1 TITLE PAGE

RA PHARMACEUTICALS, INC.

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

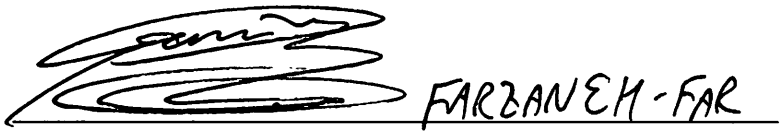
Protocol Number:	RA101495-01.201
Indication Studied:	Paroxysmal Nocturnal Hemoglobinuria
Developmental Phase of Study:	2
EudraCT Number:	2016-003522-16
Company/Sponsor Signatory:	Ra Pharmaceuticals, Inc.
Protocol Version:	Version 1.1
Release Date of Protocol:	20 October 2016

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.

SPONSOR SIGNATURE PAGE

Protocol Title: A Phase 2 Multicenter, Open-Label, Uncontrolled Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of RA101495 in Subjects with Paroxysmal Nocturnal Hemoglobinuria

Protocol Date: 20 October 2016



10/20/16

Signature of Ra Pharmaceuticals, Inc. Medical Officer Date

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CENTER INVESTIGATOR SIGNATURE PAGE

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Protocol Version 1.1

Protocol 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 Investigator Date

2 SYNOPSIS

Protocol title	A Phase 2 Multicenter, Open-Label, Uncontrolled Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of RA101495 in Subjects with Paroxysmal Nocturnal Hemoglobinuria
Protocol number	RA101495-01.201
Phase of clinical development	Phase 2
Investigational medicinal product	RA101495 administered by daily subcutaneous injection
Study Population	Adults with paroxysmal nocturnal hemoglobinuria (PNH)
Investigative Sites	Approximately 10 centers are planned in one or more of the following locations: Australia, Canada, Germany, New Zealand and United Kingdom
Planned number of subjects	Up to 20 subjects will be enrolled in the study in two cohorts: • Cohort A (Eculizumab Naïve): approximately 8-12 subjects • Cohort B (Eculizumab Switch): approximately 6-8 subjects
Study objectives	• To assess the safety and tolerability of RA101495 in subjects with PNH • To assess preliminary efficacy of RA101495 in subjects with PNH • To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of RA101495 in subjects with PNH
Study design	Study RA101495-01.201 is a multicenter, open-label, uncontrolled study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of RA101495 in subjects with PNH. The study will enroll two separate cohorts based on prior eculizumab treatment history. • Cohort A (Naïve) will include subjects who have not received eculizumab for treatment of PNH • Cohort B (Switch) will include subjects who have received treatment with eculizumab for at least 6 months prior to Screening. The planned enrollment is approximately 8-12 subjects in Cohort A and approximately 6-8 subjects in Cohort B, for a total of up to 20 subjects. Cohort A will commence enrollment prior to Cohort B. Cohort B will not be opened until safety and efficacy data from at least 2 subjects completing the Week 2 Visit in Cohort A have been reviewed by the Sponsor and Study Investigators, and evidence of hemolysis suppression is demonstrated. The study includes an 8-week screening period and a 12-week Treatment Period. During the Treatment Period, subjects will return to the clinic weekly for the first 4 weeks followed by visits every 2 weeks to evaluate safety, tolerability, efficacy, PK and PD. Additional assessments will include immunogenicity, Quality of Life (QOL) questionnaires, biomarker samples, and optional pharmacogenomics. Safety assessments include physical exam, vital signs, electrocardiogram (ECG), clinical laboratory tests, and adverse

	events (AEs). The risk of *Neisseria meningitidis* infection will be closely monitored during the study. During the screening period, prior to study entry, all subjects must have a documented negative result for *Neisseria meningitidis* colonization via a throat swab. All Cohort A (Naïve) subjects who have not been previously vaccinated against *Neisseria meningitidis* prior to study entry must be vaccinated and must receive ciprofloxacin for 14 days starting with the first dose of RA101495 at the Day 1 Visit. A booster vaccination should also be administered as clinically indicated according to the local standard of care. All Cohort B (Switch) subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster if appropriate) prior to study entry. For Cohort A (Naïve) subjects, the Day 1 Visit may be scheduled at any time after Screening and confirmation of eligibility. For Cohort B (Switch) subjects, the Day 1 Visit should be scheduled to coincide with the next scheduled dose of eculizumab (i.e. 14 ± 2 days after from the last eculizumab dose). Eculizumab should NOT be administered at the Day 1 Visit or at anytime thereafter during the study During the Treatment Period, 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. At the conclusion of the Treatment Period subjects who complete the study and are demonstrating benefit will have the option to enroll in an extension study to continue receiving treatment with RA101495. Alternatively, they may opt to receive standard-of-care treatment off study, after consultation with their treating physician. If the subject withdraws early from the RA101495-01.201 study for any reason, he/she will not be eligible for the extension study. All subjects will receive a loading dose of 0.3 mg/kg to be administered subcutaneously (SC) at the Day 1 visit. Following in-clinic education and training, all subjects will self-administer daily SC doses of 0.1 mg/kg of RA101495 for 12 weeks. Except for Day 1, on study clinic days, the dose should be administered after the PK and PD collection has been completed. From the Week 2 Visit onwards, if a subject has not achieved an adequate response (defined as a lactate dehydrogenase [LDH] <1.5 x ULN), and following evaluation of safety and tolerability data by the investigator and the medical monitor, the dose should be escalated to 0.3 mg/kg daily. The dose may also be escalated to 0.3 mg/kg daily at any time in the event of an overt breakthrough hemolysis episode (e.g. hemoglobinuria).
Duration of study participation	The total duration of study participation for all subjects will include a Screening Period of up to 8 weeks and a 12-week Treatment Period for a total of up to 20 weeks.
Study population	To be eligible for this study, subjects must meet **ALL** of the following

	inclusion criteria: 1. Male or female ≥18 years 2. Completed informed consent procedures, including signing and dating the informed consent form (ICF) 3. Diagnosis of PNH by flow cytometry 4. Cohort A (Naïve) subjects must not have received treatment with eculizumab prior to or during the Screening Period and must have a lactate dehydrogenase (LDH) level ≥2 times the upper limit of normal (xULN) during Screening 5. Cohort B (Switch) subjects must have received treatment with eculizumab for at least 6 months prior to Screening 6. Female subjects of child-bearing potential must have a negative pregnancy test at Screening and within 24-hours prior to the first dose of RA101495 7. 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. o Intrauterine contraception/device starting at the Screening visit, throughout the study, and for 4 weeks after the last dose of study drug. o 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 o 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/1.73m^2 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. Recent surgery requiring general anesthesia within the 2 weeks prior to Screening, or expected to have surgery requiring general anesthesia during the 12-week Treatment Period 9. 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) 10. 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 11. Treatment 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) 12. Unable or unwilling to comply with the requirements of the study
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). **Primary Efficacy:** • The primary evaluation period is from Week 6 to Week 12. The primary efficacy endpoint is the change-from-baseline in serum LDH levels during this period, defined as the mean LDH values of Weeks 6, 8, 10, and 12 minus the baseline value of LDH. **Secondary Efficacy:** • Changes from baseline in LDH, total bilirubin, total hemoglobin, free hemoglobin, haptoglobin, reticulocytes, and hemoglobinuria, at each of the scheduled post-baseline 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}) • Plasma concentrations of eculizumab (Cohort B only) **Pharmacodynamic:** • Changes from baseline CH_{50} • Changes from baseline in sheep RBC (sRBC) lysis for classical complement pathway • Changes from baseline in Wieslab enzyme-linked immunosorbent assay

