.3.1 THROMBOTIC ADVERSE EVENTS

All subjects should be monitored for signs and symptoms of thrombotic events at all study visits. The method of diagnosis (e.g. ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], venogram, or other [specify]) for any reported event should be recorded in the eCRF. All AEs should be recorded and reported as AEs per Section 12.2 and Section 12.3.

12.1.3.2 HEPATIC ADVERSE EVENTS

All subjects should be monitored for signs and symptoms of hepatic or biliary dysfunction. Liver function tests (LFTs) (ALP, ALT, AST, GGT, Direct Bilirubin and Indirect Bilirubin) are monitored at all study visits. The following guideline is provided:

- In subjects with isolated ALT elevation >2xULN or direct bilirubin and ALP elevation >2xULN with no other explanation for the elevation(s), contact the medical monitor to review the case details and determine if the subject should continue or discontinue study treatment. The subject should be monitored until the elevated enzymes return to Grade 1 (NCI CTACE) or lower.

- Subjects with isolated ALT elevations >3xULN concurrently with bilirubin elevation ≥2xULN and a normal ALP with no other explanation for the elevation should be permanently discontinued. The medical monitor should be contacted as soon as possible to review the case. The subject should be monitored until the elevated enzymes return to Grade 1 (NCI CTACE) or lower.

All AEs should be recorded and reported as AEs per Section 12.2 and Section 12.3.

12.1.3.3 PANCREATIC ENZYME ELEVATIONS

Subjects should be monitored during the study for symptoms of pancreatitis or cholecystitis. Pancreatic enzymes (amylase and lipase) are monitored at all study visits.

In subjects with elevations of amylase or lipase to National Cancer Institute Common terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 (>2.5xULN) or Grade 4 (>5xULN) contact the medical monitor to review the case details and determine if the subject should continue on study treatment. The subject should be monitored until amylase and/or lipase returns to Grade 1 or lower.

All AEs should be recorded and reported as AEs per Section 12.2 and Section 12.3

12.1.3.4 INJECTION SITE REACTIONS

The investigator should assess the injection site at each scheduled visit for:

- Pain, tenderness, erythema, and induration severity (Table 4)

- Erythema and induration: record the maximum linear diameter
- Blisters, ulceration, necrosis: record the maximum linear diameter and severity
- Lymphadenopathy

In addition, the investigator will, whenever possible, take de-identified photos of the injection site reaction (ISR).

Injection site reactions should be recorded as AEs per Section 12.1 and Section 12.3, and recorded on the ISR specific eCRF and AE eCRF as appropriate.

Table 4 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

12.1.3.5 INFECTION

All subjects should be monitored for signs and symptoms of *Neisseria meningitidis* infection. During the study, to mitigate the risk of infection, subjects will be counseled and reminded of early signs and symptoms of *Neisseria meningitidis* infection. A patient safety card detailing the signs and symptoms of infection with instructions to seek immediate medical attention will be provided to each subject. The card will also describe the subject's participation in the study and the risks of infection associated with inhibition of the terminal complement system. The patient safety card must be carried with the patient at all times while on treatment.

All AEs should be recorded as AEs per Section 12.2 and Section 12.3.

12.2 EVALUATION AND CLASSIFICATIONS

12.2.1 SEVERITY

The investigator should determine the severity of the reported AE by using the NCI- CTCAE (Version 4.0). These criteria will be provided in a separate manual.

For any reported AE not described in the NCI-CTCAE, the following guidelines must be considered for severity evaluation:

Adverse Event Severity	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s).
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

12.2.2 CAUSALITY

The causal relationship of the AE to study medication will be assessed by both the investigator and the Sponsor. The assessment of causal relationship to study drug should be evidence-based, and not based on the premise that all AEs are causally related to study drug until proven otherwise. Default categorization of 'related' without supportive evidence for a causal relationship to study drug is generally uninformative and does not contribute to understanding of the safety profile of the drug with respect to the intended population.

Examples of evidence that would suggest a causal relationship between the drug and the AE include occurrence of an AE that is known to be strongly associated with drug exposure (e.g. injection site reaction), or an AE that is otherwise uncommon in the study population. Lack of efficacy of study drug, in isolation, leading to unmasking of underlying symptoms and signs of disease, should not be considered evidence of relatedness.

