PEGCETACOPLAN (APL-2)

PROTOCOL APL2-308

A PHASE 3, RANDOMIZED, MULTICENTER, OPEN-LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PEGCETACOPLAN IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

US IND No.: 123087

EudraCT No.: **2018-004220-11**

Phase: 3

Version: Amendment 3

Date: 10 August 2020

Confidentiality Statement

INVESTIGATOR AGREEMENT

Long Title:	A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)
Short Title:	PRINCE
Protocol Number, Version, and Date:	10 August 2020
Study Phase:	Phase 3
Sponsor Name and Address:	Apellis Pharmaceuticals, Inc 100 5th Ave Waltham, MA 02451 USA
Investigational Test Article:	Pegcetacoplan **(**APL- 2)
US IND Number:	123087
EudraCT Number:	2018-004220-11
Indication Studied:	PNH
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.

Principal Investigator:

Name: _____

Signature: _____

Date: _____/_____/_____ (DD/MMM/YYYY)

SPONSOR INFORMATION

Sponsor

Apellis Pharmaceuticals, Inc
100 5th Ave
Waltham, MA 02451
USA

Sponsor Representative:

PPD

PPD

Signature: ____

10-Aug-2020 | 12:40 EDT

Date: _____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 3: Summary of Changes From the Previous Version

Amendment date: 10 August 2020

Updates to the protocol implemented in this amendment are provided in the table below.

Description of change	Section(s) affected by change
Nonsubstantial editorial and technical changes that did not impact content of the document have been made for grammar, clarity, and document usability.	Entire document
Removed language regarding an altitude correction factor for hemoglobin because no subjects enrolled in the study live at altitudes ≥1000 meters above sea level.	Synopsis, Section 4, Figure 2, Section 8, Section 9.1, Section 9.3, Section 10.2.3.3, Section 10.7, Section 11.1.1, formerly Appendix 5
Added a section regarding the collection of COVID-19 test results.	Section 12.8
Updated the definition of an adverse event to be consistent with the new Apellis standard language.	Section 13.1
Updated the information regarding the recording of adverse events to be consistent with the new Apellis standard language.	Section 13.2
Removed Section 13.3 (Treatment and Follow-up of Adverse Events) because this information is now included in other updated sections.	formerly Section 13.3
Updated the information regarding the reporting of adverse events to be consistent with the new Apellis standard language and updated the section number from Section 13.4 to Section 13.3 given the removal of the original Section 13.3.	Section 13.3
Updated the information regarding serious adverse events to be consistent with the new Apellis standard language and updated the section number from Section 13.5 to Section 13.4.	Section 13.4
Removed Section 13.6 (Unexpected Adverse Events or Unexpected Suspected Adverse Reactions) because this information is now included in other updated sections.	formerly Section 13.6
Updated the information regarding pregnancy to be consistent with the new Apellis standard language and updated the section number from Section 13.7 to Section 13.5	Section 13.5
Added a new section, Section 13.6, regarding drug abuse, misuse, overdose, and medication error.	Section 13.6
Removed the reference related to the altitude correction factor.	Section 16

Updated Appendix 4 (Amendment History) with the Amendment 2 summary of changes.	Appendix 4
Removed Appendix 5 because it contained the altitude correction factor information that has been removed from the protocol.	formerly Appendix 5
The previously-labeled Appendix 6 (COVID-19 Changes) is now labeled Appendix 5 due to the removal of the previous Appendix 5.	Appendix 5

1. TABLE OF CONTENTS

CCI

[redacted]

CCI

[redacted]

LIST OF TABLES

LIST OF FIGURES

2. SYNOPSIS

Protocol Number:

APL2-308

Protocol Title:

A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Version Number:

Amendment 3

Investigational Product, Dose, and Route of Administration:

- Investigational Product: pegcetacoplan (also known as APL-2)
- Doses:
  - 1080 mg twice weekly, or
  - 1080 mg every 3 days (ie, a dose on every third day)
- Route of Administration: Subcutaneous (SC) infusion

Dose adjustment may be considered based on clinical response.

Study Phase and Type:

This is a multicenter, randomized, open-label, controlled, Phase 3 study.

Number of Planned Subjects:

54 randomized subjects:

- pegcetacoplan: 36 subjects
- standard of care (SOC), excluding complement inhibitors: 18 subjects

Subjects must not have received treatment with a complement inhibitor for at least 3 months prior to screening.

Duration of Study Participation:

The study consists of 3 periods. The maximum duration of subject participation will be approximately 38 weeks:

- Screening Period: up to 4 weeks
- Randomized Controlled Period: 26 weeks
- Safety Follow-up: 8 weeks

Following the completion of the Randomized Controlled Period, subjects may be offered entry into an open-label extension study in order to continue to receive treatment with pegcetacoplan. These subjects will not complete the Safety Follow-up procedures for this study but will enter the extension study at the conclusion of the Randomized Controlled Period.

Rationale for the Study:

Phase 1 clinical experience has demonstrated that pegcetacoplan provides sustained inhibition of hemolytic activity in PNH patients who have never received treatment with a complement inhibitor (eg, eculizumab; Study APL2-CP-PNH-204 [Paddock]). To date, no safety signals have emerged from ongoing studies in PNH patients that preclude further development. Thus, this proposed Phase 3 study is to further evaluate treatment efficacy and safety of pegcetacoplan as monotherapy in patients with PNH.

Study Objectives and Endpoints:

Primary Objective

The primary objective of this study is to evaluate the efficacy of pegcetacoplan, compared to SOC (excluding complement inhibitors), in patients with PNH, as assessed by:

- Hemoglobin stabilization defined as avoidance of a >1-g/dL decrease in Hb levels from baseline in the absence of transfusion through Week 26 (Yes/No)

AND

- Reduction in lactate dehydrogenase (LDH) level from baseline to Week 26

Secondary Objectives

Secondary objectives of this study are:

- To evaluate the efficacy of pegcetacoplan, compared to SOC (excluding complement inhibitors), as assessed by:
  - Hemoglobin response (Yes/No) in the absence of transfusions (Hb response is defined as a ≥1-g/dL increase in Hb from baseline at Week 26)
  - Change from baseline to Week 26 in absolute reticulocyte count (ARC)
  - Change from baseline to Week 26 in Hb level
  - Number of packed red blood cell (PRBC) units transfused from baseline to Week 26
  - Change from baseline to Week 26 in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score
  - Normalization of Hb levels (defined as ≥1 × the upper limit of normal [ULN]) from baseline to Week 26 in the absence of transfusions (Yes/No)
  - Normalization of LDH levels of ≤1 × ULN from Week 4 to Week 26 (Yes/No)
  - Change from baseline to Week 26 in European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) scores (version 3)
  - Change from baseline to Week 26 in Linear Analog Assessment (LASA) scale scores

  - Absolute reticulocyte count normalization (<1 × ULN) at Week 26 (Yes/No)
  - Time to failure of Hb stabilization
  - Time to transfusion
- To evaluate the safety of pegcetacoplan as assessed by:
  - Incidence and severity of treatment-emergent adverse events (TEAEs)
  - Incidence of thromboembolic events
  - Changes from baseline in laboratory parameters
  - Changes from baseline in electrocardiogram (ECG) parameters
  - Incidence of anti-pegcetacoplan antibodies

Exploratory Objectives

Exploratory objectives of the study are to evaluate:

- CCI
- [redacted]
- Pegcetacoplan pharmacokinetic/pharmacodynamic (PK/PD), as assessed by:
  - Pegcetacoplan PK concentrations from baseline to Week 26
  - Change from baseline to Week 26 in PNH clone distribution (red blood cells [RBCs] and white blood cells [WBCs])
  - Change from baseline to Week 26 in complement component 3 (C3) deposition in PNH Type II and III RBCs
  - Complement levels from baseline to Week 26 (eg, total hemolytic complement activity assay [CH50], alternate complement pathway assay [AH50], and C3)

Study Design:

This is a prospective, randomized, multicenter, open-label, controlled study. Following screening, subjects will complete biweekly (biw) visits from Week 0 to Week 26. Subjects will be randomized either to pegcetacoplan or SOC (excluding complement inhibitors). Subjects randomized to the SOC (excluding complement inhibitors) treatment arm may receive pegcetacoplan escape therapy if their Hb level drops ≥2 g/dL below their baseline value.

Inclusion Criteria

At Visit 1 screening, subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Be at least 18 years old (inclusive).
2. Have LDH ≥1.5 × ULN at the screening visit.
3. Have PNH diagnosis, confirmed by high sensitivity flow cytometry (granulocyte or monocyte clone >10%).
4. Have Hb less than the lower limit of normal (LLN) at the screening visit.
5. Have ferritin greater than/equal to the LLN, or total iron binding capacity (TIBC) less than/equal to ULN at the screening visit, based on central laboratory reference ranges. If a subject is receiving iron supplements at screening, the investigator must ensure that the subject's dose has been stable for 4 weeks prior to screening, and it must be maintained throughout the study. Subjects not receiving iron at screening must not start iron supplementation during the course of the study.
6. Body mass index (BMI) ≤35 kg/m^2 at the screening visit.
7. Have a platelet count of >50,000/mm^3 at the screening visit.
8. Have an absolute neutrophil count >500/mm^3 at the screening visit.
9. Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening and must agree to use protocol-defined methods of contraception for the duration of the study and for 90 days after their last dose of study drug.
10. Males must agree to use protocol-defined methods of contraception and agree to refrain from donating sperm for the duration of the study and for 90 days after their last dose of study drug.
11. Have vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* (types A, C, W, Y, and B), and *Haemophilus influenzae* (type B) either within 2 years prior to Day 1 dosing, or agree to receive vaccination 14 days after starting treatment with pegcetacoplan (along with prophylactic antibiotic therapy for at least the 14 days between pegcetacoplan treatment initiation and vaccination and 14 days post vaccination). Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits).
12. Be willing and able to give informed consent.

Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening:

1. Treatment with any complement inhibitor (eg, eculizumab) within 3 months prior to screening.
2. Hereditary complement deficiency.
3. History of bone marrow transplantation.
4. Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to screening:

- Erythropoietin or immunosuppressants for at least 8 weeks
- Systemic corticosteroids for at least 4 weeks
- Vitamin K antagonists (eg, warfarin) with a stable international normalized ratio (INR) for at least 4 weeks
- Iron supplements, vitamin B12 or folic acid for at least 4 weeks
- Low-molecular-weight heparin for at least 4 weeks

5. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration.
6. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives, whichever is longer.
7. Planning to become pregnant or currently a breastfeeding woman.
8. History of meningococcal disease.
9. Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could put the subject at increased risk or potentially confound study data.

Randomization Criteria

At Visit 2 (Day 1), subjects must meet the following criteria in order to be randomized:

10. Subjects must have Hb ≥9 g/dL, or Hb <9 g/dL and ≥7 g/dL without signs or symptoms of sufficient severity to warrant a transfusion.
11. Negative urine pregnancy test for WOCBP.
12. No active systemic bacterial, viral, or fungal infection within the 2-week period prior to receiving treatment with pegcetacoplan.

Sample Size Justification:

A total of 48 randomized subjects (32 subjects to pegcetacoplan and 16 subjects to SOC) are required to achieve 90% power, at the 5% significance level (2-sided), using a 2-group Fisher's exact test with unequal allocation 2:1 to treatment groups (pegcetacoplan and SOC). Calculation assumes an increase of 45% in the proportion of subjects achieving Hb stabilization with pegcetacoplan compared to SOC (ie, a change from 5% [no treatment] to 50% [pegcetacoplan]). With the same number of subjects and an effect size of at least 1.2, the study will be at 96% for the LDH reduction endpoint.

To account for loss of power due to discontinuations, the study will attempt to randomize 54 subjects.

Statistical Methods:

Analysis Sets

Screened Set

The screened set will include all subjects who signed the informed consent form (ICF). This set will be used only for the purpose of describing subject disposition.

Safety Set

The safety set will include all subjects who receive at least 1 dose of study medication (pegcetacoplan), or subjects who are randomized to SOC (excluding complement inhibitors). Subjects will be analyzed according to the treatment they received.

Intent-to-Treat (ITT) Set

The ITT set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

Modified Intent-To-Treat (mITT) Set

The mITT will include all subjects in the ITT set who continue study treatment beyond Visit 4 (Week 4).

Per-Protocol (PP) Set

The per-protocol (PP) set will include all subjects in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from the PP analysis set will be made and documented prior to database lock.

Pharmacokinetic (PK) Set

The PK population will include all subjects in the ITT Set who receive pegcetacoplan and have at least 1 evaluable postdose- PK measurement.

Pharmacodynamic (PD) Set

The PD population will include all subjects in the ITT set who have at least 1 evaluable postdose- PD measurement.

Efficacy Analyses

The efficacy endpoints will primarily be evaluated with the ITT set. All statistical testing will be at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups will be accompanied by 2-sided 95% confidence intervals (CIs).

All possible efforts will be made to ensure that subjects complete all the required assessments.

Endpoints will be summarized and, where appropriate, plotted over time for each treatment group.

Baseline assessments will be performed on Day 1 prior to the start of study treatment for subjects randomized to pegcetacoplan and at Day 1 for subjects randomized to SOC.

Co-Primary Endpoints

The co-primary efficacy endpoints will be analyzed, based on the ITT set.