	(ELISA) for alternative complement pathway • Changes from baseline in C5 levels **Exploratory:** • Changes from baseline in quality of life (QOL) questionnaires (e.g. EORTC QLQ-C30, FACIT-Fatigue, and EQ-5D) • Treatment satisfaction questionnaire • Mechanistic biomarkers (e.g. complement function, complement proteins, biomarkers of inflammation, biomarkers for thrombosis, biomarkers of liver function) • Pharmacogenomic analyses (optional)
Statistical considerations	**Study Populations**: The following study populations are defined: • *Safety Population*: All subjects who receive at least 1 dose of RA101495 • *Efficacy Evaluable Population*: All subjects in the Safety Population who complete the 12-week Treatment Period • *Per Protocol Population*: All subjects in the Safety Population who complete the 12-week Treatment Period and 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 cohort separately. Where appropriate, data may be summarized for the overall study. A disposition of all consented subjects will be provided and will include a breakdown of subjects who consented, were treated, discontinued treatment, were lost to follow-up, or withdrew consent. Continuous 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 cohort and time point and also by pooling cohorts. 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 summarized by cohort. No formal statistical comparisons between cohorts will be performed. Tests to assess change-from-baseline will be applied to endpoints as appropriate. For Cohort A (Naïve), the primary efficacy endpoint will be tested against a null hypothesis of a median change-from-baseline of 0 by a 2-sided Wilcoxon signed-rank test. For Cohort B (Switch) an inferential test of the change-from-baseline primary efficacy endpoint will not be performed. Summary statistics for the primary endpoint will be provided including the mean, median, standard deviation, and standard error. **Pharmacokinetics:** Drug exposure in the different cohorts 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 cohort and overall using descriptive statistics. **Pharmacodynamics**: Pharmacodynamics will be summarized by cohort. No formal statistical comparisons between cohorts will be performed. Tests to assess change-from-baseline will be applied to endpoints as appropriate. **Determination of Sample Size**: For Cohort A (Naïve) a sample size of 8 subjects yields approximately 95% power to reject the null hypothesis that the median LDH change-from-baseline is 0 for the primary efficacy endpoint. This assumes a mean decrease in LDH from 2200 U/L at baseline to 327 U/L during the primary evaluation period (Weeks 6-12) with corresponding standard deviations of 1034 U/L and 443 U/L, respectively, and a within-subject correlation estimate of 0. This yields a change-from-baseline mean of 1873 U/L and standard deviation of 1125 U/L. The power is based on a 2-sided Wilcoxon signed-rank test, at the 0.05 significance level. For Cohort B (Switch) a sample size of 6 subjects will yield a standard error of approximately 114 U/L for an LDH mean change-from-baseline estimate. This assumes a standard deviation of 443 U/L for the baseline and post-baseline endpoints and a within-subject correlation estimate of 0.8, which yields change-from-baseline standard deviation of 280 U/L. **Interim Analysis**: During this open-label study, the Sponsor will review safety and efficacy data as it becomes available during the Treatment Period. Following completion of the 12-week Treatment Period, data will be cleaned and locked at the individual subject level, and will be available for final analysis by the Sponsor on a rolling basis. Completion and final data lock of Cohort A may occur before, and independent, of Cohort B, or vice versa.

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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
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	Electronic diary
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
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPI	glycosylphosphatidylinositol
GPI-AP	glycosylphosphatidylinositol-anchored proteins
HR	heart rate
ICF	informed consent form

Abbreviation	Definitions
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection site reaction
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function tests
MAC	membrane attack complex
MAVE	major adverse vascular event
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple-dose
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
NCI	National Cancer Institute
NHP	non human primates
NOEL	no observed adverse effect level
PD	pharmacodynamics
PI	Principal Investigator
PIG-A	phosphatidylinositolglycan complementation class A
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QOL	quality of life
RBC	red blood cell

Abbreviation	Definitions
RNA	ribonucleic acid
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-12	12-item short form health survey
SOP	standard operating procedure
sRBC	sheep Red Blood Cell
SS	steady state
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 Time and Events Table

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

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

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

a. Study visits have a Visit window of ±2 days after the actual planned Visit day for the first 4 weeks, and ±4 days from week 6 to week 12.

b. For Cohort A (Naïve) subjects, the Day 1 Visit may be scheduled at any time after Screening and confirmation of eligibility. For Cohort B (Switch) subjects, the Day 1 Visit should be scheduled to coincide with the next scheduled dose of eculizumab (i.e. 14 ±2 after from the last eculizumab dose). Eculizumab should NOT be administered at the Day 1 Visit or at any time thereafter during the study.

c. Height will be measured only at the Screening Visit.

d. All subjects must have a negative throat swab for *Neisseria meningitidis* infection for eligibility. All subjects in Cohort A must be vaccinated against *Neisseria meningitidis* and should have a booster as indicated by standard of care. All subjects in Cohort A must receive ciprofloxacin to be taken orally on Days 1 to 14. All Cohort B subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster if appropriate) prior to study entry.

e. Including LDH for primary efficacy endpoint

f. Coagulation tests should be performed, according to standard practice, on all subjects taking anticoagulant therapy.

g. For all female subjects of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit and a negative urine pregnancy test must be documented at the Day 1 Visit prior to dosing. All other pregnancy tests will be urine.

h. The injection site should be assessed at each clinic visit through Day 84 (End of Study).

i. Blood samples for PK and PD and additional biomarker sampling at the following time points in relationship to the first dose of RA101495: pre-dose (within 1 hour before first dose administration) and at 1, 3, and 6 hours post-dose on Day 1. For subjects who have a dose increase to 0.3 mg/kg, samples for PK and PD should be collected at pre-dose Day 1 of the new dose, see footnote j. On clinic visit days, PK and PD samples should be collected prior to administration of RA101495.

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

k. Blood sample for ADA on Day 1 must be obtained prior to dosing of RA101495.

l. Blood sample for optional pharmacogenomic testing must be obtained on Day 1.

m. On clinic visit days, the study drug RA101495 should be administered after blood samples for PK and PD are collected.

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

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).

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.

6.1 OVERVIEW OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria is a rare, acquired, clonal hematopoietic stem cell disorder caused by a deficiency in glycosylphosphatidylinositol (GPI) linked proteins on cell surfaces and characterized by intravascular hemolysis and venous thrombosis. Due to its rarity, accurate estimates of its prevalence are limited. The most detailed epidemiological study was performed in the United Kingdom, which estimated the incidence at 1.3 cases per 1,000,000 population/year with a prevalence of 15.9 cases per 1,000,000 population [Hill, 2006]. A subsequent study in Finland estimated prevalence to be approximately 10 per 1,000,000 population [Kairemo, 2010]. PNH is usually diagnosed in patients in their early 30s with a slight female predominance. The condition affects individuals of all races and ethnicities [Socie, 1996; Nishimura, 2004; Rosse, 2004; Schrezenmeier, 2014].

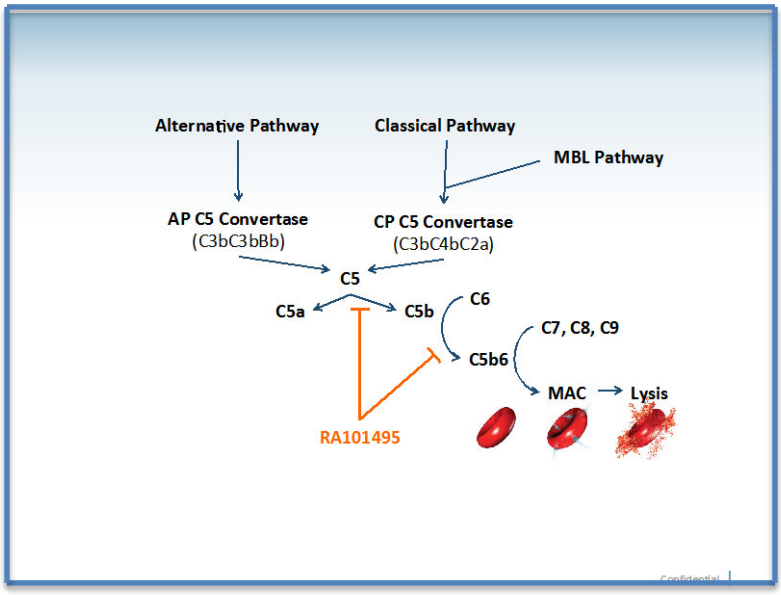
Patients with PNH may initially present with hemoglobinuria, abdominal pain, smooth muscle dystonias, and fatigue. The disease is characterized by intravascular hemolysis and thrombotic complications involving unusual sites such as hepatic, mesenteric, cerebral, and the dermal veins [Parker, 2005]. PNH is a consequence of a nonmalignant clonal expansion of one or more hematopoietic stem cells that have acquired a somatic mutation of the X-linked phosphatidylinositolglycan complementation class A (PIG-A) gene, which is required for the biosynthesis of a lipid moiety, GPI, responsible for attaching a variety of proteins to the cell surface. As a consequence of mutant PIG-A, all GPI-anchored proteins (GPI-AP) are deficient on affected stem cells and their progeny. Two GPI-APs, CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis), normally expressed on hematopoietic cells, are responsible for protecting blood cells from the lytic activity of the terminal complement membrane attack complex (MAC). Patients with PNH are unable to synthesize functional versions of these proteins on hematopoietic stem cells, resulting in the accumulation of alternative pathway complement proteins on the surface of red blood cells (RBC), C5 cleavage, formation of the MAC, and subsequent lysis. This intravascular hemolysis is the characteristic clinical manifestation of the disease [Parker, 2007].