The causal relationship of each AE is assessed using a binary system with all AEs classified as either 'related' or 'unrelated'.

Related: There is 'reasonable possibility' that the drug caused the AE. The AE follows a reasonable temporal association from the time of study drug administration. There is supportive evidence to suggest a possible causal relationship, irrespective of the degree of certainty, between the observed AE and the study drug. There is no alternative more likely explanation for the AE. Lack of study drug efficacy is not considered, by itself, to be evidence of relatedness.

Not Related: Lack of a reasonable temporal association from the administration of the study drug and the occurrence of the AE. There is evidence of an alternative explanation that is more likely as a cause of the AE.

12.3 RECORDING, REPORTING, AND MONITORING

12.3.1 RECORDING AND REPORTING

The investigator must make every effort to properly evaluate all information relevant to the reported AE in such a way that a diagnosis can be confidently made and reported. For example, it is preferable to report "pneumonia" as the AE rather than its symptoms (e.g. "rales" or "fever") as separate AEs.

When recording and/or reporting AEs or SAEs, the following elements must be included:

- the fulfilled criteria for seriousness as presented in Section 12.1.2
- the severity of the event as defined in Section 12.2.1
- the relationship of the event to study treatment as defined in Section 12.2.2

Actions taken in relation to the AE will be recorded as drug withdrawn, drug interrupted, dose reduced, dose increased, concomitant medication, other action (e.g. diagnostic testing), or no action. Any medication given to treat the AE will be recorded separately in the concomitant medication list of the eCRF.

The outcome of the AE will be recorded as date ended, ongoing, or resulting in death with date of death.

12.3.1.1 RECORDING AND REPORTING ADVERSE EVENT

Pre-existing conditions that are detected prior to administration of the first dose of study drug in the qualifying study will have been recorded as part of medical history of the qualifying study. Any AE ongoing at the last visit of the qualifying study will be recorded on a specific eCRF page for such ongoing AEs from qualifying study. The AE reporting period will start with the first administration of study drug on Day 1 and will end with the final study visit, after which no new AEs are to be reported. In addition, SAEs will be collected from the time the subject signs the study specific informed consent until 30 days after the last dose of study drug. When possible, ongoing AEs assessed as related to the study drug will be followed until resolved or stabilized.

The subjects will be monitored throughout the study for any AEs, including abnormal, clinically significant laboratory values, clinically significant findings at vital signs measurements, spontaneous reports by study subject s, and observations by the study personnel. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) after the eCRFs have been monitored and signed by the investigator.

All AEs will be recorded in the eCRF. The investigator will assess and record any AE in detail including the date and time of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date or ongoing), relationship of the AE to study drug, and any action(s) taken. All

AEs should be reported separately (ie, 1 record per event). Reporting of AEs is event-based (ie, an ongoing event will not be closed until resolved or at the end of study). For the AE description, a diagnosis is preferred over symptoms. If no diagnosis can be made, each symptom will be reported as a separate AE. Abbreviations should be avoided. Descriptive words should be used for ongoing conditions as applicable (e.g. exacerbation of herpes genitalis or worsening of eczema).

12.3.1.2 RECORDING AND REPORTING SERIOUS ADVERSE EVENT

Any SAE experienced by the subject from ICF signing up to 30 days after the last dose of study drug, regardless of severity or causality, must be recorded on the eCRF and SAE Form.

The study site must formally notify the Sponsor of the SAE within 24 hours from the time the study site becomes aware of the SAE. A formal notification must be submitted to the Sponsor regardless of the following:

- severity
- causality
- whether or not the subject received study treatment or undergone study related procedures

The IEC/IRB will be notified as required by local regulations. The investigator will be responsible for submitting the required safety information to the appropriate IEC/IRB, including any safety reports received from the Sponsor as well as any SAEs occurring at his or her site.

The Sponsor, or designee, will prepare any required safety reports for regulatory authorities and all active investigators. These reports will be provided as addenda to the Investigator's Brochure, and the investigator will place these with the brochure.

12.3.1.3 DEATH

Any event with an outcome of death should be appropriately recorded in the eCRF. All identified causes of death, including an assessment of the possible relationship of each to study treatment, must be reported as SAEs as outlined in Section 12.3.1.2. Any autopsy or other post-mortem findings (including a coroner's report) should be provided when available.