The co-primary efficacy endpoints are:

- Hemoglobin stabilization defined as decrease of ≤1 g/dL in Hb levels from baseline to Week 26 in the absence of transfusions (Yes/No)

  AND

- Reduction in lactate dehydrogenase (LDH) level from baseline to Week 26

For the first co-primary endpoint, the number and percentage of subjects who achieve Hb stabilization will be computed for treatment groups and compared between treatment groups using a stratified Cochran-Mantel-Haenszel (CMH) chi-square test. The treatment difference in percentages and 95% CI for the difference will be presented using the stratified Miettinen-Nurminen method.

Subjects who receive a transfusion through Week 26 or withdraw from the study before providing primary efficacy assessment will be categorized as failing to achieve Hb stabilization.

The second co-primary endpoint, change from baseline to Week 26 in LDH, will be analyzed using mixed model for repeated measures (MMRM) with: the effects of treatment; stratification randomization; visit, visit-by-treatment interaction; baseline LDH level and baseline LDH level-by-visit interaction using an unstructured covariance matrix. The difference between treatment groups will be estimated, along with its 95% CI and p-value.

All the subjects LDH levels prior to transfusion and/or switch to pegcetacoplan will be included in the model.

As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, the following sensitivity and supportive analyses will be performed to evaluate the robustness of the results from the primary analysis methods:

- The first co-primary efficacy endpoint will also be analyzed using a logistic regression with the effects of treatment group and stratification factors included. The odds ratio of being an Hb stabilization achiever the pegcetacoplan versus SOC group and associated 95% CI will be estimated from the final model.
- The second co-primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model (ITT set) with a last observation carried forward (LOCF) approach for handling missing data. The ANCOVA model will include terms for treatment, stratification factors, and baseline LDH level.
- The second co-primary endpoint will be analyzed using an ANCOVA model (ITT Set) with a best observation carried forward (BOCF) approach for handling missing data. The ANCOVA model will include terms for treatment, stratification factors, and baseline LDH level.
- Analyses will be repeated using the mITT and PP sets.

<u>Secondary Endpoints</u>

The secondary endpoints will be analyzed using the ITT set and will be repeated using the PP set.

Summary statistics by randomization strata and by treatment groups will presented at each assessment visit during the 26-week randomized treatment period.

Continuous endpoints will be analyzed using MMRM with the effects of: treatment; stratification factors; visit, visit-by-treatment interaction; the relevant baseline level; and the Baseline level-by-visit interaction using an unstructured covariance matrix. The difference between treatment groups will be estimated, along with its 95% CI and p-value. If a subject receives a transfusion during his/her treatment period, the pre-transfusion Hb values, reticulocyte values, and FACIT-Fatigue Scale score will be used in the model.

For categorical endpoints, the number and percentage of subjects will be tabulated by treatment group and compared between treatment groups using a stratified CMH chi-square test.

Kaplan-Meier plots will be presented for time-to-event endpoints for each treatment group, and survival estimates will be provided.

The number of units of PRBCs transfused will be compared between the treatment groups using a Wilcoxon rank-sum test. The difference between the medians will be estimated along with its 95% CI (stratified). Subjects who withdraw before Week 26 will have the number of units estimated from the duration that they were in the study (ie, number per week × 12). This equates to an analysis of the frequency of transfusions.

Safety Analyses

Safety analyses will be based on the safety set.

Safety measures assessed at study visits, including vital signs (temperature, systolic and diastolic blood pressures, pulse, and respiratory rate), clinical laboratory results, ECGs and anti-pegcetacoplan antibodies will be descriptively summarized by treatment group at baseline and for each postbaseline visit. Absolute values and changes from baseline will be summarized.

3. ABBREVIATIONS

Term	Definition
^{51}Cr	chromium 51
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AH50	alternate complement pathway assay
AIV	pegcetacoplan initiation visit
ANCOVA	analysis of covariance
ARC	absolute reticulocyte count
biw	twice weekly administration
BMI	body mass index
BOCF	best observation carried forward
C3	complement component 3
CD71+	transferrin receptor
CH50	total hemolytic complement activity assay
CI	confidence interval
C_{max}	maximum drug plasma concentration
CMH	Cochran-Mantel-Haenszel (chi-square test)
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EudraCT	European Union Drug Regulating Authorities Clinical Trials (database)
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GLP	good laboratory practice
Hb	hemoglobin
Hib	*Haemophilus influenzae* Type B (vaccine)

Term	Definition
HV	healthy volunteer
IB	investigator's brochure
ICH	International Council for Harmonisation
ICF	informed consent form
IEC	institutional ethics committee
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat (population)
LASA	Linear Analog Assessment Scale
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MAC	membrane attack complex
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
MMRM	mixed model repeated measures
NOAEL	no observed adverse effect level
PCV13	pneumococcal conjugate vaccine
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PI	principal investigator
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PP	per-protocol (set)
PPSV23	pneumococcal polysaccharide vaccine 23
PRBC	packed red blood cells
PT	prothrombin time
QLQ-C30	30-item Core Quality of Life Questionnaire
QoL	quality of life
QTc	corrected QT interval

Term	Definition
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	standard of care
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TIBC	total iron binding capacity
TMDD	target-mediated drug disposition
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

4. SCHEDULE OF EVENTS

Study period	Screening[A]	Randomized controlled period													Follow up[B]			AIV[C]
Study week	Up to –4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	34	--
Study day	Up to –28	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	239	--
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	--
Clinic visit window (±days)	N/A	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	7	7	--
Informed consent	X																		
Demographics	X																		
Height/weight	X																		
Medical history	X																		
Thrombosis history	X																		
Transfusion history	X																		
Inclusion/exclusion	X																		
Confirm Hb entry criteria[D]		X																	
Randomization		X																	
CCI	[redacted]	[redacted]													[redacted] CCI				
Vaccination			X[E]	E			X[E]	E											
Preventive antibiotics[F]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Physical examination[G]	X	X								X					X	X	X	X	

Study period	Screen-ing[A]	Randomized controlled period														Follow up[B]			AIV[C]
Study week	**Up to –4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**34**	**--**
Study day	**Up to –28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**239**	**--**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**--**
Clinic visit window (±days)	**N/A**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	**7**	**--**
12-lead electrocardiogram[H]	X	X		X		X		X		X		X			X	X	X	X	
APL-2 administration training[I]		X	I																X
APL-2 administration[I]		X																	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements[J]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X		X	X	X		X	X		X	X	X	X	X	X	
Blood[K]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics[L]		X		X		X		X				X			X		X		X
Anti-APL-2 Ab assay[L]		X		X				X			X				X		X		
Direct Antibody Test (Coombs)	X	X		X		X	X	X			X		X	X	X	X	X	X	
Lactate dehydrogenase	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology and chemistry[S]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute reticulocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haptoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation profile[M]		X		X		X			X			X			X	X	X	X	

Study period	Screen-ing[A]	Randomized controlled period														Follow up[B]			AIV[C]
Study week	**Up to –4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**34**	**--**
Study day	**Up to –28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**239**	**--**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**--**
Clinic visit window (±days)	**N/A**	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	**7**	**--**
Complement profile [T] (CH50, and AH50)		X		X		X		X				X			X		X		
C3 Profile [T]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Flow cytometry [T]	X	X		X		X				X					X	X	X	X	
Plasma (free) Hb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ferritin	X	X		X		X	X	X			X		X	X	X	X	X	X	
Pregnancy (β-HCG) or FSH[N]	X																		
Genotyping for Gilbert's Syndrome[O]	X																		
Urine pregnancy test[P]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FACIT-Fatigue Scale		X		X		X		X		X		X			X	X	X	X	
LASA Scale		X		X		X		X		X		X			X	X	X	X	
EORTC QLQ-C30 Questionnaire		X		X		X		X		X		X			X	X	X	X	
Adverse events[Q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense investigational product[r,		X	X	X	X	X	X	X	X	X	X	X	X	X					X

Study period	Screen-ing[A]	Randomized controlled period														Follow up[B]			AIV[C]
Study week	Up to –4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	34	--
Study day	Up to –28	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	239	--
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	--
Clinic visit window (±days)	N/A	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3	7	7	--
Return investigational product		X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Abbreviations: Ab = antibodies; AE = adverse event; AH50 = alternate complement pathway assay; AIV = APL-2 Initiation Visit; APL-2 = pegcetacoplan; β-HCG = beta-human chorionic gonadotropin; C3 = complement component 3; CH50 = total hemolytic complement activity assay; COVID-19 = coronavirus disease 2019; CRFs = case report forms; ECG = electrocardiogram; eCRF = electronic case report form; EORTC-QLQ-C30 = 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle-stimulating hormone; Hb = hemoglobin; LASA = Linear Analog Assessment Scale; N/A = not applicable; PCV13 = pneumococcal conjugate vaccine (13-valent); PI = principal investigator; PK = pharmacokinetic(s); PPSV23 = pneumococcal polysaccharide vaccine (23-valent); PRBC = packed red blood cell; QTc = corrected QT interval; QTcF = Fridericia's corrected QT interval; SC subcutaneous; SOC = standard of care; WOCBP = women of childbearing potential.

A Within 5 days prior to Visit 2 (Week 0), each subject's Hb must be evaluated by a local or central laboratory. If the subject meets the protocol-specified transfusion criteria, the subject must receive a PRBC transfusion so that the subject's Hb levels no longer meets the protocol-specified requirements for PRBC transfusion. The posttransfusion Hb value should be confirmed by a local or central laboratory. Patients must not be randomized if they meet the protocol-specified requirements for transfusion, and the Hb assessment to confirm eligibility should be scheduled so that the subject does not fall outside the screening window (up to Day –28). All Hb levels must be recorded in the eCRF.

B All subjects who complete Visit 15 (Week 26) and do not elect to participate in the open-label extension study will be asked to return to the investigator site for the Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34) follow-up visits. Subjects who discontinue treatment will be encouraged to continue to attend study visits to complete study assessments (except for treatment with pegcetacoplan) as detailed in the Schedule of Events. At minimum, subjects who discontinue dosing should complete follow-up procedures outlined in the Schedule of Events 2, 4, and 8 weeks after treatment discontinuation. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the investigator's brochure.

C Following Visit 2 (Week 0), subjects assigned to the SOC (excluding complement inhibitors) treatment arm who have a Hb level measured by the central laboratory (or local laboratory if necessary due to COVID-19) that is ≥2 g/dL below the baseline value will be switched to escape therapy with pegcetacoplan. These subjects will return to the site for a pegcetacoplan initiation visit. Following the pegcetacoplan initiation visit, subjects will maintain their regular visit schedule.

D The ≤5 day pre-Visit 2 Hb qualification assessment must be assessed to confirm subject eligibility at Visit 2 before the subject can be randomized into the study.

E In order to receive treatment with pegcetacoplan, subjects must have documented evidence of vaccination against the following within 2 years of screening: *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations), *Streptococcus pneumoniae* (with a PCV13 or PPSV23 vaccine), and *Haemophilus influenzae* type B (Hib vaccine).

Subjects randomized to pegcetacoplan: For subjects randomized to pegcetacoplan who do not have documented evidence of receiving any of the above vaccinations within 2 years prior to screening, the required missing vaccination(s) will be administered at Visit 3 (Week 2), prior to dosing with pegcetacoplan (along with boosters administered during the study at or after Visit 7 [Week 10], if required [see below]). Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). The PI will discuss with the sponsor regarding individual patient circumstances.

If the subject requires vaccination against *Neisseria meningitidis*, a booster (for both vaccinations) should be administered after at least 8 weeks (Visit 7). If the subject requires vaccination against *Streptococcus pneumoniae*, PCV13 will be administered at Visit 3, and PPSV23 will be administered after at least 8 weeks (Visit 7).

Subjects randomized to SOC (excluding complement inhibitors): Subjects who are initially randomized to SOC (excluding complement inhibitors) who become eligible for pegcetacoplan escape therapy will receive any required vaccination(s) 2 weeks after initiation of treatment with pegcetacoplan. If required, as detailed above), the *Neisseria meningitidis* booster (for both vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s).

F In order to receive treatment with pegcetacoplan, subjects will require preventive antibiotics if they need to be vaccinated, as detailed in Footnote E above. In addition, subjects who do not require vaccination are recommended to receive preventive antibiotic therapy, as detailed below.

Subjects randomized to pegcetacoplan: Subjects will be required to take ciprofloxacin 500 mg twice daily from Visit 2 (Day 1) to Visit 3 (Week 2) and continue to receive antibiotic prophylaxis until at least 14 days post vaccination. From that point forward, it is recommended that all subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

Subjects randomized to SOC (excluding complement inhibitors): Subjects who are initially randomized to SOC (excluding complement inhibitors) do not need to initiate preventive antibiotic therapy at Day 1. If a subject becomes eligible for and initiates pegcetacoplan escape therapy, the subject should take ciprofloxacin 500 mg twice daily for 2 weeks, beginning on the first day of treatment with pegcetacoplan and continue to receive antibiotic prophylaxis until at least 14 days post vaccination. After 2 weeks of ciprofloxacin, it is recommended that subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

G A full physical examination should be conducted, as indicated by the study schedule. A symptom-driven physical examination may be performed at other visits, at the PI's discretion.

H Triplicate 12-lead ECGs are to be performed within 1 hour predose at Visit 2 (Day 1). Triplicate 12-lead ECGs will be performed prior to dosing at all other visits, if pegcetacoplan administration is occurring at the study site. During the study, if the QTcF at any on-treatment ECG is ≥500 ms (mean of QTcF replicate values), the investigator should perform 3 additional ECGs over 20-60 minutes; if the mean QTcF of the 3 repeat ECGs is ≥500 ms, the site should instruct the subject to return the following day to perform repeat triplicate ECGs. An evaluation will be performed to look for other factors which may have contributed to QTc prolongation (eg, new concomitant medications, hypokalemia, etc.).