6.2 MECHANISM OF ACTION OF RA101495

RA101495 inhibits complement activation at the level of C5 (See Figure 1), a clinically validated target for the treatment of PNH. RA101495 binds with high affinity to complement C5 and prevents its cleavage by C5 convertase into the cleavage products C5a and C5b. Inhibition of C5 cleavage therefore prevents the assembly and cytolytic

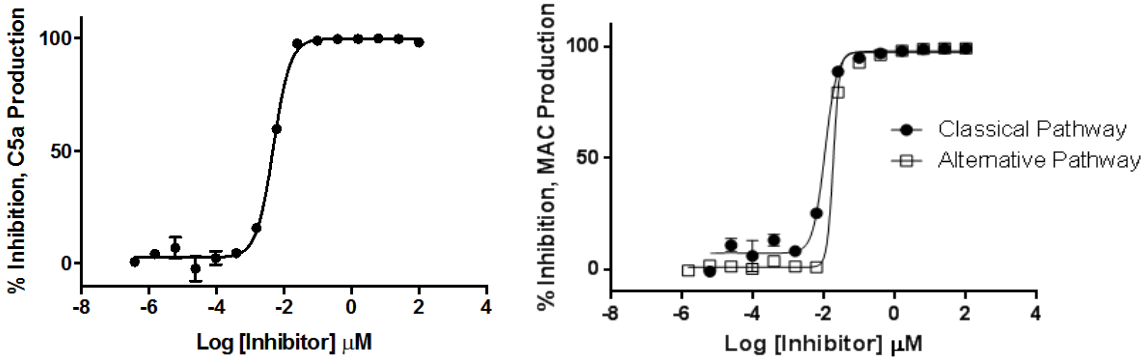
activity of MAC on GPI-AP-deficient erythrocytes. RA101495 can also bind to C5b to block binding of C6, which further prevents the assembly of the C5b-9 MAC. Using surface plasmon resonance and analysis of a high-resolution co-crystal structure, RA101495 has been shown to bind to a specific site on C5 distinct from the eculizumab-binding site and exhibits a strong and rapid association with C5 coupled with a slow dissociation rate.

Figure 1 Mechanism of Action of RA101495 in Complement System



The dose-dependent inhibition by RA101495 of C5a formation upon activation of the Classical Pathway is depicted in the left panel of Figure 2. The right panel of Figure 2 shows the inhibition by RA101495 of C5b formation (as measured by C5b-9 or MAC formation) upon activation of the Classical and Alternative complement pathways. In these experiments, the relative levels of both C5a and MAC were measured by enzyme-linked immunosorbent assays (ELISAs) using antibodies specific for C5a and C5b-9.

Figure 2 Inhibition of C5a (left) and C5b-9 (MAC; right) Formation by RA101495



Note: Inhibitor is RA101495

Abbreviations: C5=complement component 5; MAC=membrane attack complex.

6.3 CLINICAL TRIAL EXPERIENCE WITH RA101495

Clinical trial experience with RA101495 to date includes a single Phase 1 study (RA10145-1001) in healthy volunteers. The study RA101495-1001 was a randomized, double-blind, placebo-controlled, single-ascending-dose (SAD) and multiple-dose (MD) study designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of RA101495.

The first part of the study (SAD) evaluated a single dose of RA101495 versus placebo at 4 dose levels (0.05, 0.1, 0.2 and 0.4 mg/kg) in separate cohorts. The SAD enrolled 22 subjects; 14 received RA101495 (0.05 mg/kg in two subjects; 0.1, 0.2 and 0.4 mg/kg in four subjects each) and eight subjects received placebo, two per each dose level.

The second part of the study (MD) evaluated 7 daily doses of RA101495 versus placebo at a single dose level (0.2 mg/kg). The MD enrolled six subjects; four received RA101495 and two received placebo.

RA101495 when administered as a single dose and with 7-day repeat dosing displayed consistent and predictable PK that tightly correlated with the PD effect (inhibition of hemolysis and suppression of complement activity).

The plasma concentrations of RA101495 following single-dose SC administration (SAD) showed dose-dependent increases across all dose levels examined (0.05, 0.1, 0.2, and 0.4 mg/kg) (Figure 3). The mean C_{max} ranged from 1010 to 5873 ng/mL across doses. The mean AUC_{0-24} ranged from 21,440 to 112,300 ng* h/mL across doses. The mean half-life ($t_{1/2}$) was consistent across dose levels and ranged from 155.6 to 185.4 hours.

In the multiple dose (MD) portion of the study, the day 1 mean C_{max} and AUC_{tau} were 2533 ng/mL and 50,010 ng*h/mL respectively, which were consistent with results from the 0.2 mg/kg single-dose cohort over the same post-dose period. Following daily sc administration for 7 days, the C_{max} and AUC_{tau} increased by approximately 2.9 and 3.0-fold respectively (Figure 4). Day 7 time to maximum plasma concentration (median T_{max} = 3.0 hours), total body clearance (mean CL/F = 1.3 mL/h/kg)), elimination rate constant ($K_{el} = 0.0043h^{-1}$) and half-life ($t_{1/2}$ = 161.9 h) were all similar to single dose administration indicating that the absorption and elimination of RA101495 does not change significantly with repeat daily sc administration. The apparent volume of RA101495 distribution (V_z/F) showed some increase with administration of multiple doses of RA101495 (0.2 mg/kg SAD mean V_z/F = 71.4 mL/kg; 0.2 mg/kg MD mean day 7 V_z/F = 311.6 mL/kg). However, the day 7 V_z/F for RA101495 was still less than total body water suggesting that RA101495 does not distribute into the extravascular space upon repeat SC administration.

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Figure 3 **Mean (SD) Plasma RA101495 Concentrations Over Time by Dose Group Following Single-Dose SC Administration in Healthy Volunteers (Study RA101495-1001)**

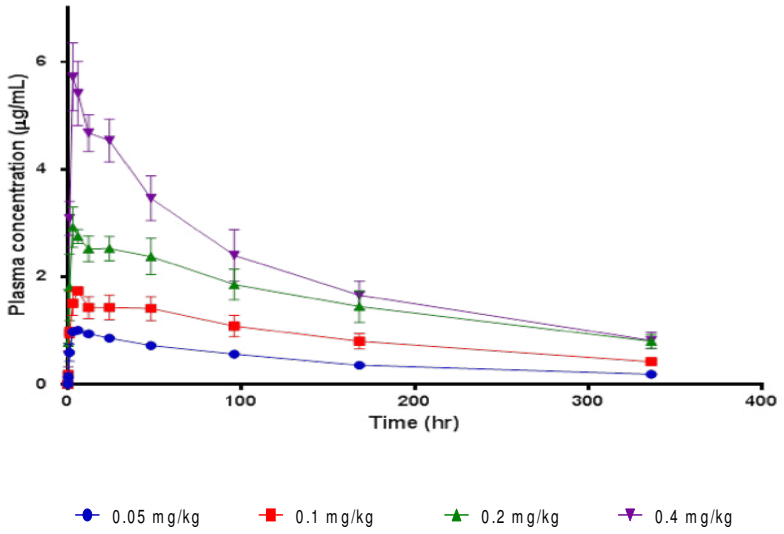
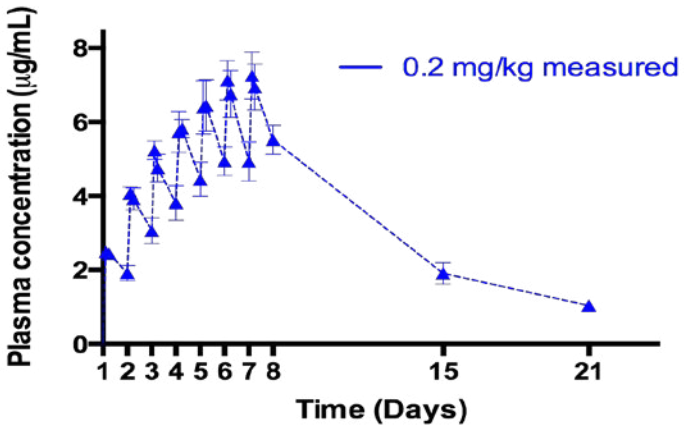


Figure 4 **Mean (SD) Plasma RA101495 Concentrations Over Time by Dose Group Following Multiple-Dose SC Administration of 0.2 mg/kg for 7 Days in Healthy Volunteers (Study RA101495-1001)**



RA101495 demonstrated strong pharmacodynamic effects on terminal complement. RA101495 administered as a single dose achieved rapid dose-dependent inhibition of *ex-vivo* hemolysis as measured by a sheep red blood cell (sRBC) lysis assay (Figure 5). The maximum PD effect was apparent approximately 3 hours after a single dose. The maximal percent inhibition of hemolysis compared to baseline reached ≥90% for the 0.1, 0.2, and 0.4 mg/kg single-dose cohorts and 60% for the lowest dose (0.05 mg/kg) cohort. Mean hemolysis levels remained below baseline for up to 2 days in the 0.05 mg/kg cohort, up to 4 days in the 0.1 mg/kg cohort, and for up to 7 days in the 0.2 and 0.4 mg/kg cohorts.

RA10495 administered for 7-days achieved inhibition of hemolysis that was rapid and sustained at ≥95% across the dosing period in all subjects, (Figure 6). The mean percent inhibition of hemolysis compared to baseline reached >95% beginning at the first time point, 3 hours after dosing on Day 1, and continued throughout 7 days of dosing; all individual subjects showed ≥90% inhibition of hemolysis at all time points. At 24 hours after the last dose, inhibition of hemolysis was observed to be ≥97% in all subjects. Eight days after the last dose of RA10495, the mean inhibition of hemolysis remained ≥56%. Two subjects had inhibition of hemolysis >70% through 8 days after the last day of dosing. Hemolysis returned to pre-dose levels in all subjects within two weeks following the last dose.