12.3.2 MONITORING

All AEs and SAEs should be monitored by the investigator until resolution or stabilization.

12.3.2.1 POST-STUDY EVENTS

Any SAE that was continuing at the time of subject discontinuation or study completion should be monitored by the investigator until resolution or stabilization.

SAEs that occur after the subject discontinues from or completes the study and are considered by the investigator to be related to study treatment or procedures should be reported using the same procedures outlined in Section 12.3.1.2.

12.4 SPECIAL CIRCUMSTANCES

12.4.1 PREGNANCY

Subjects and their partners should avoid pregnancy throughout the course of the study. Pregnancy in a study subject or partner must be reported to the Sponsor within 1 working day of the site becoming aware of the pregnancy. Subjects with a positive pregnancy test before study drug dosing must not be dosed.

Information regarding a pregnancy occurrence in a study subject or partner and the outcome of the pregnancy will be collected.

Pregnancy in a study subject or partner is not, in itself, considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to the Sponsor within 24 hours of the site becoming aware of the event. The procedure of elective abortion should not be reported as an AE.

12.4.2 OTHER

Certain safety events, called 'Special Situations', that occur in association with study medication(s) may require reporting. These Special Situations include, but are not limited to, the following:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving medicinal product (with or without subject/subject exposure to the sponsor's medicinal product, e.g. name confusion)

Special situations should be reported on the Special Situations CRF whether they result in an AE/SAE or not. Special Situations associated with an AE/SAE should also be reported on the corresponding AE/SAE forms.

13 STATISTICAL AND ANALYTICAL PLANS

13.1 SAMPLE SIZE DETERMINATION

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.

13.2 ANALYSIS POPULATIONS

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

13.2.1 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).

13.2.2 PER PROTOCOL POPULATION

The Per Protocol Population will include all subjects in the Safety Population who have no major protocol violations.

13.2.3 PHARMACOKINETIC POPULATION

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

13.2.4 PHARMACODYNAMIC POPULATION

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

13.3 STATISTICAL PLAN

13.3.1 GENERAL CONSIDERATIONS

Data will be summarized within each dose level separately. Where appropriate, data will be pooled across dose levels. There will be no adjustments for multiple comparisons. Details of the statistical analysis methodology will be provided in a Statistical Analysis Plan.

13.3.2 SUBJECT DISPOSITION

A disposition of all consented subjects will be provided. This will include a breakdown of subjects who consented, were treated, discontinued treatment, and were lost to follow-up, or withdrew consent. Additionally, a summary of subjects included in the analysis populations defined in Section 13.2 will be provided.

13.3.3 DEMOGRAPHY AND BASELINE DISEASE CHARACTERISTICS

Quantitative variables will be summarized with the mean, median, and range. Categorical variables will be summarized using counts and proportions.

13.3.4 EXTENT OF EXPOSURE

The number of injections and 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. Additionally the number of subject -years on drug will be summarized by dose and overall.

13.3.5 SAFETY ANALYSIS

Safety analysies will be performed by the dose level as well as pooled across dose levels.

13.3.5.1 ADVERSE EVENTS

Adverse events will be coded using MedDRA (version 18.0 or higher).

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 at this study, if the event was present at the time of treatment start.

TEAEs will be summarized for each dose level separately. Pooled summaries will also be provided for eculizumab-naïve, eculizumab-switch, and inadequate responder populations separately.

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.

13.3.5.2 ADVERSE EVENTS OF SPECIAL INTEREST

Thrombotic AEs will be summarized separately by system organ class, preferred term, and dose. The events in Table 5 will be evaluated in the assessment of thrombotic AEs: MAVE criteria [Hillmen, 2007]) will be evaluated in the assessment of thrombotic AEs:

Table 5 Thrombotic Event Description (MAVE criteria)

Thrombophlebitis/Deep vein thrombosis	Mesenteric/Visceral arterial thrombosis
Pulmonary embolus	Hepatic/Portal vein thrombosis
Myocardial infarction	Dermal thrombosis
Transient ischemic attack	Gangrene (non-traumatic, non-diabetic)
Renal vein thrombosis	Cerebral arterial occlusion/ cerebrovascular accident
Acute peripheral vascular occlusion	Cerebral venous occlusion
Amputation (non-traumatic, non-diabetic)	Renal arterial thrombosis
Mesenteric/Visceral vein thrombosis	Other
Unstable angina	

13.3.5.2.1 HEPATIC ADVERSE EVENTS

Hepatic and biliary AEs and will be summarized separately by system organ class, preferred term, and dose level. Liver function tests will be summarized by changes from baseline and graded in severity using the NCI CTCAE criteria.