I Subjects randomized to pegcetacoplan: For subjects randomized to the pegcetacoplan treatment arm, research nurses or other appropriately qualified research personnel will administer the first pegcetacoplan SC infusion at Visit 2 (Day 1) and will train subjects on how to self-administer. Following Visit 2, appropriately qualified research personnel will supervise self-administration of pegcetacoplan for at least the following 3 doses (which will be administered prior to Visit 3). Supervision of self-administration may be conducted at the subject's home, at the study site, or at an off-site location convenient for the subject. Supervision of self-administration must continue until the subject is qualified to self-administer.

Following self-administration qualification, subjects may self-administer pegcetacoplan SC infusions without supervision. Subjects may continue to self-administer infusions at the study site on those days when a study visit occurs, but this is not required. Self-administration conducted at the study site will be

supervised to ensure that the subject continues to remain compliant with the administration guidelines. On all other days, subjects may self-administer at home, at the study site, or at an off-site location convenient to the subject.

Subjects randomized to SOC (excluding complement inhibitors): Subjects randomized to the SOC (excluding complement inhibitor) treatment arm that are assigned to pegcetacoplan escape therapy during the study will have research nurses or other appropriately qualified research personnel administer the first pegcetacoplan SC infusion and provide self-administration training at the study visit in which pegcetacoplan escape therapy is initiated. Following this visit, appropriately qualified research personnel will supervise self-administration of pegcetacoplan for at least the following 3 doses at the subject's home, the study site, or an off-site location convenient for the subject. Supervision of self-administration must continue until the subject is qualified to self-administer, and pegcetacoplan will be self-administered and supervised at the study site on days of study visits, if the subject elects to administer pegcetacoplan during the study visit.

J Vital signs will be measured before venipuncture and ECG. Monitoring of vital signs will occur at Visit 2 (Day 1) predose and 2 hours post dose (±30 minutes). In addition, monitoring of vital signs will occur predose and 2 hours post dose (±30 minutes) during the pegcetacoplan Initiation Visit, if applicable. At all other visits, if the subject elects to administer pegcetacoplan during the visit, vital signs should be measured predose.

K If pegcetacoplan will be administered at the study visit, blood samples must be taken predose. The date and time of the last dose of pegcetacoplan should be recorded on the eCRF, as well as the date and time of the blood sample draw (to be used for PK analysis).

L Samples for PK and anti-pegcetacoplan assay assessments should not be collected for subjects randomized to the SOC (excluding complement inhibitors) treatment arm unless they become eligible for and elect to receive pegcetacoplan escape therapy. If a subject from the SOC (excluding complement inhibitors) treatment arm is to begin receiving pegcetacoplan escape therapy, a predose PK sample should be collected at the pegcetacoplan initiation visit and at each subsequent visit, as detailed in the Schedule of Events.

M The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan.

N β-HCG for WOCBP; FSH for postmenopausal women.

O Sample for genotyping to be obtained via buccal swab test completed at the Screening Visit.

P Urine pregnancy test should be completed for WOCBP prior to dosing on Day 1.

Q On the days of clinic visits, an assessment of the pegcetacoplan infusion site will be made as a part of the AE assessment. If pegcetacoplan is administered at the visit, the site staff will observe the dosing and pump-use safety will be assessed and the infusion site will be checked again within 30 minutes after study drug administration. The infusion site assessments will be performed by an appropriately trained staff, as delegated by the investigator. The infusion site and surrounding area will be inspected for redness, swelling, induration, and bruising. The subject will be asked about the presence of pain and/or tenderness, and any issue related to pump use. The date, time, and outcome of the infusion-site assessment will be recorded on the source documents and CRFs. Subjects will be instructed to notify the PI or other study personnel in the event that an infusion site reaction occurs after self-administration of APL 2. All clinically relevant AEs, as determined by the investigator, from infusion site or related to pump use will be recorded as AEs.

R Subjects randomized to pegcetacoplan treatment arm or receiving pegcetacoplan escape therapy only. Dispensation will depend on the subject's dose regimen. Please consult the dispensation schedule.

S Hb, LDH, and reticulocyte count should be collected PRIOR to any transfusion. The assessment may be performed at a central or certified local laboratory.

T Samples for PD assessments (Complement profile, C3 Profile, and Flow Cytometry) should be collected for subjects randomized both to the SOC (excluding complement inhibitors) and pegcetacoplan treatment arms.

5. INTRODUCTION

This study is being conducted as part of a series of studies for the clinical development of pegcetacoplan. The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will comprise adult male and female subjects with paroxysmal nocturnal hemoglobinuria (PNH).

5.1. Paroxysmal Nocturnal Hemoglobinuria

PNH is an acquired, rare, clonal, nonmalignant hematologic disease characterized by complement-mediated red blood cell (RBC) hemolysis, with or without hemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction. The onset of PNH is often insidious. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive.

It has been known for many years that PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional CD55 and CD59 on their surface to protect them against this process. As such, these erythrocytes are particularly susceptible to the membrane attack complex (MAC) and have been shown to lyse readily in the presence of complement activation.

Any therapy that effectively inhibits MAC formation is anticipated to be a plausible candidate-treatment for PNH. Eculizumab is a monoclonal anti-C5 antibody that inhibits the formation of the MAC, and eculizumab treatment has been approved for the treatment of this serious condition. However, inhibition of MAC formation does not appear to be sufficient to fully control the disease, as many PNH patients receiving eculizumab treatment still suffer from anemia, with only roughly 13% of patients being classified as complete responders (ie, achieving transfusion independence and normal hemoglobin [Hb] levels). Most of the patients (53%) were classified as partial responders with decreased transfusion needs and reduced lactate dehydrogenase (LDH), and 33% of patients were poor responders, with unchanged transfusion needs and persistent symptoms (DeZern et al. 2013).

Recent studies have suggested that significant opsonization of PNH erythrocytes by complement component 3 (C3) fragments is observed in patients receiving eculizumab treatment. This opsonization is believed to cause the removal of erythrocytes by the spleen and the liver, resulting in extravascular hemolysis. Extravascular hemolysis can be significant in a subset of eculizumab-treated PNH patients and is considered to be the principal contributor to the lack of complete eculizumab response in most patients.

5.2. Pegcetacoplan

Pegcetacoplan (also known as APL-2) is formed by a pentadecapeptide (combining a bioactive cyclic tridecapeptide C3-inhibiting moiety and a 2–amino acid linker) covalently coupled to each end of a linear 40-kDa polyethylene glycol (PEG) chain, so that there are 2 peptide moieties per molecule of pegcetacoplan.

The peptide portion of the drug binds to complement C3 and is a broad inhibitor of the complement cascade, a biological process that is part of innate immunity and is involved in

multiple inflammatory processes. The PEGylation of the molecule imparts slower elimination from mammalian systems following administration.

Pegcetacoplan infusion (drug product) is a solution of pegcetacoplan in 5% dextrose or a solution of pegcetacoplan in acetate-buffered mannitol or a solution of pegcetacoplan in acetate-buffered sorbitol for subcutaneous (SC) administration. Pegcetacoplan is being developed for the treatment of PNH.

Further details can be found in the current version of the pegcetacoplan investigator's brochure (IB).

5.2.1. Rationale for Treatment with Pegcetacoplan

Extravascular hemolysis, one of the parameters contributing to the ongoing need for RBC transfusions despite eculizumab therapy, is believed to be mediated by C3b opsonization rather than C5-dependent MAC-mediated intravascular hemolysis (Risitano et al. 2009). While eculizumab is effective in addressing CD59 deficiency by preventing C5-dependent MAC-mediated hemolysis, PNH cells are also deficient in CD55, which normally accelerates the dissociation of C3-convertase enzymes, inhibiting the production of C3 fragments and subsequent opsonization. As a result, in the setting of eculizumab therapy, surviving PNH RBCs become opsonized with C3b, targeting them for clearance through extravascular hemolysis by macrophages bearing complement receptors in the liver and spleen.

Evidence for C3b-mediated extravascular hemolysis was observed in 3 patients exhibiting a "suboptimal hematologic response [to eculizumab] and massive C3 RBC binding" using chromium-51 (^{51}Cr)–labeled RBCs. Although these subjects were still receiving eculizumab and had normal LDH levels, they demonstrated markedly reduced RBC half-lives (10, 11, and 13 days, with a normal range of 25-35 days) and excess counts on images of the spleen and liver (Risitano et al. 2009). In contrast, C3b opsonization of RBCs is not observed in PNH patients who have not been treated with eculizumab, presumably because RBCs in these patients are rapidly lysed by MAC (Risitano et al. 2009).

In summary, while C5 inhibition has had a dramatic positive impact on the lives of many PNH patients, anti-C5 therapy has also led to the emergence of a subpopulation of PNH patients with persistent extravascular hemolysis and RBC transfusion requirements, despite continuous eculizumab therapy, that appear to result at least in part from C3b opsonization of RBCs. It is reasonable, therefore, to expect that a treatment able to inhibit both MAC formation and C3 opsonization will provide improved therapeutic benefit to PNH patients, compared to eculizumab.

5.2.2. Summary of Clinical Experience

Clinical data from studies with pegcetacoplan in subjects with PNH indicates that pegcetacoplan is effective in providing broad control of intravascular and extravascular hemolysis, as evidenced by increased and stable Hb levels, along with improvement in Functional Assessment of Chronic Illness Therapy- (FACIT-) Fatigue Scale score, normalization of LDH, normalization of absolute reticulocyte count (ARC), normalization of total bilirubin levels, along with reduction in C3 fragment opsonization and increased numbers of PNH RBCs. To date, pegcetacoplan at doses of ≥270 mg/dL has been generally safe and well tolerated when administered via SC infusion. No

expected serious adverse drug reactions (ADRs) have been identified, and no deaths have occurred that are considered related to treatment with pegcetacoplan.

Results from the Phase 3 APL2-302, a randomized, multicenter, open-label, active-comparator controlled study in adults with PNH, showed that pegcetacoplan at a dose of 1080 mg SC every 2 weeks controlled the hematologic manifestations of PNH, with superiority for control of anemia, as compared with the C5 inhibitor, eculizumab. Pegcetacoplan was superior to eculizumab with regard to change from baseline (CFB) in Hb level. At Week 16, the pegcetacoplan group (n = 41) had an adjusted mean hemoglobin CFB of 2.4 g/dL from a baseline of 8.7 g/dL, compared to the eculizumab group (n = 39) who had a CFB of –1.5 g/dL from a baseline of 8.7 g/dL, resulting in a 3.8 g/dL difference between treatment groups (P<.0001).

Additionally, pegcetacoplan met noninferiority on the key secondary endpoints of transfusion avoidance and absolute reticulocyte count (ARC). Transfusion avoidance was shown in 85% in the pegcetacoplan group, but only 15.4% in the eculizumab group. The adjusted mean CFB in absolute reticulocyte count was –136 $x10^9$/L, in the pegcetacoplan group vs 28 $x10^9$/L in the eculizumab group, resulting in a treatment difference of –164 $x10^9$/L.

Pegcetacoplan did not demonstrate noninferiority to eculizumab in the change from baseline in LDH. However, the adjusted mean CFB were comparable at Week 16; –15 U/L in the pegcetacoplan group vs –10 U/L in the eculizumab group. Noninferiority for the FACIT-Fatigue score was not assessed due to the prespecified hierarchical testing; however, the adjusted mean CFB was 9.2 points in the pegcetacoplan group vs -2.7 points in the eculizumab group with a difference of 11.9 points between treatment groups. The magnitude of this treatment difference in FACIT-Fatigue score (a 3-point increase is generally accepted as clinically significant), as well as the consistency of results favoring pegcetacoplan across all primary and secondary endpoints, suggests that these improvements in fatigue are meaningful, even though the study was conducted in an open-label fashion.

The safety of pegcetacoplan was comparable to eculizumab in this randomized controlled Phase 3 study, with a similar incidence of adverse events in each study group. The most common adverse events reported during the randomized controlled treatment period were injection site reactions (ISR), hemolysis, abdominal pain, and diarrhea. While some TEAEs occurred more frequently in the pegcetacoplan group (eg, ISRs and diarrhea), others occurred more frequently in the eculizumab group (eg, hemolysis and headache). TEAEs such as ISRs and diarrhea that occurred more frequently in the pegcetacoplan group did not limit overall tolerability, as none were serious, severe, or led to study drug discontinuation. The incidence of serious adverse events (SAEs) were comparable between the 2 treatment groups. There were 4 serious infections during the study, but none required study drug discontinuation, and none were cases of meningitis. Although there were 3 subjects who discontinued pegcetacoplan due to hemolysis (7.3% in the pegcetacoplan group vs. 0 in the eculizumab group), adverse events of hemolysis occurred less frequently in the pegcetacoplan group than in the eculizumab group (9.8% vs 28.2%, respectively). Therefore, discontinuation of pegcetacoplan due to hemolysis does not reflect a safety concern, but rather a return to the currently approved PNH therapy, eculizumab. Overall, pegcetacoplan was generally well tolerated with an acceptable safety profile that can be managed effectively with monitoring.