Figure 5 **Mean (SD) Red Blood Cell Lysis Over Time by Dose Group Following Single-Dose SC Administration in Healthy Volunteers (Study RA101495-1001)**

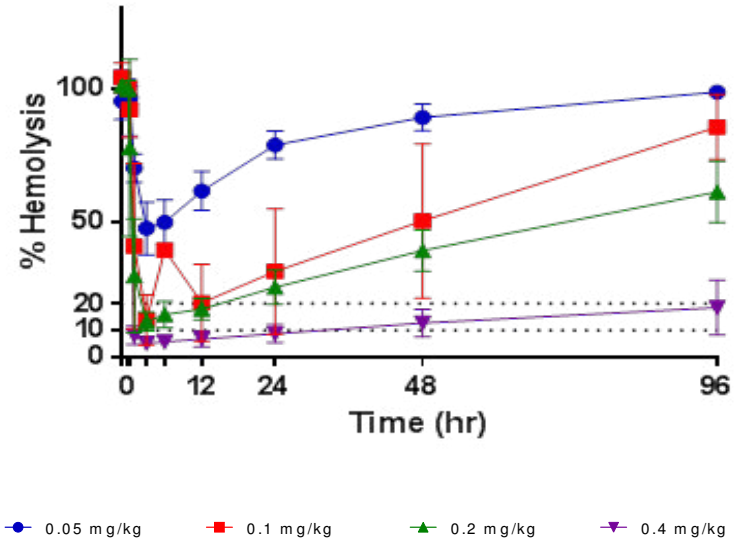
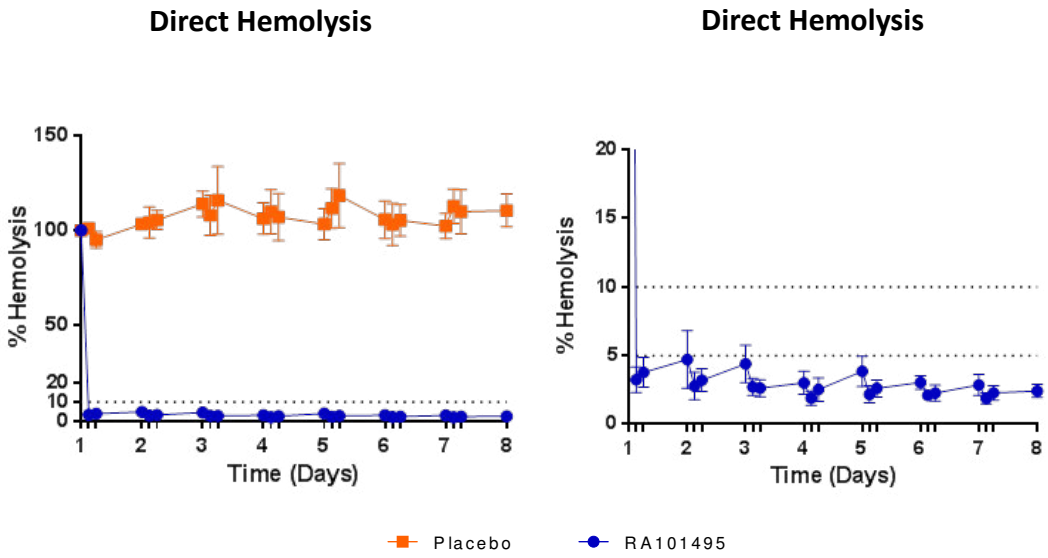


Figure 6 **Mean (SD) Red Blood Cell Lysis Over Time by Dose Group in the Multiple-Dose Cohort Once Daily for 7-Days in Healthy Volunteers in (Study RA101495-1001)**



Note: Figure on the right is a duplicate of the figure on the left with an expanded y-axis.

Safety: Across all the SAD cohorts, 7 of the 14 of the subjects treated with RA101495, had adverse events (AEs), which occurred more frequently in the highest dose cohort (0.4 mg/kg). All subjects in the MD (0.2 mg/kg) had at least 1 AE. All AEs resolved. In all cohorts of the SAD and MD, there were no AEs that led to study drug discontinuation. No serious AEs (SAE) or deaths occurred during the study.

In the SAD the most common AEs regardless of causality in subjects who received single-doses of RA101495 were injection site erythema (3 subjects, cohort 4), upper respiratory tract infection (URI) (1 subject, cohort 1; 2 subjects, cohort 4), and headache (2 subjects, cohort 4). Other AEs that occurred in 1 subject each were bronchitis (cohort 1); catheter site phlebitis (cohort 3); fatigue (cohort 4); and back pain (cohort 4). AEs in subjects who received placebo were diarrhea, myalgia, headache, and rash, all in 1 subject each.

All AEs of injection site erythema events were reported in subjects who received the highest single-dose of RA101495 (0.4 mg/kg). All were reported as Grade 1 in severity with no pain, tenderness, swelling, or induration. No treatment was required and all events resolved spontaneously and rapidly following dosing. All these AEs were considered related to study drug by the investigator.

In the MD cohort, the most common AE in subjects who received multiple-doses of RA101495 regardless of causality was injection site erythema (3 subjects) and headache (2 subjects). Other AEs were dyspepsia, URI, back pain, dizziness, contact dermatitis, miliaria, and rash; all in 1 subject each. One subject had injection site pain due to a booster vaccination. AEs in subjects who received placebo were URI (2 subjects) and injection site reaction, injection site pain, back pain, and headache; all in 1 subject each.

Three subjects who received RA101495 had Grade 1 injection site erythema. One of these 3 subjects reported 4 separate AEs of injection site erythema (on Day 1, Day 2, Day 5, and Day 6). The other 2 subjects had 1 event each (1 on Day 1 and 1 on Day 5). All AEs of injection site erythema were reported at a severity of Grade 1 with no pain, tenderness, swelling, or induration. No treatment was required and all events resolved spontaneously prior to the next dose. All were considered related to study drug by the investigator. One subject on placebo had a Grade 1 injection site reaction (stinging and numbness) and Grade 1 injection site pain (stinging). Both events were assessed as mild, of Grade 1 severity and resolved spontaneously.

In all cohorts, laboratory and electrocardiogram (ECG) changes from baseline were considered not clinically significant, and none were reported as adverse events.

6.4 DEVELOPMENT RATIONALE

RA101495 is being developed to treat patients with PNH. Based on PK and PD data generated to date, RA101495 has the potential to provide several advantages over the only currently approved therapy for PNH, eculizumab.

Daily administration of RA101495 is expected to result in near complete and sustained suppression of C5 for improved control of hemolysis. Continuous inhibition of hemolysis is important in the prevention of breakthrough hemolysis. Eculizumab at the approved dose of 900 mg biweekly has been associated with breakthrough hemolysis in some patients requiring dose increases beyond the approved dose described in the current product label [Hill 2005]. Breakthrough hemolysis with eculizumab treatment typically occurs towards the end the biweekly infusion cycle and has been shown to be associated with sub-therapeutic eculizumab levels at those time points [Nakayama, 2016; Brodsky, 2014]. Daily dosing with RA101495 is designed to ensure that C5 is continuously inhibited and is therefore expected to eliminate end-of-cycle breakthrough episodes.

As a self-administered SC product, RA101495 has the potential to improve treatment satisfaction and improve dosing convenience for patients with PNH, and may enable a reduction in the cost of providing care. The current standard-of-care requires health professionals to administer eculizumab via a biweekly intravenous (IV) infusion. Published studies of patient preferences for SC versus IV therapy show a clear preference for SC administration, and SC administration has been shown to increase compliance, patient satisfaction and QOL, as well as reduce treatment costs, drug requirements, and the complications of intravenous access [Stoner, 2015; Besarab, 2002]. Phase 2 studies of RA101495 will include quantitative instruments for evaluating QOL.

6.5 DOSE JUSTIFICATION FOR STUDY

6.5.1 RATIONALE FOR STARTING DOSE (0.1 MG/KG)

The 0.1 mg/kg/day dose was selected to satisfy the following criteria:

- Predicted steady state drug levels for the nominal as well as the maximum dose (based on weight bracketing) are below the no observed adverse effect level (NOAEL) values for C_{max} and $AUC_{0\text{-}24}$ observed in toxicology studies (Table 2)

- Predicted steady state C_{max} and AUC_{0-24} are not expected to exceed the values observed during the Phase 1 RA101495-1001 MD study in healthy volunteers (Table 2)

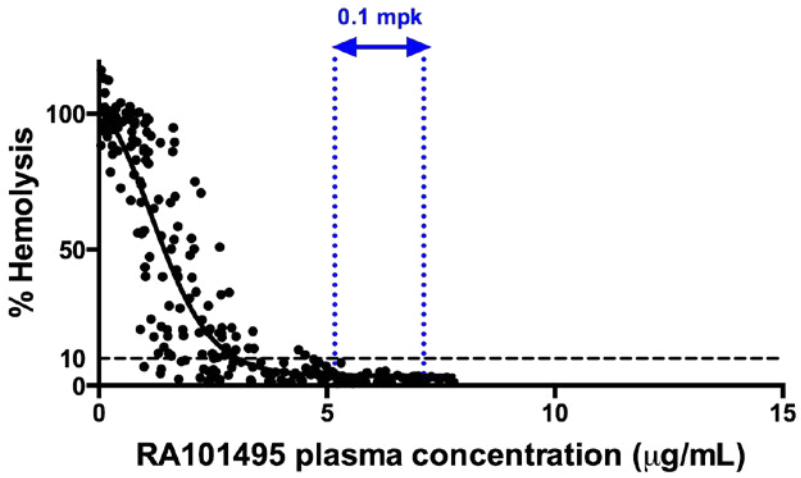
- Inhibition of hemolysis is expected to be maintained at ≥90% at all times (following a loading dose of 0.3 mg/kg; see Section 6.5.2). This prediction is supported by overlaying the expected RA101495 plasma concentrations at steady state, with the PK/PD relationship obtained from Phase 1 studies in healthy volunteers (Figure 7). Adequate and sustained control of hemolysis is a key component of both efficacy and safety in PNH. In this disease, even a modest transient decrease in complement blockade can lead to immediate "breakthrough" intravascular hemolysis and recrudescence of severe PNH symptoms. This consideration is particularly important with respect to the potential for missed doses.