13.3.5.2.2 PANCREATIC ENZYME ELEVATIONS

Pancreatic AEs and will be summarized separately by system organ class, preferred term, and dose level. Pancreatic elevations will be summarized by changes from baseline and graded in severity using the NCI CTCAE criteria.

13.3.5.2.3 INJECTION SITE REACTIONS

ISRs will be summarized separately by system organ class, preferred term, and dose level. The summary will include additional details on these events as described in Section 11.2.3 and Section 12.1.3.

13.3.5.2.4 INFECTION

AEs related to infection with *Neisseria meningitidis* will be summarized separately by system organ class, preferred term, and dose level.

13.3.5.3 CLINICAL LABORATORY EVALUATION

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

13.3.5.4 ELECTROCARDIOGRAM

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

13.3.5.5 VITAL SIGNS

Descriptive statistics for vital signs (heart rate, body temperature, and blood pressure) at each assessment timepoint will be presented.

13.3.5.6 PHYSICAL EXAMINATION

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

13.3.6 EFFICACY ANLYSIS

Efficacy endpoints will be summarized using descriptive statistics. Tests to assess change-from-baseline will be performed as appropriate.

13.3.6.1 PHARMACOKINETIC ANALYSIS

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

13.3.6.2 PHARMACODYNAMIC ANALYSIS

Pharmacodynamic endpoints will be summarized. No formal statistical comparison between doses will be performed. Tests to assess change-from-baseline will be performed as appropriate.

13.3.6.3 EXPLORATORY ANALYSES

The quality of life endpoints will be summarized descriptively.

13.3.6.3.1 BIOMARKER ANALYSIS

The completion of analyses will be conditional based on the results of this or other clinical studies, and samples may be selected for analysis on the basis of clinical outcome (see Section 11.6.2). The results of the biomarker investigations will be reported separately from the main clinical study report.

13.3.7 INTERIM ANALYSIS

During the study, the Sponsor will conduct periodic interim analyses of the study data which may include safety, tolerability, PK, PD and efficacy endpoints.

14 ETHICAL CONSIDERATIONS

This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirement(s).

14.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMMUNICATIONS

Prior to study initiation, the investigator/institution should have written and dated approval/favorable opinion from the IEC/IRB for the study protocol, written ICF, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information to be provided to subjects. A current copy of the Investigator's Brochure must be provided to the IEC/IRB as part of the written application. During the study, the investigator/institution should provide to the IEC/IRB all documents subject for review.

14.1.1 PROGRESS REPORTS

The investigator should submit written summaries of the study status to the IEC/IRB annually, or more frequently, if requested by the IRB/IEC.

14.1.2 FINAL INVESTIGATOR REPORT

Upon completion of the study, the investigator/institution should provide a summary of the study's outcome to the IEC/IRB and the regulatory authorities with any required reports.

14.2 INFORMED CONSENT OF STUDY SUBJECTS

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF and written information should receive the IEC/IRB's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study, including the written information and the approval/ favorable opinion by the IEC/IRB. Before informed consent may be obtained, the investigator should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

Prior to participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written ICF and any other written information provided to the subjects. During a subject's participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

14.3 PROTOCOL COMPLIANCE

The investigator/institution should conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if required) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IEC/IRB of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number). When an important deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the Medical Monitor for the study.

Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the subject's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

The investigator should document and explain any deviation from the approved protocol.

14.4 PROTECTION OF CONFIDENTIALITY

Prior to study participation, the investigator shall inform the subject or the subject's legally acceptable representative that the monitor(s), auditor(s), IEC/IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.

In addition, prior to study participation, the subject must be informed that the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available; if the results of the study are published, the subject's identity will remain confidential.