6. RATIONALE

Phase 1 clinical experience has demonstrated that pegcetacoplan provides sustained inhibition of hemolytic activity in PNH patients who have never received treatment with a complement inhibitor (eg, eculizumab; Study APL2-CP-PNH-204 [Paddock]). To date, no safety signals have emerged from ongoing studies of pegcetacoplan in PNH patients that would preclude further development. Thus, this proposed Phase 3 study is to further evaluate treatment efficacy and safety of pegcetacoplan as monotherapy in patients with PNH.

6.1. Purpose of the Study

This is a 2-arm, controlled study comparing pegcetacoplan administration against standard of care (SOC) for patients with PNH.

The SOC arm will exclude any concurrent or recent (within 3 months) use of complement inhibitors.

6.2. Dose Selection

6.2.1. Target Level of Pegcetacoplan Serum Concentration

The toxicological data accumulated from the animal studies were used to guide dose selection during the Phase 1 single ascending dose and multiple ascending dose studies in healthy volunteers (HVs) (Study CCI , Study CCI , and Study CCI). In particular, the highest doses were selected, based on exposure predicted by a PK model, and compared with the exposures observed at the no observed adverse effect level (NOAEL) in cynomolgus monkeys.

The planned dose of pegcetacoplan is 1080 mg SC twice weekly, equivalent to 308 mg/day. Dose selection is based on past clinical experience with SC pegcetacoplan, coupled with nonclinical toxicological studies. Daily doses up to 360 mg/day have been tested in past and ongoing clinical trials and have been found to be well tolerated, with exposures that are well below the pegcetacoplan levels associated with the NOAEL in monkeys. While doses of 180 mg/day and above have been shown to be pharmacologically active in both HVs and PNH patients, clinical and biomarker responses increased in a dose-dependent manner and with the maximum benefits being observed at doses of either 270 or 360 mg/day.

Using a target-mediated drug disposition (TMDD) pharmacokinetic/pharmacodynamic (PK/PD) model (Mager and Jusko 2001), the relationship between dosing regimen and pegcetacoplan serum concentration is well-understood and well-predicted by the model. Figure 1 is the predicted PK profile for the planned dose of 1080 mg twice weekly (green line), compared to the NOAEL PK data observed in the pivotal 9-month chronic toxicological study in monkeys (Study CCI [black line]). For comparison with previous human exposure, also included is the summary PK data from the ongoing PNH study, CCI (270 mg/day Cohort [blue line]), and healthy volunteer study, CCI , at 360 mg/day (brown line) and 1300 mg biweekly (biw) (light blue line). Both studies demonstrated pegcetacoplan to be safe and well tolerated. The figure illustrates that the PK exposure at the proposed Phase 3 dosing regimen should only derive a small increase in PK exposure previously observed in the PNH study 270 mg/day Cohort (Study APL-CP0514), a lower PK exposure (maximum concentration [C_{max}]) than that

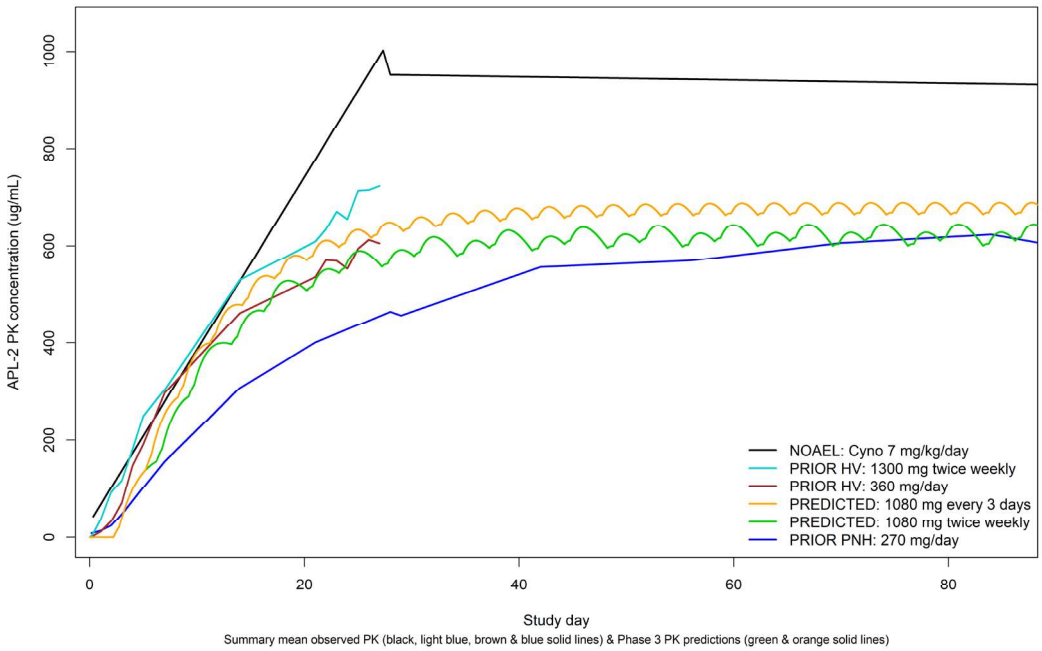
observed in Study CCI (higher dose, 1300 mg biw) and should be safely below that observed at the NOAEL.

6.2.2. Dosing Adjustment Option

If a subject does not respond sufficiently to the planned dose of 1080 mg twice weekly, the dosing regimen may be changed to 1080 mg every 3 days upon agreement with the sponsor. The premise being that, to derive a sufficient response in some subjects, a higher level of pegcetacoplan serum concentrations may need to be targeted. The adjusted dosing regimen will result in a higher PK exposure than that originally planned (twice weekly versus once every 3 days). As illustrated in Figure 1, the increase in PK exposure will be small, continue to be lower (C_{max}) than that observed in study CCI (higher dose, 1300 mg twice weekly) and safely below that observed at the NOAEL.

Details on the criteria to be used to determine whether a subject should receive the dosing adjustment is provided in Section 10.2.3.2.

Figure 1: Predicted PK profile (green line) at the planned dose of 1080 mg biw, compared to the summary PK data at the NOAEL (CCI [black line]), ongoing PNH study APL-CP0514 270 mg/day cohort (blue line) and healthy volunteer study CCI for both the 360 mg/day (brown line) and 1300 mg biw cohorts (light blue line).



6.3. Risk/Benefit

There is an anticipated health benefit for study participants from receipt of study drug. At the proposed dose levels of pegcetacoplan, a significant decrease in complement-mediated hemolytic

activity was observed in all pegcetacoplan-treated subjects (both treatment-naive and those treated previously with eculizumab) in PNH Phase 1b studies. Pegcetacoplan is, therefore, expected to reduce complement-mediated hemolytic activity in PNH patients. In this context, a careful evaluation of the risk/benefit ratio should be made.

A number of safety monitoring procedures are being monitored and assessed within this protocol (including, but not limited to: physical examination, vital signs monitoring at specified intervals, 12-lead electrocardiogram [ECG], hematology, serum chemistry, urinalysis, coagulation, and prompt reporting of predefined adverse events [AEs]) in order to ensure the subjects' safety.

Infusion site and pump-use safety will be assessed during clinical visits, where pegcetacoplan is administered (see Section 12.1.13).

The volume of blood planned for collection from each subject over the course of the study (see Section 12.6) will be kept to a minimum to limit the impact on the overall health of these anemic subjects.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenza* type B. Subjects will be required to have documented evidence of vaccination against these within 2 years of screening or will be required to receive vaccination upon initiation of pegcetacoplan therapy. Section 10.9 provides the details of the vaccination requirements and procedures for this study.

Prophylactic antibiotic therapy is required for any subject who necessitates vaccination(s) up until, and for 14 days after the required vaccination(s) has/have been administered. Following this, or for any subject who does not require vaccination, prophylactic antibiotic therapy is recommended. Section 10.10 provides the details of the prophylactic antibiotic therapy requirements and procedures for this study. Administration of prophylactic antibiotic therapy should be conducted, at the discretion of the treating investigator, in accordance with local treatment guidelines for patients with PNH who are receiving treatment with a complement inhibitor.

Body temperature and vital signs will be monitored at all clinic visits, as well as relevant blood parameters throughout the study, to assess for signs of infection. Subjects will be provided with emergency study cards that include a list of symptoms associated with the aforementioned infections. This study card also guides subjects with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms. In the event of a suspected infection, the principal investigator (PI) should provide guidance on appropriate action to be taken, thereafter.

The use of silica reagents in coagulation panels should be avoided. Apellis previously conducted an investigation into prolonged activated partial thromboplastin time (aPTTs) observed in subjects treated with pegcetacoplan. It was confirmed that false positive aPTT prolongation occurred when coagulation panels were performed using a Stago Analyzer and, specifically, silica reagents. It was determined that there was interference between the silica reagents and PEGylated pegcetacoplan, resulting in artificially prolonged aPTTs.

Details regarding the dosing regimen and administration of pegcetacoplan are provided in Section 10. Subjects should be instructed to take their pegcetacoplan treatment as prescribed, and

to contact the investigator immediately for guidance in the event of any missed doses. Discontinuation with pegcetacoplan or noncompliance with the prescribed dose regimen may lead to the potential for an increased risk for serious hemolysis. The sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with pegcetacoplan.

Apellis is not currently aware of any evidence associating pegcetacoplan use with specific risks or complications of coronavirus disease 2019 (COVID-19). Apellis recognizes the need to consider the public health risks of the COVID-19 pandemic within the context of conducting a clinical trial. Since these risks may change as the pandemic evolves, and may vary based on geographic location, Apellis will continue to evaluate the risk/benefit around study conduct on an ongoing and patient-by-patient basis.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of pegcetacoplan, compared to SOC (excluding complement inhibitors), in patients with PNH, as assessed by:

- Hemoglobin stabilization defined as avoidance of a >1 g/dl decrease in Hb levels from baseline in the absence of transfusion through Week 26 (Yes/No)

AND

- Reduction in lactate dehydrogenase (LDH) level from baseline to Week 26

7.2. Secondary Objectives

Secondary objectives of this study are:

- To evaluate the efficacy of pegcetacoplan, compared to SOC (excluding complement inhibitors), as assessed by:
    - Hemoglobin response (Yes/No) in the absence of transfusions (Hb response is defined as a ≥1 g/dL increase in Hb from baseline at Week 26)
    - Change from baseline to Week 26 in absolute reticulocyte count
    - Change from baseline to Week 26 in Hb level
    - Number of packed red blood cell (PRBC) units transfused from baseline to Week 26
    - Change from baseline to Week 26 in Functional Assessment of Chronic Illness Therapy- (FACIT-) Fatigue Scale score
    - Normalization of Hb levels (defined as ≥1 × the upper limit of normal [ULN]) from baseline at Week 26 in the absence of transfusions (Yes/No)
    - Normalization of LDH levels of ≤1 × ULN from Week 4 to Week 26 in the absence of transfusions (Yes/No)
    - Change from baseline to Week 26 in European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ C30) scores (Version 3)
    - Change from baseline to Week 26 in Linear Analog Assessment (LASA) scale scores
    - Absolute reticulocyte count normalization (<1 × ULN) at Week 26 (Yes/No)
    - Time of failure of Hb stabilization
    - Time to transfusion
- To evaluate the safety of pegcetacoplan as assessed by:
    - Incidence and severity of treatment-emergent adverse events (TEAEs)

- Incidence of thromboembolic events
- Changes from baseline in laboratory parameters
- Changes from baseline in ECG parameters
- Incidence of anti-APL2 antibodies

7.3. Exploratory Objectives

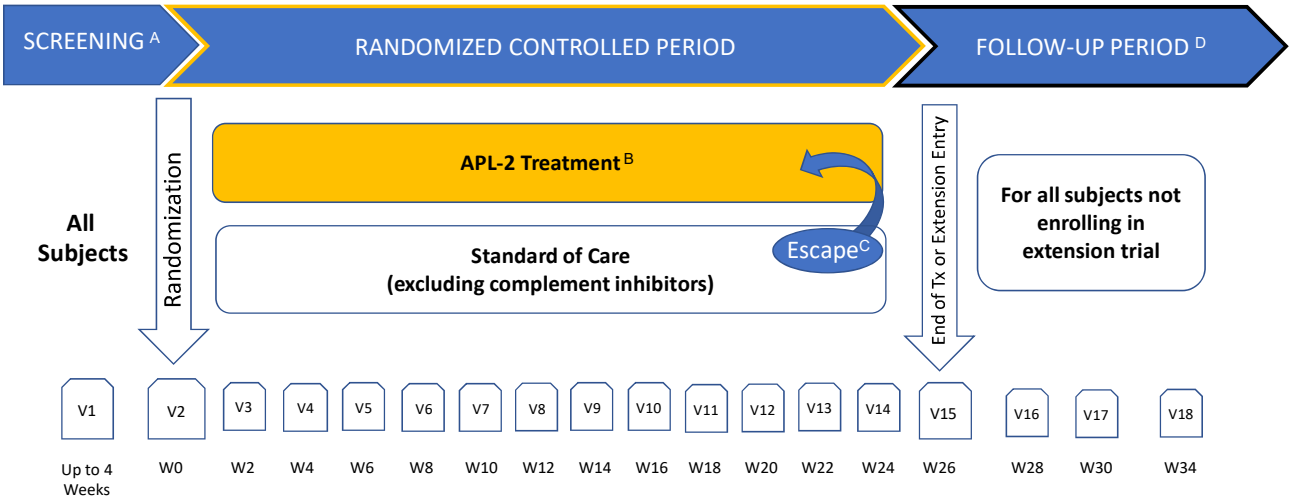
Exploratory objectives of the study are to evaluate:

- CCI
- [redacted]
- Pegcetacoplan PK/PD, as assessed by:
  - Pegcetacoplan PK concentrations from baseline to Week 26
  - Change from baseline to Week 26 in PNH clone distribution (RBCs and white blood cells [WBCs])
  - Change from baseline to Week 26 in C3 deposition in PNH Type II and III RBCs
  - Complement levels from baseline to Week 26 (eg, total hemolytic complement activity assay [CH50], alternate complement pathway assay [AH50], and complement component 3 [C3])

8. STUDY DESIGN

Figure 2 depicts the study design. This is a randomized, multicenter, open-label, controlled study. The study will consist of a screening period of up to 4-weeks, followed by a randomized controlled period of 26 weeks. A total of approximately 54 patients with PNH who meet all of the inclusion criteria and none of the exclusion criteria will be randomized (2:1 ratio) to receive either pegcetacoplan or to remain on their current SOC (excluding complement inhibitors) only from Visit 2 (Day 1) to Visit 15 (Week 26). All patients who complete Visit 15 (Week 26) may roll over into a separate open-label, long-term extension study, or will complete the safety follow-up (Visit 16 [Week 28], Visit 17 [Week 30], and Visit 18 [Week 34]).