Table 2 Experimental and Predicted PK Values for RA101495 in Humans

Pharmacokinetic Parameter	**Statistic**	**RA101495 (2 mg/kg) NOAEL NHP**	**RA101495 (0.2 mg/kg) QDx7; Day 7 Human (SD)**	**RA101495 (0.1 mg/kg) Steady State Prediction in Human**	
				Nominal (Minimal) 0.1 mg/kg QD	Maximum dose* 0.14 mg/kg QD
C_{max} (µg/mL)	Mean	33.8	7.29 (0.66)	6.57	7.12
AUC_{0-24}(h·µg/mL)	Mean	573	151.3 (12)	141.5	152.8

*Indicates the potential maximum dose received by patients due to weight bracketed dosing

Figure 7 Predicted PK and PD Effects Resulting From Weight-Bracketed Dosing of RA101495 (0.1mg/kg daily)

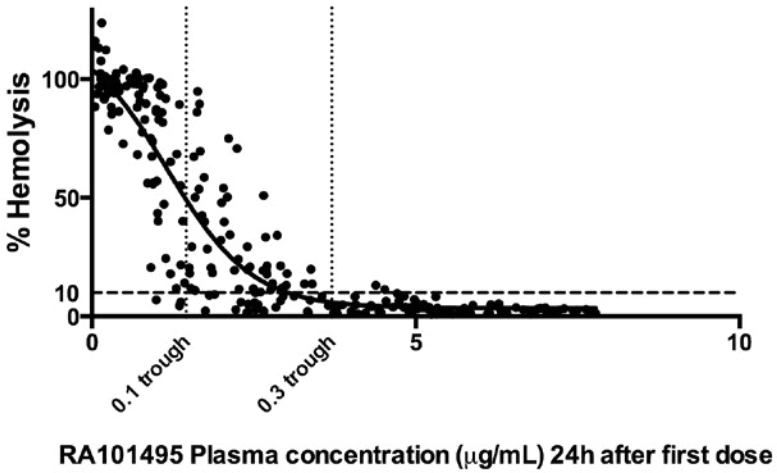


Note: Predicted plasma concentration range (blue lines) resulting from weight-bracketed dosing of RA101495 at 0.1mg/kg daily and expected PD effect (% hemolysis).

6.5.2 RATIONALE FOR USE OF LOADING DOSE

In order to achieve and maintain hemolysis control efficiently, the Sponsor proposes the use of a single loading dose of 0.3 mg/kg to adequately suppress hemolysis after the first dose. Single doses of up to 0.4mg/kg SC were studied and were well-tolerated in the phase 1 SAD study in human volunteers. The rationale for the use of a 0.3mg/kg loading dose is supported by overlaying the expected RA101495 plasma trough concentrations after the first dose, with the PK/PD relationship obtained from Phase 1 studies in healthy volunteers (Figure 8). Based on the PK/PD model described in the supplementary report, the loading dose does not impact expected exposures at steady state (Figure 9).

Figure 8 RA101495 Loading Dose (0.3mg/kg) and Predicted Control of Hemolysis After the First Dose

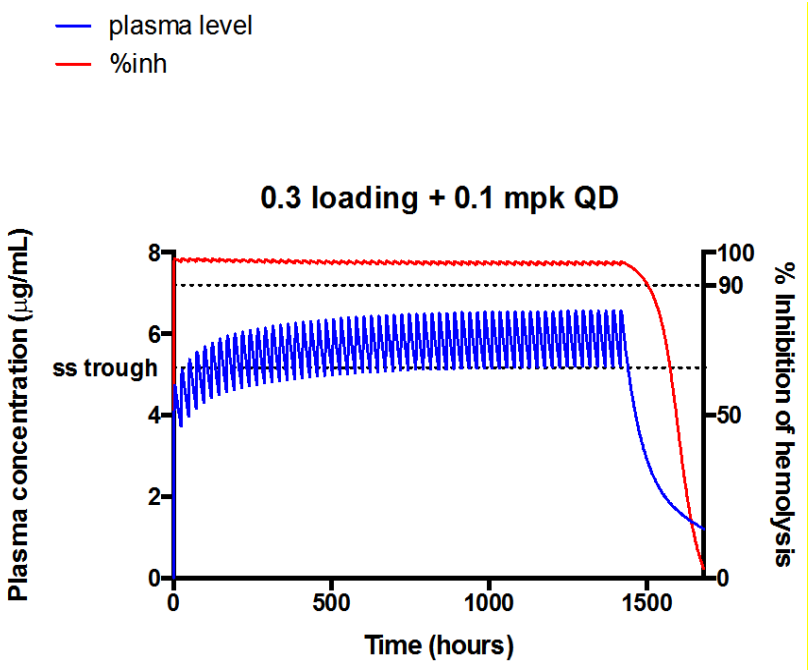


Note: A loading dose of 0.3mg/kg is predicted to achieve the target PD effect (>90% hemolysis inhibition) at trough levels, to facilitate immediate control of hemolysis after the first dose.

6.5.3 RATIONALE FOR DOSE ESCALATION TO 0.3MG/KG DAILY AFTER WK 2

As illustrated in Figure 9, RA101495 drug levels corresponding to 90% of the expected steady state values are estimated to be achieved by day 10. The corresponding inhibition of hemolysis is estimated to be greater than 95% at both peak and trough drug levels. From the Week 2 Visit onwards, if a subject has not achieved an adequate response (defined as an LDH <1.5 x ULN), and following evaluation of safety and tolerability data by the investigator and the medical monitor, the dose should be escalated to 0.3 mg/kg daily. The dose may also be escalated to 0.3 mg/kg daily at any time in the event of an overt breakthrough hemolysis episode (e.g. hemoglobinuria).

Figure 9 Simulation of PK (blue) and PD (red) of RA101495 with a Loading Dose of 0.3mg/kg on Day 1 Followed by 0.1mg/kg Daily Thereafter.



Note: Loading Dose of 0.3 mg/kg SC does not impact steady state PK of RA101495

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 OBJECTIVES

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

7.2 ENDPOINTS

7.2.1 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 evaluation will also include a determination of anti-drug antibodies (ADA). Laboratory assessments will include PNH clone size.

7.2.2 EFFICACY

Primary efficacy:

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

Secondary efficacy:

- Changes from baseline in LDH, total bilirubin, total hemoglobin, free hemoglobin, haptoglobin, reticulocytes, and hemoglobinuria, at each of the scheduled post-baseline assessment time-points.

7.2.3 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})
- Plasma concentrations of eculizumab (Cohort B only)

7.2.4 PHARMACODYNAMIC

- Changes from baseline CH_{50}
- Changes from baseline in sRBC lysis for the classical complement pathway
- Changes from baseline in Wieslab ELISA for alternative complement pathway
- Changes from baseline in C5 levels