14.5 DISCLOSURE OF STUDY RESULTS

The Sponsor will post the results of the study in a publicly accessible database in accordance with the applicable laws and regulations.

15 REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

15.1 QUALITY ASSURANCE

Quality assurance and quality control systems shall be implemented and maintained with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

An agreement must be secured from all involved parties to ensure direct access to all study related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor, and of inspection by regulatory authorities.

15.1.1 MONITORING

On-site monitoring visits will be conducted before, at regular intervals during, and after the study, as appropriate, by Sponsor-approved monitors. At a minimum, the accuracy and completeness of the eCRF entries, source documents, and other study-related records will be checked against one another during these visits. After each monitoring visit, a report of any significant findings/facts, deviations, and deficiencies will be communicated to the investigator. The actions taken to address the findings and secure compliance should be documented.

15.1.2 AUDIT

An audit may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

15.2 CLINICAL RESEARCH ORGANIZATIONS

A Clinial Research Organization will be utilized to assist in the conduct of this study. Accredited central laboratories will be used for the analysis of safety laboratory samples and for the bioanalytical testing of PK and PD blood samples.

15.3 DATA MANAGEMENT

15.3.1 CASE REPORT FORMS

Case report forms must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable. The case report form data for this study are being collected with an eCRF. The documentation related to the validation of the eCRFs will be maintained in the Trial Master File. The Trial Master File will be maintained by the CRO and the Sponsor.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by

investigative site personnel. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Access to the electronic data capture system will be password-protected and will be removed from the investigator site at the end of the site's participation in the study. Data from the eCRF will be archived on appropriate data media and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts that media.

15.3.2 SOURCE DOCUMENTS

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, ECGs, X-rays, ultrasounds, angiograms, venograms, CT scans, and/or MRI scans. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

15.4 PREMATURE TERMINATION OR SUSPENSION OF THE STUDY

If the Sponsor terminates or suspends the study, the investigator/institution should promptly inform the IEC/IRB and provide the IEC/IRB a detailed written explanation of the termination or suspension. If the IEC/IRB terminates or suspends its approval/favorable opinion of the study, the investigator/institution should promptly notify the Sponsor and provide the Sponsor with a detailed written explanation of the termination or suspension.

15.5 CLINICAL STUDY REPORT

Whether the study is completed or prematurely terminated, the clinical study report will be prepared and provided to the regulatory agencies as required by the applicable regulatory requirement(s).

15.6 PUBLICATION POLICY

The Sponsor recognizes the importance of communicating the results of scientific studies, including clinical trials, and therefore, strongly supports their publication of trial findings in peer-reviewed scientific journals and presentation of data at professional society seminars or conferences. The Sponsor also has legitimate corporate and investor responsibilities, including, but not limited to, protecting confidential information about its proprietary products and obtaining patent protection for its intellectual property.

Therefore, the following procedures apply to any communication (including written, oral, or electronic; manuscript, abstract, other publication, or presentation) of results or information arising from this study (including any ancillary studies involving trial subjects) to any third parties:

- The proposed communication will be prepared in collaboration with the Sponsor. The first publication from this study is expected to be a summary of partial or complete data, jointly produced by the Sponsor and the participating investigators. The participating investigators will be invited to contribute as co-authors in the joint communication. If a joint communication with a summary of all protocol results has not been submitted for publication within eighteen (18) months of completion or termination of the study at all participating sites and final locking of the study database, the participating investigators will be free to publish separately, subject to the procedures set forth in this section.
- The final proposed version must be submitted to the Sponsor for review and comment at least 30 days prior to presentation, submission for publication, or other dissemination.
- In the event the Sponsor reasonably determines that a proposed communication contains confidential or patentable material, they may require either of the following:
    - The material be removed from the communication
    - The communication may be delayed to permit filing the appropriate intellectual property protection. These procedures apply regardless of whether the study is completed as planned or is terminated prematurely for any reason.

All publications will give Ra Pharmaceuticals, Inc. and/or its research personnel appropriate credit (ie, authorship or acknowledgement) for any direct contribution made by them.

Authorship will be decided jointly by the investigators and the Sponsor. Manuscripts will conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, including, but not limited to, the standards for authorship contained therein.

16 REFERENCES

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