Figure 2: APL2-308 Study Design



Abbreviations: APL-2 = pegcetacoplan; Tx = treatment; V = visit; W = week.

[a] Screening may occur up to 4 weeks prior to Visit 2. Subjects may proceed from Visit 1 to Visit 2 once eligibility is confirmed (there is no required duration between screening at Visit 1 and Visit 2). Within 5 days prior to Visit 2, each subject's Hb must be evaluated by a local or central laboratory. If the subject meets the protocol-specified transfusion guidelines (see Section 10.7), the subject must receive a PRBC transfusion so that the subject's Hb level no longer meets the protocol-specified requirements for PRBC transfusion. The posttransfusion Hb value should be confirmed by a local or central laboratory. Patients must not be randomized if they meet the protocol-specified requirements for transfusion.

[b] Subjects randomized to pegcetacoplan will be assigned pegcetacoplan at a dose of 1080 mg twice weekly. The dose may be adjusted to pegcetacoplan at a dose of 1080 mg every 3 days (see Section 10.2.3.2).

[c] Subjects assigned to the SOC (excluding complement inhibitors) treatment arm will commence escape pegcetacoplan therapy if they are classified as a failure for the first co-primary endpoint (see Section 10.2.3.3).

[d] All subjects who complete Visit 15 (Week 26) and do not elect to participate in the open-label extension study will be asked to return to the investigator site for the Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34) follow-up visits. Subjects who discontinue treatment will be encouraged to continue to attend study visits to complete study assessments (except for treatment with pegcetacoplan), as detailed in the Schedule of Events. At a minimum, subjects who discontinue dosing should complete follow-up procedures outlined in the Schedule of Events 2, 4, and 8 weeks after treatment discontinuation. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the investigator's brochure.

Randomization will be stratified by the number of PRBC transfusions within the 12 months prior to screening (<4; ≥4) *(ie, number of transfusion events regardless of PRBC units transfused).*

The protocol-specified transfusion threshold is that a PRBC transfusion will be administered if Hb is <7 g/dL or ≥7 and <9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion. The corrected pretransfusion and posttransfusion Hb and number of units transfused must be documented in the case report form (CRF) (see Section 10.7).

Within 5 days prior to Visit 2 (Week 0), each subject's Hb must be evaluated by a local or central laboratory. If the subject meets the protocol-specified transfusion guidelines described above, the subject must receive a PRBC transfusion so that the subject's Hb level no longer meets the protocol-specified requirements for PRBC transfusion. The post-transfusion Hb value should be confirmed by a local or central laboratory. Subjects must not be randomized if they meet the protocol-specified requirements for transfusion, and the Hb assessment to confirm eligibility should be scheduled so that the subject does not fall outside the screening window (up to Day –28). Screening-period Hb requirements to determine Hb eligibility are depicted in Figure 3.

On Day 1, subjects will be randomized to either pegcetacoplan or SOC (excluding complement inhibitors) using a 2:1 ratio. During the randomized controlled period, subjects will return to the clinical site every 2 weeks until Week 26 for efficacy and safety assessments.

Subjects randomized to the SOC (excluding complement inhibitors) arm will continue to receive SOC treatment (with transfusions allowed per the instructions of the protocol), but will not be allowed to receive treatment with a complement inhibitor (eg, eculizumab) unless they qualify for pegcetacoplan escape therapy (see Section 10.2.3.3). Similarly, subjects randomized to pegcetacoplan will not be allowed to receive treatment with other complement inhibitors.

If, at any point during the study, any subject assigned to the SOC (excluding complement inhibitors) treatment arm that qualifies as a failure for the first co-primary endpoint will be offered early escape therapy with pegcetacoplan (see Section 10.2.3.3).

Subjects who reach Visit 15 (Week 26) will be offered entry into an open-label extension study to continue treatment with pegcetacoplan. Visit 15 of Study APL2-308 will serve as the first visit for the open-label extension. These subjects will not complete the follow-up procedures detailed in this protocol.

All subjects who complete Visit 15 (Week 26) and do not elect to participate in the open-label extension study will be asked to return to the investigator site for the Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34) follow-up visits. Subjects who discontinue treatment will be encouraged to continue to attend study visits to complete study assessments (except for treatment with pegcetacoplan), as detailed in the Schedule of Events (Section 4). At minimum, subjects who discontinue dosing should complete follow-up procedures outlined in the Schedule of Events (Section 4) 2, 4, and 8 weeks after treatment discontinuation. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered, and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the IB.

An external, independent data monitoring committee (DMC) will assess the safety/tolerability data of the study periodically.

Subjects who fail the screening procedures should not be rescreened for the study unless this is agreed upon in advance and documented in writing by the sponsor.

9. SUBJECT SELECTION

The study is planned to randomize approximately 54 subjects with PNH.

9.1. Inclusion Criteria

At Visit 1 screening, subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Be at least 18 years old (inclusive).
2. Have LDH ≥1.5 × ULN at the screening visit.
3. Have PNH diagnosis, confirmed by high sensitivity flow cytometry (granulocyte or monocyte clone >10%).
4. Have Hb less than the lower limit of normal (LLN) at the screening visit.
5. Have ferritin greater than/equal to the LLN, or total iron binding capacity (TIBC) less than/equal to ULN at the screening visit, based on central laboratory reference ranges. If a subject is receiving iron supplements at screening, the investigator must ensure that the subject's dose has been stable for 4 weeks prior to screening, and it must be maintained throughout the study. Subjects not receiving iron at screening must not start iron supplementation during the course of the study.
6. Body mass index (BMI) ≤ 35 kg/m^2 at the screening visit.
7. Have a platelet count of >50,000/mm^3 at the screening visit.
8. Have an absolute neutrophil count >500/mm^3 at the screening visit.
9. Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening and must agree to use protocol-defined methods of contraception for the duration of the study and for 90 days after their last dose of study drug.
10. Males must agree to use protocol-defined methods of contraception and agree to refrain from donating sperm for the duration of the study and for 90 days after their last dose of study drug.
11. Have vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* (types A, C, W, Y, and B), and *Haemophilus influenzae* (type B) either within 2 years prior to Day 1 dosing, or agree to receive vaccination 14 days after starting treatment with pegcetacoplan (along with prophylactic antibiotic therapy for at least the 14 days between pegcetacoplan treatment initiation and vaccination and for 14 days post vaccination). Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits).
12. Be willing and able to give informed consent.

9.1.1. Approved Methods of Contraception

Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (eg,

Depo-Provera) or removable birth control device (eg, NuvaRing or Ortho Evra patches); sexual abstinence (*defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments);* and/or surgical sterilization (at least 6 months before dosing). Sexual abstinence is only accepted when it is the preferred and usual lifestyle of the subject. Subjects not practicing abstinence as defined above and/or subjects practicing coitus interruptus (pull-out method) must agree to use an approved method of contraception during the study and 90 days after their last dose of study drug.

9.2. Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening:

13. Treatment with any complement inhibitor (eg, eculizumab) within 3 months prior to screening.
14. Hereditary complement deficiency.
15. History of bone marrow transplantation.
16. Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to screening:
    - Erythropoietin or immunosuppressants for at least 8 weeks
    - Systemic corticosteroids for at least 4 weeks
    - Vitamin K antagonists (eg, warfarin) with a stable international normalized ratio (INR) for at least 4 weeks
    - Iron supplements, vitamin B_{12}, or folic acid for at least 4 weeks
    - Low-molecular-weight heparin for at least 4 weeks
17. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration.
18. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives, whichever is longer.
19. Planning to become pregnant or currently a breastfeeding woman.
20. History of meningococcal disease.
21. Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could put the subject at increased risk or potentially confound study data.

9.3. Randomization Criteria

At Visit 2 (Day 1), subjects must meet the following criteria in order to be randomized:

1. Subjects must have Hb ≥9 g/dL, or Hb ≥7 g/dL and <9 g/dL without signs or symptoms of sufficient severity to warrant a transfusion.
2. Negative urine pregnancy test for WOCBP.
3. No active systemic bacterial, viral, or fungal infection within the 2-week period prior to receiving treatment with pegcetacoplan.

10. STUDY TREATMENTS

10.1. Identity of Investigational Product

The test product is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan (54 mg/mL) in acetate-buffered sorbitol, supplied in stoppered glass vials. Additional information regarding the investigational product is provided in the pegcetacoplan IB.

10.1.1. Blinding the Treatment Assignment

This is an open-label study. Treatment assignment will not be blinded.

10.2. Administration of Investigational Product

10.2.1. Interactive Response Technology (IRT) for Investigational Product Management

A centralized IRT will be utilized for (but not limited to) the following investigational product management tasks: randomization; investigational product supply management; inventory management and supply ordering; expiration tracking; and return of investigational product (if applicable). Please refer to the IRT Manual for further information.

10.2.2. Allocation to Treatment

Subjects who meet all the inclusion criteria and none of the exclusion criteria at screening (Visit 1), along with the randomization criteria at Visit 2 (Day 1), will be eligible to enter the study. Subjects will be randomly assigned at a 2:1 ratio to either the pegcetacoplan treatment arm or the SOC (excluding complement inhibitors) controlled treatment arm.

Subject numbers are assigned to all subjects as they consent to take part in the study.

The randomization number represents a unique number corresponding to the treatment arm allocated to the subject, once eligibility has been determined.

The randomization will be stratified by the number of PRBC transfusions within the 12 months prior to Day –28 (<4; ≥4) (ie, number of transfusion events regardless of PRBC units transfused).

Individual subject treatment will be automatically assigned by the IRT.

10.2.3. Pegcetacoplan Dosing

Starting at Visit 2 (Day 1), subjects assigned to the pegcetacoplan treatment arm will receive SC infusions pegcetacoplan at a dosage of 1080 mg twice weekly. During the course of the study, subjects may be switched to an alternate dosing regimen of pegcetacoplan at 1080 mg every 3 days, if warranted, based on clinical response and agreement from the sponsor (see Section 10.2.3.2).

Dosing diaries will be utilized for pegcetacoplan and are to be completed for each dose administered at the study site or outside regular clinic visits. Subjects should not deviate from their pegcetacoplan dosing schedule: Day 1 and Day 4 of each treatment week (eg, Monday/Thursday/Monday) or every 3 days (eg, Monday/Thursday/Sunday).

Note: Discontinuation with pegcetacoplan or noncompliance with the prescribed dose regimen may lead to the potential for an increased risk for serious hemolysis. Subjects should be

instructed to take their pegcetacoplan treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. If withdrawal of pegcetacoplan treatment is necessary or a subject completes the trial and does not elect to participate in the extension study, slow weaning should be considered, and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the IB.

10.2.3.1. Pegcetacoplan Administration

Pegcetacoplan will be administered as a 20-mL SC infusion. The preferred site of infusion will be the abdomen; however, if a subject does not tolerate administration to the abdomen, alternative sites may be considered.

For subjects randomized to the pegcetacoplan treatment arm, research nurses or other appropriately qualified research personnel will administer the first pegcetacoplan SC infusion at Visit 2 (Day 1) and will train subjects on how to self-administer. Following Visit 2, appropriately qualified research personnel will supervise self-administration of pegcetacoplan for the following 3 doses (which will occur prior to Visit 3 [Week 4]). Supervision of self-administration may be conducted at the subject's home, at the study site, or at an off-site location convenient for the subject. Supervision of self-administration must continue until the subject is qualified to self-administer.

Subjects randomized to the SOC (excluding complement inhibitors) treatment arm may qualify to receive pegcetacoplan escape therapy, as described in Section 10.2.3.3. Subjects assigned to pegcetacoplan escape therapy will have research nurses or other appropriately qualified research personnel administer the first pegcetacoplan SC infusion and provide self-administration training at the study visit in which pegcetacoplan escape therapy is initiated, with the 3 doses following that visit supervised by appropriately qualified research personnel as detailed above.

Following self-administration qualification, subjects may self-administer pegcetacoplan SC infusions without supervision at home, or at an off-site location convenient to the subject. Subjects may choose to continue to self-administer pegcetacoplan infusions at the study site on scheduled dosing days when a study visit coincides, although this is not required. Self-administration conducted at the study site will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.