7.2.5 EXPLORATORY

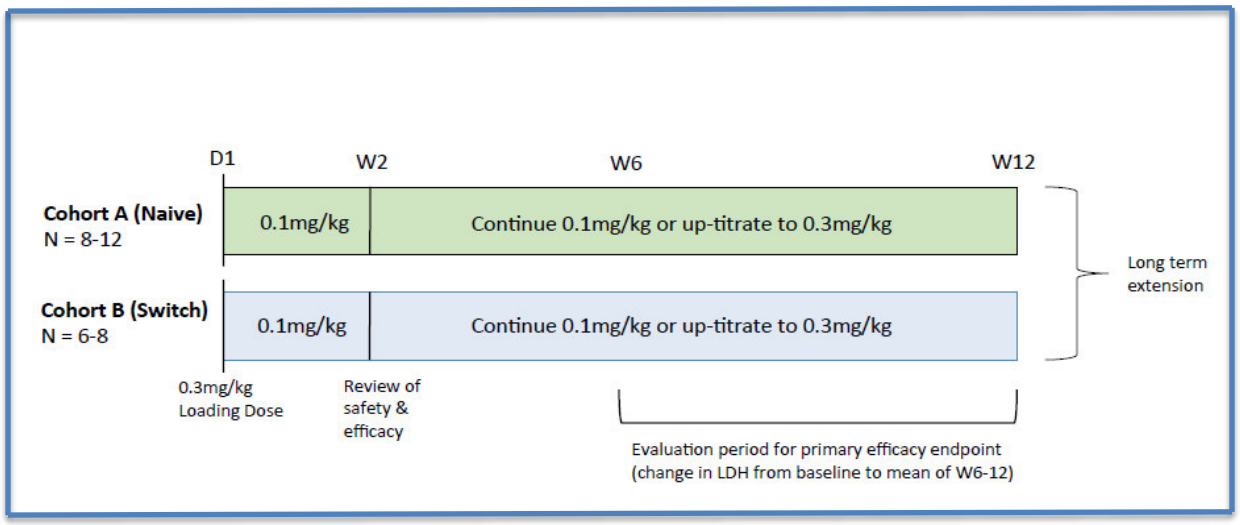
- Changes from baseline in QOL questionnaires (e.g. EORTC QLQ-C30, FACIT-Fatigue, and EQ-5D)
- Treatment satisfaction questionnaire
- Mechanistic biomarkers (e.g. complement function, complement proteins, biomarkers of inflammation, biomarkers for thrombosis, biomarkers of liver function)
- Pharmacogenomic analyses (optional) (See Section 11.6.4)

8 STUDY DESIGN

8.1 OVERVIEW OF STUDY DESIGN

Study RA101495-01.201 is a multicenter, open-label, uncontrolled study to evaluate safety, efficacy, pharmacokinetics and pharmacodynamics of RA101495 in subjects with PNH. A schematic of the RA101495-01.201 study design is provided Figure 10.

Figure 10 RA101495-01.201 Study Design



The study will enroll two separate cohorts where subjects are assigned based on prior eculizumab treatment history.

- Cohort A (Naïve) will enroll subjects who have not received eculizumab for treatment of PNH prior to or during the Screening Period
- Cohort B (Switch) will enroll subject who have received eculizumab treatment for at least 6 months prior to Screening

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

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

The study includes an 8-week screening period and a 12-week Treatment Period. During the Treatment Period, subjects will return to the clinic weekly during the first 4 weeks followed by visits every 2 weeks to evaluate of safety, tolerability, efficacy, PK and PD.

Additional assessments will include immunogenicity, QOL questionnaires, biomarker samples and optional pharmacogenomics.

Safety assessments will include reporting of AEs and SAEs (including MAVE criteria), clinical laboratory tests, ECGs, vital signs, and physical examinations. Safety evaluations will also include a determination of anti-drug antibodies (ADA).

All subjects must have a negative result for *Neisseria meningitidis* colonization via a throat swab prior to study entry. All Cohort A (Naïve) subjects who have not been previously vaccinated must be vaccinated against *Neisseria meningitidis* and receive ciprofloxacin for 14 days of starting with the first dose of RA101495 at the Day 1 Visit. A booster vaccination should be administered as clinically indicated consistent with local standard of care. All Cohort B (Switch) subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster if appropriate) prior to study entry.

For Cohort A (Naïve) subjects, the Day 1 Visit may be scheduled at any time after Screening and confirmation of eligibility.

For Cohort B (Switch) subjects, the Day 1 Visit should be scheduled to coincide with the next scheduled dose of eculizumab (i.e. 14 ±2 days after from the last eculizumab dose). Eculizumab should NOT be administered at the Day 1 Visit or at anytime thereafter during the study.

During the Treatment Period 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.

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

All subjects will receive a loading dose of 0.3 mg/kg to be administered SC at the Day 1 visit. Following in-clinic education and training, all subjects will self-inject daily SC doses of 0.1mg/kg of study drug every 24 hours at approximately the same time each day for the subsequent 12 weeks. On study clinic days, the dose should be administered after the PK and PD collection has been completed.

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

8.1.1 RATIONALE FOR STUDY DESIGN

The current study in PNH subjects is designed as an open-label study and does not include a placebo group. Given the severity of the disease, and the availability of an approved treatment, it is considered inappropriate to administer a placebo to subjects with PNH.

The starting dose selected for the study is 0.1 mg/kg (following a loading dose of 0.3 mg/kg). This dose level of RA101495 is anticipated to achieve and maintain ≥90% sustained inhibition of hemolysis based on the Phase 1 healthy volunteer study and pharmacokinetics and pharmacokinetic modeling (see Section 6.5 Dose Justification). A second, higher dose level (0.3 mg/kg) will be available for those subjects who do not adequately respond to the starting dose (i.e. with LDH ≥1.5xULN) or who experience overt breakthrough hemolysis (e.g. hemoglobinuria).

Dose presentation and administration of RA101495 will be determined by a target weight-based approach, accomplished using fixed-dose-by-weight brackets supporting a weight range of 43 to 109 kg. This method of dosing will insure that no subject receives a sub-therapeutic dose (Section 10.1.3). Avoidance of sub-therapeutic doses is critically important in PNH to minimize the risk of breakthrough hemolysis.

The primary endpoint for the study is the change in LDH from baseline to the primary evaluation period (mean of values at the Week 6, Week 8, Week 10, and Week 12 visits). LDH, an enzyme that catalyzes the conversion of lactate to pyruvic acid and vice versa, is highly abundant in erythrocytes and is a well-established marker of intravascular hemolysis in PNH. In a Phase 3 clinical study, eculizumab reduced hemolysis as assessed by the reduction of mean (± SD) serum LDH levels from 2200 ± 1034 U/L at baseline to 700 ± 388 U/L after one week, and maintained this effect through week 26 (327 ± 433 U/L) [Hillmen 2006].

Since the approval of eculizumab, LDH has emerged as a clinically accepted marker for monitoring the response to therapy, and for identifying subjects experiencing breakthrough hemolysis [Soliris® 2016, Soliris® 2015]. In subjects approaching the end of the 14-day eculizumab dosing interval, there is a close correlation between the return of complement activity, clinical manifestations of breakthrough intravascular hemolysis, and elevations in LDH [Hill 2005].

It is expected that, based on daily subcutaneous administration, RA101495 will provide more consistent pharmacodynamic coverage of complement inhibition, and may have the potential to reduce the risk of breakthrough hemolysis seen with eculizumab.

8.2 STUDY PERIODS

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

8.2.1 SCREENING PERIOD

The Screening Visit will occur at least 2 days, but no more than 56 days, before the first dose of RA101495 on Day 1.

8.2.2 TREATMENT

All subjects will receive treatment with RA101495 from Day 1 to Day 84 during the Treatment Period. Subjects completing the 12-week Visit and are demonstrating benefit, in consultation with the treating physician, will have the option to enroll in a long-term open-label extension study to continue receiving treatment with RA101495. If a subject chooses not to participate in the extension study, the subject will receive standard-of-care treatment off–study as recommended by the treating physician.

8.3 SUBJECT REGISTRATION PROCEDURES

8.3.1 SCREENING AND ENROLLMENT

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

At the Screening Visit, subjects will be assigned a unique subject number. The following assessments will be performed during screening.

- Demographic and baseline characteristics
- Medical history, including a detailed history of PNH diagnosis information, symptoms, complications, and treatment over the 6 months prior to Screening
- Review and documentation of prior (within the previous 30 days) and concomitant medications
- Physical examination, including height and 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 (including LDH), hematology, and coagulation
- Urine sample for urinalysis
- Serum pregnancy for females of childbearing potential only
- Throat swab for *Neisseria meningitidis*

The inclusion and exclusion criteria will be reviewed to determine subject eligibility for study participation at the Screening Visit and prior to drug dosing on Day 1.

8.3.2 TREATMENT GROUP ASSIGNMENT

Eligible subjects will be assigned to one of two cohorts based on their prior treatment history for PNH. The two cohorts are:

- Cohort A (Naïve) subjects who have not have received treatment with eculizumab prior to or during the Screening Period
- Cohort B (Switch) subjects who have received treatment with eculizumab for at least 6 months prior to Screening

8.3.3 BLINDING

This is an open-label study.

8.4 DISCONTINUATION CRITERIA

8.4.1 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCT

If a subject prematurely discontinues the investigational medicinal product (IMP), RA101495, at any time prior to completion of the Day 84 Visit during the Treatment Period, the subject should return to clinic for an End-of-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, PNH clone size
- Urine sample for urinalysis
- Serum pregnancy for females of childbearing potential only
- Return of electronic diary (e-diary) to site
- Completion of QOL questionnaires
- Completion of treatment satisfaction questionnaire
- Record AEs
- Blood samples for:
    - PK analysis
    - PD analysis
    - ADA determination
    - Additional biomarkers

- Return of all used and unused study drug syringes and injection device to site

8.4.2 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 an End-of-Study Visit, as described in Section 8.4.1. All unused study drug syringes must be returned to the clinic as described in Section 10.2.

8.5 EARLY STUDY TERMINATION

The Sponsor may terminate this study early, either in its entirety, in one or other cohort, 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.

8.6 END OF STUDY

The end-of-study is defined as the date of the last subject's last visit. Subjects who complete the Treatment Period, and are deriving benefit from RA101495, will have the option to enter a long-term extension study.

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. Male or female ≥18 years
2. Completed informed consent procedures, including signing and dating the informed consent form (ICF).
3. Diagnosis of PNH by flow cytometry
4. Cohort A (Naïve) subjects must not have received treatment with eculizumab prior to or during the Screening Period and must have a lactate dehydrogenase (LDH) level ≥2 times the upper limit of normal (xULN) during Screening
5. Cohort B (Switch) subjects must have received treatment with eculizumab for at least 6 months prior to Screening
6. Female subjects of child bearing potential must have a negative pregnancy test at Screening and within 24-hours prior to the first dose of RA101495
7. 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:
    - 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. Calculated glomerular filtration rate of <30 mL/min/1.73m^2 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 (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. Recent surgery requiring general anesthesia within the 2 weeks prior to Screening, or expected to have surgery requiring general anesthesia during the 12-week Treatment Period

9. 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)

10. 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

11. Treatment 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)

12. 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

Enrolled subjects who prematurely discontinue study treatment for any reason prior to the Day 84 Visit may be replaced, at the discretion of the Sponsor, in order to obtain an adequate number of evaluable subjects (see Section 13.2).

10 INVESTIGATIONAL MEDICINAL PRODUCTS AND TREATMENTS

10.1 STUDY TREATMENT ADMINISTRATION

10.1.1 IDENTITY OF INVESTIGATIONAL MEDICINAL PRODUCT AND TREATMENT

The investigational medicinal product (IMP) RA101495 will be supplied as a sterile, preservative-free, aqueous solution pre-filled into 1 mL glass syringes with a 29 gauge ½ inch staked needle placed within a self-administration device.

Subjects will be instructed to self-administer SC doses daily. The dose (dose volume) for each injection will depend on the dose requirement and subject's bodyweight (see Section 10.1.3 and Section 10.1.4).

10.1.2 TREATMENT GROUPS

All eligible subjects in Cohort A and Cohort B will receive a single loading dose of 0.3mg/kg RA101495 SC followed by study drug at 0.1 mg/kg SC once daily.

10.1.2.1 DOSE ESCALATION

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

For subjects who have a dose increase to 0.3 mg/kg, samples for PK and PD should be collected at pre-dose of the first day of the new dose, then at scheduled visits per the Time and Events Table (Table 1).

10.1.3 DOSING SCHEDULE

For Cohort A (Naïve) subjects, the Day 1 Visit may be scheduled at any time after Screening and confirmation of eligibility.

For Cohort B (Switch) subjects, the Day 1 Visit should be scheduled to coincide with the next scheduled dose of eculizumab (i.e. 14 ± 2 days after from the last eculizumab dose). Eculizumab should NOT be administered on the Day1 Visit or at anytime thereafter during the study.

Subjects in Cohort A (Naïve) and Cohort B (Switch) will receive a loading dose of 0.3 mg/kg dose of RA101495 on Day 1, which will be administered during the study Visit by the site staff. During the remainder of the Treatment Period, subjects will self-administer the daily dose (0.1 mg/kg or 0.3 mg/kg) every 24 hours at approximately the same time each day. 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 PRESENTATION

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 bodyweight 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 0.10 to 0.14 mg/kg); in the 0.3 mg/kg dose, subjects will receive a minimum dose of 0.3 mg/kg (range 0.3 mg/kg to 0.41 mg/kg). Table 3 summarizes dose presentations for RA101495 0.1 mg/kg and 0.3 mg/kg doses. Subjects who present with a higher body weight (>109 kg) will be accommodated on a case-by-case basis, in consultation with the medical monitor.

Table 3 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	0.150	6	≥43 to <61	0.10 to 0.14
0.1	2	0.220	8.8	≥61 to <88	0.10 to 0.14
0.1	3	0.310	12.4	≥88 to <109	0.11 to 0.14
0.3	4	0.416	16.6	≥43 to <56	0.30 to 0.39
0.3	5	0.574	23	≥56 to <77	0.30 to 0.41
0.3	6	0.810	32.4	≥77 to <109	0.30 to 0.42

10.1.4.1 MISSED DOSES

If a subject misses one dose (i.e. 1 day) of RA101495, the subject should document the missed dose in his/her subject e-diary and take the next planned dose as scheduled. The subject should 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 every 2 weeks, beginning on Day 1 of the Treatment Period.

Subjects will be trained and provided 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

RA101495 will be provided as a sterile, preservative-free, aqueous solution for injection containing 40 mg/mL of active ingredient, RA101495, in a formulation of 50 mM sodium

phosphate and 76 mM sodium chloride at a pH of 7.0 pre-filled into a 1 mL glass syringe with a ½ inch, 29 gauge staked needle. Six dosage strengths will be supplied as shown in Table 3.

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 room temperature (20°C to 25°C [68°F to 77°F]) for up to 30 days protected from sources of heat, light and damage. Storage of IMP outside of room temperature should be avoided.

Subjects will be instructed to self-inject SC doses daily every 24 hours at approximately the same time each day. The subject will be provided with an injection device for use during the study. Subject may inject in the abdomen (preferred site), thigh or upper arm.

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 the subject should return the used container containing all used syringes to the site. The unused study drug (unused syringes) should be retained by the subject and be used first in the immediate two weeks.

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

10.2.4 DRUG ACCOUNTABILITY

An e-diary where the subject documents study drug administration will be used to reconcile accountability during the study. The number of study drug syringes dispensed used, and returned will be documented.

10.3 COMPLIANCE

Subjects will be required to record the date, time, and location of injections each day in an e-diary. The e-diary entries will be evaluated to determine compliance with study drug administration. If a subject does not confirm daily dosing using the e-diary, the investigator will receive an automated notification to contact the subject.

11 STUDY ASSESSMENTS

Please refer to Table 1 for the timing of study assessments.

11.1 SUBJECT AND BASELINE DISEASE CHARACTERISTICS

11.1.1 DEMOGRAPHIC DATA

The following demographic data will be collected: date of birth, gender, ethnicity, and race.

11.1.2 DISEASE AND PRIOR TREATMENT HISTORY

A detailed history of PNH for a minimum of 6 months prior to Screening will be obtained, including (but not limited to) the following data: date of diagnosis, PNH clone size at diagnosis (if available), history of thrombotic events, history of transfusions, and history of PNH-specific prior therapy (e.g. immunosuppressives, anticoagulants, associated bone-marrow disorders).

For Cohort B (Switch) subjects, the date eculizumab treatment was initiated and dose received will be documented. A dosing history for each subject (including dates and all dosage changes for a minimum of 6 months prior to Screening) will also be recorded.

11.1.3 PRIOR AND CONCOMITANT MEDICATIONS

In addition to PNH-specific prior therapy (Section 11.1.2), all prescriptions and over-the-counter medications taken during the 30 days prior to the screening visit 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 to assess subject eligibility.

Detailed medical history regarding the occurrence of specific events or conditions (e.g. underlying bone marrow pathology, major vascular events, pulmonary hypertension, impaired renal or hepatic function, infections, malignancies) for a minimum of 6 months prior to Screening will also be collected.

11.2.2 PHYSICAL EXAMINATION

Physical examinations will include the following assessments:

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

Any abnormalities found will be recorded in the eCRF.

11.2.3 VITAL SIGNS

Vital signs (heart rate, body temperature, and blood pressure) will be measured in the sitting position after resting for at least 5 minutes. 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 described in the eCRF and the investigator will assess clinical significance. 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 (see Table 1).

11.2.5 *NEISSERIA MENINGITIDIS* TESTING

All subjects must have a negative result for *Neisseria meningitidis* colonization via a throat swab prior to study entry. The throat swabs for *Neisseria meningitidis* will be obtained at Screening and sent to a certified laboratory for analysis to confirm absence of colonization.

11.2.5.1 *NEISSERIA MENINGITIDIS* PROPHYLACTIC TREATMENT

All subjects who have not been previously vaccinated will receive prophylactic treatment with *Neisseria meningitidis* vaccine and ciprofloxacin. These subjects must be vaccinated against *Neisseria meningitidis* prior to starting their first dose of RA101495. A booster vaccination should be administered as clinically indicated, consistent with local standard of care. All previously unvaccinated subjects will be treated with oral ciprofloxacin from Day 1 to Day 14. All Cohort B (Switch) subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster if appropriate) prior to study entry.

11.2.6 ADVERSE EVENT RECORDING

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

11.2.7 LABORATORY SAFETY ASSESSMENTS

11.2.7.1 BLOOD CHEMISTRY AND HEMATOLOGY

Clinical chemistry and hematology analytes to be collected are identified in Table 4 and should be performed as specified in the Time and Events 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 4 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	
bilirubin (total, direct, and indirect)	mean corpuscular volume (MCV)
blood urea nitrogen (BUN)	platelet count
calcium	RBC count
chloride	reticulocyte count
creatinine	white blood cell (WBC) count and differential (%)
gamma-glutamyl transferase (GGT)	**Coagulation**
glucose	international normalized ratio (INR)/prothrombin time (PT)
lactate dehydrogenase (LDH)	
lipase	fibrinogen
potassium	partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT)
sodium	
total protein	**Other**
uric acid	C-reactive protein (CRP)
	creatine phosphokinase (CPK)

11.2.7.2 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. Hemoglobinuria will be assessed using a urine colorimetric scoring system.