NOTE: Self-administration may also be conducted by a member of the subject's household or family member, etc. It is not intended to be restricted to the individual subject. Please refer to the Study Operations Manual for further details regarding the self-administration qualification.

10.2.3.2. Pegcetacoplan Dose Adjustments

Following commencement of monotherapy with pegcetacoplan, ie, at Day 1 (randomization; for subjects assigned to the pegcetacoplan treatment arm) or at any point following assignment to escape therapy with pegcetacoplan (see Section 10.2.3.3), LDH will be monitored as part of the scheduled assessments at the planned clinic visits. After Visit 4 (Week 4; after steady state has been achieved), for any subject receiving pegcetacoplan monotherapy, if LDH is >2 × ULN on 1 occasion, a pegcetacoplan dose increase to 1080 mg every third day should be considered (see Section 6.2). Any adjustment in dose will be discussed and confirmed, in writing, by Apellis. In the event of a dose increase, LDH will be monitored biweekly (unscheduled assessments, if applicable) for at least 4 weeks to assess the impact of the dose adjustment on LDH levels.

Decisions to escalate or de-escalate between the 2 pegcetacoplan dose regimens may be made by the sponsor.

Doses above pegcetacoplan at 1080 mg every third day may be considered, if clinically indicated. Prior to implementation review by the DMC and institutional review board (IRB)/independent ethics committee (IEC) will occur and consist of examination of all cumulative safety, tolerability and efficacy data (eg, physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) and a thorough assessment of all safety data. PK/PD data and predicted exposure for subsequent doses, based on emerging PK data, will also be reviewed prior to determining any proposed dose adjustment.

10.2.3.3. Pegcetacoplan Escape Therapy

Following Visit 2 (Week 0), subjects assigned to the SOC (excluding complement inhibitors) treatment arm who have an Hb level measured by the central laboratory that is ≥2 g/dL below the baseline value will be offered the opportunity to receive escape therapy with pegcetacoplan.

In addition, if a subject presents with a thromboembolic event during this period, and the investigator excludes other possible causes of thrombosis and believes that the event was secondary to PNH, he/she may request a discussion with Apellis' clinical team to evaluate whether the subject might be a candidate for escape therapy. Approval, if granted, will be documented in writing.

Once it is confirmed that a subject randomized to the SOC (excluding complement inhibitors) treatment arm qualifies for and agrees to receive pegcetacoplan escape therapy, the subject should be encouraged to return to the site for an unscheduled visit to begin treatment with pegcetacoplan. Procedures for this visit are provided in Section 11.3.

10.3. Labeling, Packaging, Storage, and Handling

10.3.1. Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the following: protocol number; dosage form (including product name and quantity in pack); route of administration; directions for use; storage conditions; batch number and/or packaging reference; the statements, "For clinical trial use only," and/or "CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use," and name/address of sponsor.

Space is allocated on the label so that the site representative can record a unique subject identifier and date dispensed by the site to the subject.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy national, local, or institutional requirements, but it must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

10.3.2. Packaging

Investigational product is supplied in 20-cc glass vials.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement, in advance, by the sponsor.

10.3.3. Infusion Supplies

The sponsor will supply syringes, vial adapters, infusion sets, and ambulatory syringe infusion pumps, as required. Refer to the Study Operations Manual for further details.

10.3.4. Storage

The investigational product should be stored refrigerated at 2 to 8°C.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

A pharmacist or appropriately qualified designated person will be responsible for storing the investigational product at the site appropriately and dispensing the vials of investigational product to the subject. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored at the site throughout the duration of the study and that records are maintained.

Subjects who are dispensed investigational product must be instructed on appropriate transportation requirements and storage conditions in their home environment. Subjects will not be required to log or record the temperature at which their investigational product is stored.

10.4. Investigational Product Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records must be maintained of all investigational product dispensed, used, returned, and/or destroyed. The investigator is responsible for ensuring the retrieval of all required study supplies from subjects.

At the conclusion of the study, any unused investigational product will either be destroyed at the investigator site or be returned to the sponsor or designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

10.5. Subject Compliance

Subjects must be instructed to bring their empty/used investigational product packaging to every visit. The pharmacist/nominated person will record details on the drug accountability form.

Subjects will be instructed on the specific investigational product packaging that will be required to return to the site.

10.6. Control: Standard of Care (Excluding Complement Inhibitors)

Subjects randomized to SOC (excluding complement inhibitors) are eligible to receive any treatment considered to be local SOC except for complement inhibitors. Any transfusions received must be reported.

Iron supplementation requirements are detailed in Section 10.8.

10.7. Transfusions

Transfusion history collected at the Screening Visit (Visit 1; up to Week –4) is described in Section 12.1.3.

During the study treatment period (Visit 2 [Week 0] to Visit 15 [Week 26]), transfusions will be administered if subjects have either of the following:

- Hb is <7 g/dL
- Hb ≥7 g/dL - <9 g/dL with symptoms.

In addition, Hb, LDH, and reticulocyte count should be collected PRIOR to any transfusion. The assessment may be performed at a central or certified local laboratory.

If these criteria are not met and the PI believes that a transfusion is necessary, the PI should discuss with the sponsor before administering the transfusion. Transfusions that do not meet this criterion will be considered protocol deviations and may lead to data being excluded from the primary analysis.

10.8. Prior and Concomitant Treatment

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 9.2), and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the subject takes or undergoes within 28 days (or 2 years for documentation of vaccination [see Section 11.2.2.2]) prior to the start of screening (Visit 1) until the first dose of study drug will be recorded on the subject's CRF.

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page. Except for complement inhibitors (other than pegcetacoplan [eg, eculizumab]) and/or phlebotomy/venesection for iron overload, any concomitant medication deemed necessary for the subject's SOC during the study, or for the treatment of any AE (along with the allowed medications described below) may be given at the discretion of the investigator. It is the responsibility of the investigator to ensure that the details regarding all medications are recorded in full in the subject's CRF.

The following concomitant medications are allowed if the following conditions apply, and dose adjustments are not expected during the randomized controlled period (Visit 2 to Visit 15):

- Erythropoietin, if the subject has been receiving a stable dose for at least 8 weeks before screening.
- Immunosuppressants, if the subject has been receiving a stable dose for at least 8 weeks before screening.
- Corticosteroids, if the subject has been receiving a stable dose for at least 4 weeks before screening.
- Vitamin K antagonists (eg, warfarin) with a stable INR for at least 4 weeks before screening.
- Iron supplements, vitamin B_{12}, or folic acid, if the subject has been receiving a stable dose for at least 4 weeks before screening. If patients have previously received and tolerated iron chelation, this may be continued or reinitiated throughout the study if clinically indicated and upon discussion with the sponsor's medical monitor.
- Low-molecular-weight heparin, if the subject has been receiving a stable dose for at least 4 weeks before screening.

If clinically indicated and deemed in the best interest of the subject, the frequency or dose level of any of the above may be adjusted by the investigator in consultation with the Apellis medical monitor.

10.9. Vaccination

In order to receive treatment with pegcetacoplan, subjects must have documented evidence of vaccination against the following within 2 years of screening:

- *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations)
- *Streptococcus pneumoniae* (with a PCV13 or PPSV23 vaccine)
- *Haemophilus influenzae* type B (Hib vaccine).

Subjects randomized to pegcetacoplan: For subjects randomized to pegcetacoplan who do not have documented evidence of receiving any of the above vaccinations within 2 years prior to screening, the required missing vaccination(s) will be administered at Visit 3 (Week 2), prior to dosing with pegcetacoplan (along with boosters administered during the study at or after Visit 7 [Week 10], if required [see below]). Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). The PI will discuss with the sponsor regarding individual patient circumstances.

If the subject requires vaccination against *Neisseria meningitidis*, a booster (for both vaccinations) should be administered after at least 8 weeks (Visit 7).

If the subject requires vaccination against *Streptococcus pneumoniae*, PCV13 will be administered at Visit 3, and PPSV23 will be administered after at least 8 weeks (Visit 7).

Subjects randomized to SOC (excluding complement inhibitors): Subjects who are initially randomized to SOC (excluding complement inhibitors) who become eligible for pegcetacoplan

escape therapy will receive any required vaccination(s) 2 weeks after initiation of treatment with pegcetacoplan. If required as detailed above, the *Neisseria meningitidis* booster (for both vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s).

10.10. Prophylactic Antibiotics

In order to receive treatment with pegcetacoplan, subjects will require preventive antibiotics, as detailed below.

Subjects randomized to pegcetacoplan: Subjects will be required to take ciprofloxacin 500 mg twice daily from Visit 2 (Week 0) to Visit 3 (Week 2) and continue to receive antibiotic prophylaxis until 14 days post vaccination. From that point forward, it is recommended that subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

Subjects randomized to SOC (excluding complement inhibitors): Subjects who are initially randomized to SOC (excluding complement inhibitors) do not need to initiate preventive antibiotic therapy at Day 1. If a subject becomes eligible for and initiates pegcetacoplan escape therapy, the subject is required to take ciprofloxacin 500 mg twice daily for 2 weeks, beginning on the first day of treatment with pegcetacoplan and continue to receive antibiotic prophylaxis until 14 days post vaccination. After 2 weeks of ciprofloxacin, it is recommended that subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

10.11. Rescue Antibiotics

Body temperature, vital signs, and relevant blood parameters will be monitored regularly throughout the study to assess for signs of infection. Subjects will be provided with emergency study cards that include a list of symptoms associated with infections. This study card also guides subjects with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms. In the event of a suspected infection, the PI should provide guidance on appropriate action to be taken, thereafter. Action to be taken may include administration of a broad-spectrum antibiotic.

11. STUDY PROCEDURES

Please see the Schedule of Events (Section 4) for a summary of the schedule of study participation and procedures. The schedule of visit dates should be established, either prior to or at the time of screening, allowing subjects an opportunity to assess whether there are likely to be significant conflicts with other activities or planned absences. To the extent possible, subjects will be expected to adhere to the visit schedule and any re-scheduling of visits outside of the window specified in the Schedule of Events (Section 4) must be agreed upon, in advance, with the PI and sponsor.

11.1. Screening Period: Visit 1 (up to Week –4 [Day –28])

Screening procedures are listed in the Schedule of Events (Section 4).

The subject will be screened to confirm that the subject-selection criteria for the study has been met. Informed consent will be obtained at screening prior to any study-related procedures being conducted (see Section 15.3).

A screen failure is a subject who has given informed consent and failed to meet at least 1 of the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s).

Subjects should not be rescreened once they have been designated as a screen failure unless this is discussed in advance with the sponsor and documented in writing.

Sufficient supplementation of iron, folic acid, and vitamin B12 must be confirmed prior the initiation of the Randomized Controlled Period. Subjects taking supplements need to be on a stable dose ≥4 weeks prior to screening.

The following assessments will be performed:

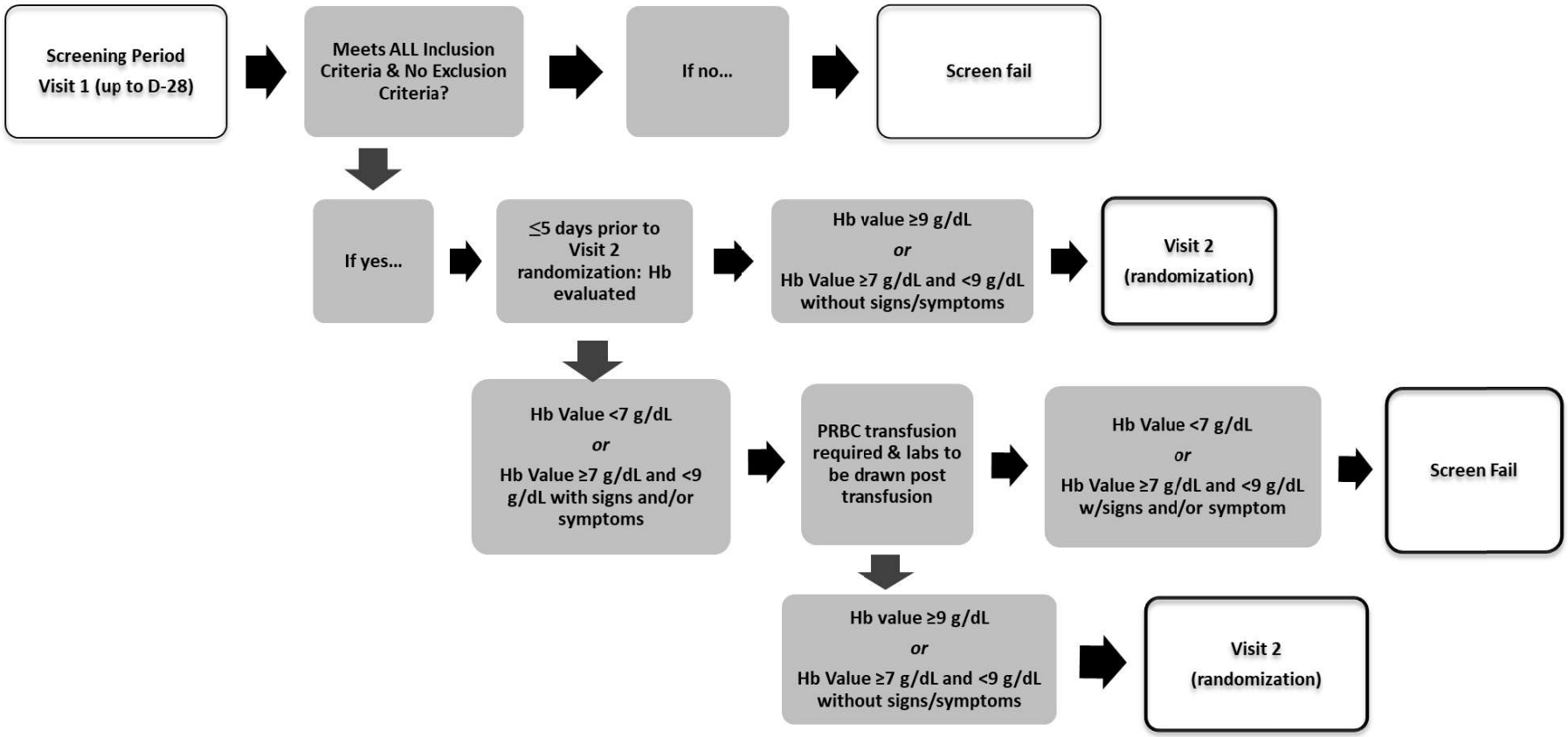
- Informed consent
- Demographics
- Height/Weight
- Medical history (including thrombosis history)
- Transfusion history
- Review of inclusion/exclusion criteria
- Physical examination
- Triplicate 12-lead ECG
- Prior and concomitant medications
- Vital sign measurements
- Urinalysis
- Blood tests (see Schedule of Events [Section 4] for details)
- Buccal swab test (genotyping for Gilbert's Syndrome)

- Adverse event assessment

11.1.1. Hemoglobin Stability: Randomization Criteria

Within 5 days prior to Visit 2 (Week 0), each subject's Hb must be evaluated by a local or central laboratory. It is not required that the subject's lab draw occur at the study site. If the subject meets the protocol-specified transfusion guidelines described above, the subject must receive a PRBC transfusion so that the subject's Hb level no longer meets the protocol-specified requirements for PRBC transfusion. The posttransfusion Hb value should be confirmed by a local or central laboratory. Subjects must not be randomized if they meet the protocol-specified requirements for transfusion as outlined in Section 10.7. The blood draw to confirm Hb eligibility for study entry should be scheduled so that the subject is able to receive transfusion if necessary for study entry without falling out of the 28-day screening window. Figure 3 provides a graphic depiction of the Hb confirmation process for study entry between Visit 1 and Visit 2.

Figure 3: Screening Period Hemoglobin Requirements for Visit 2 Eligibility



11.2. Randomized Controlled Period: Visit 2 (Week 0) to Visit 15 (Week 26)

11.2.1. Visit 2: Day 1

Following completion of the Screening Period, subjects will enter the Randomized Controlled Period and will be randomized to either the pegcetacoplan treatment arm or SOC (excluding complement inhibitors) treatment arm. Assessments will be performed as listed below and in the Schedule of Events (Section 4).

Baseline values for subjects randomized to the pegcetacoplan treatment arm will be those measurements taken prior to the start of study treatment.

Prior to randomization and dosing:

- CCI [redacted]
- Triplicate 12-lead ECG: within 1 hour predose
- Physical examination
- Concomitant medications review
- Confirm inclusion/exclusion criteria
- Vital sign measurements
- Urinalysis
- Blood tests (see schedule of events [Section 4] for details)
- Urine pregnancy test
- FACIT-Fatigue scale
- LASA for Quality of Life
- EORTC QLQ-C30
- Randomization

For subjects randomized to pegcetacoplan treatment arm only:

- Dispense investigational product and infusion materials
- Train subject to perform home infusion
- Pegcetacoplan infusion
- Assess infusion site
- Vital sign measurements (2 hours post dose [±30 minutes])

Subjects will be required to have documented evidence of vaccination against *Streptococcus pneumoniae*, and *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenza* type B within 2 years of screening or will be required to receive vaccination upon initiation of pegcetacoplan therapy. Section 10.9 provides the details of the vaccination requirements and procedures for this study.

Prophylactic antibiotic therapy is required for any subject taking pegcetacoplan. Section 10.10 provides the details of the prophylactic antibiotic therapy requirements and procedures for this study.

11.2.2. Visit 3 to Visit 15 (Week 2 to Week 26)

Through the Randomized Controlled Period, subjects randomized to the pegcetacoplan treatment arm will receive self-administered SC doses 1080 mg of pegcetacoplan twice weekly or every 3 days, and subjects randomized to the SOC (excluding complement inhibitors) treatment arm will continue their SOC therapy. Subjects assigned to the SOC (excluding complement inhibitors) treatment arm may be assigned to pegcetacoplan escape therapy during the course of the Randomized Controlled Period if they meet the criteria to switch to escape therapy as detailed in Section 10.2.3.3.

Study visits at the investigator site will be conducted biweekly from Visit 3 (Week 2) to Visit 15 (Week 26). All visits will have a ±3-day visit window.

Subjects may self-administer pegcetacoplan infusions at the study site but are not required to do so if the visit is not occurring on a scheduled dosing occasion. Outside of study visit days, subjects will self-administer pegcetacoplan infusions at the subject's home or at an off-site location convenient for the subject.

Assessments will be performed as listed below and in the Schedule of Events (Section 4).

- Vital sign measurements (performed prior to ECG and venipuncture)
- Triplicate 12-lead ECG (prior to blood draw: Weeks 4, 8, 12, 16, 20, and 26 only)
- Concomitant medications review
- Adverse event review
- Urinalysis (Weeks 4, 8, 10, 12, 16, 18, 22, 24, and 26 only)
- Blood tests (see Schedule of Events [Section 4] for details)
- Urine pregnancy test
- FACIT-Fatigue scale (Weeks 4, 8, 12, 16, 20, and 26 only)
- LASA for Quality of Life (Weeks 4, 8, 12, 16, 20, and 26 only)
- EORTC QLQ-C30 (Weeks 4, 8, 12, 16, 20, and 26 only)
- Physical examination (Week 16 only)
- Vaccination (Week 2 and Week 10 [if necessary], or following initiation of pegcetacoplan escape therapy; see Section 10.9)

For subjects randomized to pegcetacoplan treatment arm or receiving pegcetacoplan escape therapy:

- Dispense investigational product and infusion materials
- Reconcile used investigation product returned by the patient

For subjects administering pegcetacoplan at the study visit:

- Infuse pegcetacoplan
- Assess infusion site

Subjects who reach Visit 15 (Week 26) of the Randomized Controlled Period will be offered entry into an open-label extension study, if eligible, per the extension study's inclusion and exclusion criteria. For subjects who elect to enter the open-label extension study, Visit 15 will also serve as the first visit of the open-label extension study and follow-up procedures as detailed in this protocol will not be conducted.

Subjects who do not enter the open-label extension study will complete the follow-up visits and will exit the study (see Section 11.4).

11.2.2.1. Pegcetacoplan Administration Training

Please see Section 10.2.3.1 for self-administration training requirements for subjects randomized to the pegcetacoplan treatment arm, or subjects who begin pegcetacoplan escape therapy during the course of the Randomized Controlled Period.

11.2.2.2. Vaccination and Prophylactic Antibiotic Procedures

Subjects will be required to have documented evidence of vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenza* type B within 2 years of screening or will be required to receive vaccination upon initiation of pegcetacoplan therapy. Section 10.9 provides the details of the vaccination requirements and procedures for this study.

Prophylactic antibiotic therapy is required for any subject that necessitates vaccination(s) until the required vaccination(s) has/have been administered and for 14 days post vaccination. Section 10.10 provides the details of the prophylactic antibiotic therapy requirements and procedures for this study.

11.3. Pegcetacoplan Initiation Visit (for SOC [Excluding Complement Inhibitors] Treatment Arm Failures)

Following Visit 2 (Week 0), subjects assigned to the SOC (excluding complement inhibitors) treatment arm who have a Hb level measured by the central laboratory that is ≥2 g/dL below the baseline value will be switched to escape therapy with pegcetacoplan.

These subjects will return to the site for a pegcetacoplan initiation visit. Assessments will be performed as listed below and in the Schedule of Events (Section 4).

Prior to dosing:

- Concomitant medications review
- Adverse event review
- Vital sign measurements
- PK sample (see Schedule of Events [Section 4] for details)

- Dispense investigational product and infusion materials
- Train subject to perform home infusion
- Pegcetacoplan infusion
- Assess infusion site
- Vital sign measurements (2 hours post-dose [±30 minutes])

Following the pegcetacoplan initiation visit, subjects will maintain their regular visit schedule.

11.4. Follow-up (if Required): Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34)

All subjects who complete Visit 15 (Week 26) and do not elect to participate in the open-label extension study will be asked to return to the investigator site for the Visit 16 (Week 28), Visit 17 (Week 30), and Visit 18 (Week 34) follow-up visits.

In addition, subjects who discontinue treatment and elect to withdraw prior to completing Visit 15 (Week 26) should complete the procedures outlined in this section 2, 4, and 8 weeks after treatment discontinuation.

The Visit 16 (Week 28) follow-up visit has a visit window of ±3 days. The Visit 17 (Week 30) and Visit 18 (Week 34) follow-up visits have a visit window of ±7 days.

Assessments listed below and outlined in the Schedule of Events (Section 4), will be performed:

- Vital sign measurements (performed prior to ECG and venipuncture)
- Triplicate 12-lead ECG
- Concomitant medications
- Adverse event review
- Urinalysis
- Blood tests (see Schedule of Events [Section 4] for details)
- Urine pregnancy test
- FACIT-Fatigue scale
- LASA for Quality of Life
- EORTC QLQ-C30
- Physical examination
- Reconcile used investigational product returned by the patient

11.5. Unscheduled Visits

Subjects may be asked to return to the clinical facility for additional visits if considered necessary by the PI or as relevant to subjects' dosing regimens.

Unscheduled visits may include (but are not limited to) any of the procedures listed in the Schedule of Events (Section 4). Examples of unscheduled visits include:

- Initiation of pegcetacoplan escape therapy (see Section 11.3)
- Subjects return to the clinic to complete additional assessments and/or procedures, at the discretion of the investigator
- Subjects return to the clinic for pegcetacoplan dosing (based on patient's dose, dosing schedule, ability to self-administer pegcetacoplan, and potential dose adjustments)
- LDH assessment in case of dose adjustment
- Safety monitoring

11.5.1. Data Monitoring Committee

A DMC will review cumulative safety/tolerability data (eg, physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs), efficacy (Hb and LDH levels, haptoglobin level, ARC, and RBC transfusions), and PK data. The DMC will have the responsibility to conduct a thorough safety assessment at regular predefined intervals during the Randomized Controlled Period of the study, as described in the DMC charter.

In addition, an *ad hoc* data review may be recommended by the DMC or requested by the sponsor at any time during the study.

The remit, roles, and responsibilities of the DMC will be specified in a separate DMC charter.

11.6. Treatment Discontinuation and Study Withdrawal

11.6.1. Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

Subjects who discontinue treatment will be encouraged to continue to attend study visits to complete study assessments (except for treatment with pegcetacoplan) as detailed in the Schedule of Events (Section 4). At minimum, subjects who discontinue dosing should complete follow-up procedures outlined in the Schedule of Events (Section 4) 2, 4, and 8 weeks after treatment discontinuation (Follow-up Visits; see Section 11.3). If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered, and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications, as detailed in the IB.

Any subject withdrawn due to an AE (whether serious or nonserious) or clinically significant abnormal laboratory test values will be evaluated by the investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

Subjects who discontinue will not be replaced.

11.6.2. Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event which, in the opinion of the investigator, could jeopardize the safety of the subject. Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, pregnancy, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.
- Withdrawal by subject.
- Lost to follow-up.
- Pregnancy.
- Other (If "Other" is selected, the investigator must specify on the CRF).
- Death.
- Failure to meet randomization criteria.
- Noncompliance with investigational product.
- Noncompliance with protocol requirements or study-related procedures.
- Physician decision.
- Site terminated by sponsor.
- Study terminated by sponsor, the Food and Drug Administration (FDA), or other regulatory authorities.
- Withdrawal by parent/guardian.
- Phlebotomy/venesection for iron overload.

11.6.3. Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that he/she return to the site for final safety evaluations and to return any unused investigational product.

12. ASSESSMENTS

12.1. Assessments

Assessments to be performed during the study are described below. Every effort should be made to ensure that the protocol-required assessments are completed as described.

If deemed necessary, additional safety measurements may be performed, at the discretion of the PI.

12.1.1. Medical History

Medical history will be collected at the Screening Visit (Visit 1; up to Week –4). Medical history relating to Hb levels and pretransfusion Hb levels in the past year prior to study enrollment will be collected.

12.1.2. Thrombosis History

Thrombosis history will be collected at the Screening Visit (Visit 1; up to Week –4).

12.1.3. Transfusion History

At the Screening Visit, (Visit 1; up to Week –4), transfusion history from the previous 12 months must be obtained and recorded in the patient CRF. Historical information to be obtained will be:

- Date of transfusion
- Type of infusion (whole blood, PRBCs, or other)
- Number of units transfused
- Pretransfusion Hb value and associated date of sample (must be within 14 days prior to transfusion)

12.1.4. Body Height and Weight

Body height and body weight will be measured at the Screening Visit (Visit 1; up to Week –4).

12.1.5. Subject Demographics

Subject demographics will be collected at the Screening Visit (Visit 1; up to Week –4).

12.1.6. Physical Examination

All physical examinations will include, at a minimum, assessment of the following: general, head, ears, eyes, nose and throat, dentition, thyroid (endocrine), heart, chest, lungs, abdomen, skin, extremities, back/neck, musculoskeletal, and lymph nodes.