11.2.7.3 PREGNANCY TEST

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

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

11.2.8 PNH CLONE

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

11.2.9 IMMUNOGENICITY

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

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

11.3 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.

11.4 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Blood samples for the measurement of plasma concentrations of RA101495 and metabolites will be collected on all subjects. Subjects in Cohort B will also have a blood sample for measurement of eculizumab plasma concentrations.

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

- CH_{50}
- sRBC lysis for classical complement pathway
- Wieslab ELISA for alternative complement pathway
- C5 levels

Blood samples for PK and PD will be collected at the following time points in relationship to the first dose of RA101495: pre-dose (within 1 hour before first dose administration) and at 1, 3, and 6 hours post-dose on Day 1. For subjects who have a dose increase to 0.3 mg/kg, samples for PK and PD should be collected at pre-dose Day 1 of the new dose.

For subjects in Cohort B only, blood samples for PK of eculizumab should be collected at screening, Day 1, Day 15, Day 29, and Day 43. The sample should be collected prior to administration of RA101495.

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.

11.5 ELECTRONIC DIARY CARD

Subjects will be required to record the following information each day in a subject e-diary during study participation:

- Confirmation of administration of daily (every 24 hours) dose of RA101495 that includes date, time, and location of injection of RA101495

Subject e-diaries will be collected/dispensed at the time points shown in the Time and Events Table (Table 1). Subjects will be given detailed instructions on how to complete entries in subject diaries throughout study participation.

11.6 EXPLORATORY ASSESSMENTS

11.6.1 QUALITY OF LIFE ASSESSMENTS

Quality of life assessments will be performed according to the Time and Events Table (Table 1). The following QOL questionnaires will be used during this study:

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

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 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].

11.6.1.3 EQ-5D

The EQ-5D is a standardized instrument for measuring generic health status. The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has 3 levels: no problems, some problems, extreme problems [EuroQol, 1990]. Subjects answer questions based on symptoms and health status on the day the questionnaire is completed.

11.6.2 TREATMENT SATISFACTION QUESTIONNAIRE

A treatment satisfaction questionnaire using a 5-point Likert response scale will be administered to all subjects to assess overall satisfaction with SC administration of the study medication at the end of the 12-week Treatment Period.

A more targeted questionnaire using a 5-point Likert response scale will be administered to the Cohort B (Switch) subjects only to assess their preference for daily SC self-injection at home compared with biweekly infusions given by a health-care professional in the clinic.

11.6.3 BIOMARKERS

Blood samples will be collected at designated time points, concomitant with PK and PD sampling (see Table 1). 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 safety of RA101495 in PNH subjects. 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 may be reported separately from the main clinical study report.

11.6.4 PHARMACOGENOMIC ASSESSMENTS

Participation in the pharmacogenomic assessment is optional and subjects must consent to the pharmacogenomic analysis using a separate consent form.

For subjects who opt to participate in pharmacogenomics studies, a blood sample will be obtained on Day 1. All genomic analyses will be performed at an accredited laboratory. Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

Genomic studies will be performed (e.g. deoxyribonucleic acid [DNA] sequencing, DNA copy number analysis, ribonucleic acid [RNA] expression profiling) to explore whether specific genomic features correlate with response or resistance to study drug.

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 genomic investigations may be reported separately from the main clinical study report.

12 SAFETY REPORTING

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

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

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

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 (weekly for the first 4 weeks followed by every 2 weeks). 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 as AEs per Section 12.1 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 weekly for the first 4 weeks followed by every 2 weeks during the study. 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 as AEs per Section 12.1 and 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 weekly for the first 4 weeks followed by every 2 weeks during the study.

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 as AEs per Section 12.1 and Section 12.3

12.1.3.4 INJECTION SITE REACTIONS

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

- Pain, tenderness, erythema, and induration severity (Table 5)
- 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 5 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. Subjects are monitored every 2 weeks for adverse events.

To reduce the risk of infection, during the screening period, all subjects must have a negative result for *Neisseria meningitidis* colonization via throat swab prior to study entry. All Cohort A (Naïve) subjects who have not been previously vaccinated must be vaccinated against *Neisseria meningitidis* and receive ciprofloxacin for 14 days of starting with the first dose of RA101495 at the Day 1 Visit. A booster vaccination should be administered as clinically indicated, consistent with local standard of care. All cohort B (Switch) subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster if appropriate) prior to study entry.

During the Treatment Period, 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 12.1 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 discontinued, 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 ADVERSE EVENTS

Pre-existing conditions that are detected prior to administration of the first dose of study drug will be recorded as part of medical history. For all subjects, 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. 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 subjects, and observations by the study

personnel. Adverse events will be coded using 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 (i.e. 1 record per event). Reporting of AEs is event-based (i.e. 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 SERIOUS ADVERSE EVENTS

Any SAE experienced by the subject from signing the ICF through 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 underwent 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 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/patient 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

For Cohort A (Naïve) a sample size of 8 subjects yields approximately 95% power to reject the null hypothesis that the median LDH change-from-baseline is 0 for the primary efficacy endpoint. This assumes a mean decrease in LDH from 2200 U/L at baseline to 327 U/L during the primary evaluation period (Weeks 6 -12) with corresponding standard deviations of 1034 U/L and 443 U/L, and a within-subject correlation estimate of 0. This yields a change-from-baseline mean of 1873 U/L and standard deviation of 1125 U/L. The power is based on a 2-sided Wilcoxon signed-rank test at the 0.05 significance level.

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

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

13.2 ANALYSIS POPULATIONS

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

13.2.1 SAFETY POPULATION

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

13.2.2 EFFICACY EVALUABLE POPULATION

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

13.2.3 PER PROTOCOL POPULATION

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

13.2.4 PHARMACOKINETIC POPULATION

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

13.2.5 PHARMACODYNAMIC POPULATION

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

13.3 STATISTICAL PLAN

13.3.1 GENERAL CONSIDERATIONS

Data will be summarized within each cohort separately. Where appropriate, data may be summarized for the overall study. 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 SAFETY ANALYSIS

Safety analyses will be performed on the individual cohorts.

13.3.4.1 ADVERSE EVENTS

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

Incidence rates for treatment emergent adverse events (TEAE) 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 treatment start that was not present at the time of treatment start; or
- An AE that increases in severity after treatment start, if the event was present at the time of treatment start.

AEs occurring before the first dose of study drug will be summarized separately.

13.3.4.2 ADVERSE EVENTS OF SPECIAL INTEREST

13.3.4.2.1 THROMBOTIC ADVERSE EVENTS

Thrombotic AEs will be summarized separately by system organ class, preferred term, and cohort. The events in Table 6 (MAVE criteria [Hillmen 2007]) will be evaluated in the assessment of thrombotic AEs:

Table 6 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	

Abbreviation: MAVE=major adverse vascular event.

13.3.4.2.2 HEPATIC ADVERSE EVENTS

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

13.3.4.2.3 PANCREATIC ENZYME ELEVATIONS

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

13.3.4.2.4 INJECTION SITE REACTIONS

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

13.3.4.2.5 INFECTION

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

13.3.4.3 CLINICAL LABORATORY EVALUATION

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

13.3.4.4 ELECTROCARDIOGRAMS

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.

13.3.4.5 VITAL SIGNS

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

13.3.4.6 PHYSICAL EXAMINATION

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

13.3.5 EFFICACY ANALYSIS

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

For Cohort A (Naïve), the primary efficacy endpoint will be tested against a null hypothesis of a median change-from-baseline of 0 by a 2-sided Wilcoxon signed-rank test.

For Cohort B (Switch) an inferential test of the change-from-baseline primary efficacy endpoint will not be performed. Summary statistics for the primary endpoint will be provided including the mean, median, standard deviation, and standard error.

13.3.6 CLINICAL PHARMACOLOGY ANALYSIS

13.3.6.1 PHARMACOKINETIC ANALYSIS

Drug exposure in the different cohorts 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 cohort using descriptive statistics.

13.3.6.2 PHARMACODYNAMIC ANALYSIS

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

13.3.7 INTERIM ANALYSIS

During this open-label study, the Sponsor will review safety and efficacy data as it becomes available during the Treatment Period. Following completion of the 12-week Visit , data will be cleaned and locked at the individual subject level, and will be

available for final analysis by the Sponsor on a rolling basis. Completion and final data lock of Cohort A may occur before, and independent of, Cohort B, or vice versa.

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 IEC/IRB.

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.

A separate consent form will be provided for sample collection for pharmacogenomic testing.

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 (e.g. 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 Clinical 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 from 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 from one or both cohorts, 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.

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