The investigator (or designee) at the study site will examine each subject, as outlined in the Schedule of Events (Section 4).

A symptom-driven physical examination may be performed at various unscheduled time points, if deemed necessary by the investigator.

12.1.7. Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured prior to dosing, as outlined in the Schedule of Events (Section 4).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with subjects in a seated position after resting for 5 minutes, except when they are supine or semireclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the PI.

Vital signs will be measured before venipuncture and ECG assessment, vital signs collected post dose will be timed from the completion of the study drug administration.

Additional monitoring of vital signs will occur 2 hours post dose (±15 minutes) at Visit 2 (Day 1) for subjects randomized to pegcetacoplan and at the pegcetacoplan Initiation Visit for subjects randomized to SOC who subsequently meet treatment failure criteria.

12.1.8. Electrocardiogram Monitoring

Triplicate 12-lead ECGs will be measured at the time points outlined in the Schedule of Events (Section 4) with 3 readings taken ≥1 minute and ≤5 minutes apart. Predose ECGs will be taken following resting in the supine position for 10 minutes in a quiet environment and prior to any blood sampling procedures.

All ECGs will be recorded at the sites using the equipment provided by the vendor performing the centralized ECG analysis.

The ECGs will be classified as normal, having a not clinically significant abnormality, or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, PR interval, QRS duration, and QT interval (uncorrected and corrected using both Bazett's [QTcB] and Fridericia's [QTcF] methods) will be reviewed for eligibility and ongoing safety.

During the study, if the QTcF ECG is ≥500 ms (mean of QTcF replicate values), the investigator should perform 3 additional ECGs over 20-60 minutes; if the mean QTcF of the 3 repeat ECGs is ≥500 ms, the site should instruct the subject to return the following day to perform repeat triplicate ECGs. An evaluation will be performed to look for other factors which may have contributed to QTc prolongation (eg, new concomitant medications, hypokalemia, etc.).

The full set of ECGs should be sent as soon as possible to the ECG central laboratory for verification; if the QTcF (mean of QTcF replicate values) has declined to below 500 ms and is returning towards baseline, dosing may continue. If the mean QTcF remains ≥500 ms, the investigator, medical monitor, and cardiology consultant will assess the timing of additional ECGs and possible discontinuation of pegcetacoplan dosing. Recommendation for discontinuation of pegcetacoplan will be made on an individualized management plan, based on the totality of the data. Because abrupt discontinuation of pegcetacoplan could result in rebound hemolysis and an associated risk of thrombosis, attention will be directed towards avoiding unnecessary dosing interruptions and all decisions regarding dosing will be clearly documented.

12.1.9. Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale

The FACIT-Fatigue Scale is a 13-item Likert scaled instrument which is self-administered by the subjects during clinic visits, as outlined in the Schedule of Events (Section 4). Subjects are

presented with 13 statements and asked to indicate their responses as it applies to the past 7 days. The 5 possible responses are: "Not at all" (0); "A little bit" (1); "Somewhat" (2); "Quite a bit" (3); and "Very much" (4). With 13 statements, the total score has a range of 0 to 52. Before calculating the total score, some responses are reversed to ensure that the higher score corresponds to a higher quality of life. The FACIT-Fatigue Scale and scoring guidelines are provided in Appendix 1.

12.1.10. Linear Analog Scale Assessment (LASA) for Quality of Life

The LASA consists of 3 items asking respondents to rate their perceived level of functioning. Specific domains include: activity level, ability to carry out daily activities, and an item for overall QoL. A representation of the scale is presented in Appendix 2. Scores for the 3 individual components of the scale and the combined score will be included in the analysis; this will be described in the Statistical Analysis Plan (SAP).

12.1.11. European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Quality of Life Questionnaire

The EORTC QLQ-C30 (version 3.0) consists of 30 questions comprised of both multi-item scales and single-item measures to assess overall quality of life in subjects. Questions are designated by functional scales, symptom scales, and global patient QoL/overall perceived health status. Scoring guidelines from EORTC will be used to calculate patients' scores. The QLQ-C30 and scoring guidelines are provided in Appendix 3.

12.1.12. Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Schedule of Events (Section 4). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or recommended by the DMC. The clinical laboratory tests include (but are not limited to) the following (see Section 12.1.12.1, Section 12.1.12.2, Section 12.1.12.3, Section 12.1.12.4, Section 12.1.12.5, and Section 12.1.12.6):

12.1.12.1. Hematology

- Hb
- Hematocrit
- RBC count
- Platelet count
- WBC count with differential
- Reticulocytes

12.1.12.2. Coagulation

- Prothrombin time (PT)
- Fibrinogen
- aPTT
- D-Dimer

NOTE: The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan.

12.1.12.3. Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated creatinine clearance (using Cockcroft-Gault formula) –screening only
- Bilirubin (total and direct)
- Albumin
- Alkaline phosphatase (ALP)
- LDH
- Haptoglobin
- Gamma-glutamyl transferase (GGT)
- LDH isoenzymes
- Creatine kinase (CK)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Uric acid
- Glucose
- Sodium
- Potassium
- Chloride
- Ferritin
- Erythropoietin (EPO)

12.1.12.4. Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte esterase

If an abnormality is noted for protein, blood, nitrite, and/or leukocyte esterase, a microscopic examination will be performed.

12.1.12.5. Other Panels

Plasma (free) Hb

Direct Coombs

Samples for genotyping (for Gilbert's Syndrome) will be obtained via buccal swab tests done at the screening visit.

12.1.12.6. Human Chorionic Gonadotropin (Serum Pregnancy Test) and Follicle-Stimulating Hormone

A serum pregnancy test will be performed for females only. Follicle-stimulating hormone (FSH) measurement will be performed for postmenopausal females at Visit 1 (up to Week –4) screening period only.

12.1.13. Infusion Site and Pump-Safety Assessment

On the days of clinic visits, if pegcetacoplan is administered at the visit site, an assessment of the pegcetacoplan infusion site will be made as a part of the AE assessment. If pegcetacoplan is administered at the visit the site staff will observe the dosing and pump use safety will be assessed and the infusion site will be checked again within 30 minutes after study drug administration. The infusion site assessments will be performed by an appropriately trained staff, as delegated by the investigator. The infusion site and surrounding area will be inspected for redness, swelling, induration, and bruising. The subject will be asked about the presence of pain and/or tenderness, and any issue related to pump use. The date, time, and outcome of the infusion site assessment will be recorded on the source documents and CRFs.

Subjects will be instructed to notify the PI or other study personnel in the event that an infusion site reaction occurs after self-administration of pegcetacoplan. All clinically relevant AEs, as determined by the investigator, from infusion site or related to pump use will be recorded as AEs.

12.2. Pharmacokinetic Assessments

12.2.1. Blood Sampling and Processing

Blood samples for PK assessment of pegcetacoplan will be collected via direct venipuncture at all visits as detailed in the Schedule of Events (Section 4). If pegcetacoplan is to be administered at the study site the blood sample must be taken predose.

The date and time of the last dose of pegcetacoplan should be recorded in the eCRF, along with the date and time of the PK sample.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate sample handling manual prior to study initiation.

Note: Samples for PK assessment should not be collected for subjects randomized to the SOC (excluding complement inhibitors) treatment arm unless they become eligible for and elect to receive pegcetacoplan escape therapy. If a subject from the SOC (excluding complement inhibitors) treatment arm is to begin receiving pegcetacoplan escape therapy, a predose PK sample should be collected at the pegcetacoplan initiation visit and at each subsequent visit as detailed in the Schedule of Events (Section 4).

12.2.2. Analytical Method

Serum sample analysis will be performed using good laboratory practice- (GLP-) compliant validated procedures and methods. The methods used and the results obtained will be included in the final report as an appendix.

12.3. Flow Cytometry Assessments

Blood samples for flow cytometry assessment will be collected via direct venipuncture at the time points delineated in the Schedule of Events (Section 4). Flow cytometry assessment will include, but not be limited to: PNH clonal distribution of RBCs; PNH clonal distribution of immature reticulocytes (CD71+), monocytes, and granulocytes; and C3 deposition on RBCs.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate sample handling manual prior to study initiation.

12.4. Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Schedule of Events (Section 4) for PD assessment of complement activation through the classical (ie, CH50) and alternative (ie, AP50) pathways. Blood samples will also be collected to measure C3 levels. Other relevant PD markers may also be assessed.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate Laboratory Reference Manual, prior to study initiation.

12.5. Antidrug Antibody Assessment

Subjects who test positive for anti–pegcetacoplan peptide antibodies or anti-PEG antibodies will be followed until the antibody levels revert to baseline and characterize their antibodies for titer, binding to the cyclic pentadecapeptide and PEG domains, and the neutralizing capacity.

Subjects who discontinue dosing will need to have antidrug antibody (ADA) samples collected at the follow-up visits.

Subjects who test positive for anti- pegcetacoplan peptide antibodies or anti-PEG antibodies at any time will be followed with ADA samples being collected every 6 months until the antibody levels revert to baseline. Samples that test positive will be characterized by an assay that will determine antibody titer, binding to the cyclic peptide or PEG domains, and measure neutralizing capacity.

The proposed ADA sampling schedule was established to capture the ADA signal at baseline, along with any potential early onset and the dynamic profile (transient or persistent) of antibody formation while minimizing pegcetacoplan level in the sample.

12.6. Blood Volume for Study Assessments

Table 1: Blood Volume During Study

Assay	Number of time points	Approximate volume per time point * (mL)	Approximate sample volume over course of study (mL)
Pharmacokinetics	7	5	35
Anti-pegcetacoplan peptide antibody and anti-PEG antibody	6	5	30
Hematology	17	4	68
Chemistry (including pregnancy screening)	17	7.5	127.5
Coagulation profile	8	2.7	21.6
Complement profile (CH50, and AH50)	7	8	56

Table 1: Blood Volume During Study (Continued)

C3 Profile	16	8	128
Flow cytometry, PNH clones and C3 deposition	8	2	16
Plasma (free) Hb	17	6	102
Direct Coombs	12	3	36
Total Approximate Blood Volume For Study:			**620.1***

Abbreviations: Ab = antibody; AH50 = alternate complement pathway assay; C3 = complement component 3; CH50 = total hemolytic complement activity assay; Hb = hemoglobin; PNH = paroxysmal nocturnal hemoglobinuria.
*Represents the standard collection volume planned over the duration of the study; actual volume may vary.

12.7. Pregnancy Tests

For WOCBP, a serum pregnancy test will be performed at screening Visit 1 (up to Week –4), and subjects with a positive test will be excluded from the study. A follow-up urine pregnancy test will be performed at Visit 2 (Day 1) (a negative urine pregnancy test must be received before dosing with study drug). A urine pregnancy test will also be performed at each site visit, if applicable. A final urine pregnancy test will be performed at the follow-up Visit 16 (Week 32) or the Early Termination Visit. Male subjects will be counseled to avoid donating sperm during the time between the first dose at Visit 2 (Day 1) through 90 days after their last dose of study drug.

12.8. COVID-19 Assessment

If a subject has been tested for COVID-19, the results, if available, will be documented in the eCRF.

13. ADVERSE EVENTS

13.1. Definition

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can, therefore, be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation and will be recorded during the study at the investigational site. All identified AEs must be recorded and described on the appropriate AE or SAE page of the eCRF.

Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE reporting. If these changes in laboratory values are assessed as clinically significant and/or lead to discontinuation of administration of investigational product, these should be reported as an AE. If these laboratory values are linked to a diagnosis, only the diagnosis should be reported as an AE.

13.2. Recording Adverse Events

Adverse events and SAEs will be collected from the signing of the informed consent form (ICF) until the completion of Visit 15 (for subjects who roll over into the open-label extension), or until the completion of follow-up (for subjects who do not roll over).

Any events that occur prior to dosing will be categorized as pretreatment events; events occurring after dosing will be recorded as TEAEs (start date of dosing and, therefore, categorization of the event will be dependent on randomization assignment).

For each AE, the investigator will evaluate and report the onset date (and time if applicable), resolution date (and time if applicable), intensity, causality, action taken, serious outcome, and whether or not it caused the subject to discontinue the study.

If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the investigational product. Subjects experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the follow-up visit should receive follow-up as appropriate.

All SAEs must be reported to the sponsor/Apellis Safety via eCRF within 24 hours of becoming aware of the event, whether or not the event is deemed treatment related. If the electronic data capture (EDC) system is not operational, the site must complete the paper SAE form and email to CCI immediately and also within 24 hours of becoming aware of the event. The reported information submitted as a paper SAE must be entered into the EDC system once it becomes operational.

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

13.3. Reporting Adverse Events

The sponsor has the responsibility to inform concerned health authorities, ethics committees, and investigators about Serious Unexpected Serious Adverse Reactions (SUSARs) in line with GCP guidance and applicable regulatory requirements.

If required, specific SAEs should be reported to the concerned ethics committees in compliance with local requirements.

13.3.1. Relationship of Events to Study Treatment

All AEs that occur during this study will be recorded. The PI will review each event and assess its relationship to study drug treatment (definitely related, possibly related, unlikely related, not related). The date and time of onset, time relationship to drug dosing, duration, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal or unknown [lost to follow-up]) of each event will be noted.

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Definitely Related	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon) Rechallenge satisfactory, if necessary
Possibly Related	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely Related	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
Not Related	Event or laboratory test abnormality, is plausibly related to the participant's clinical state, underlying disease, or the study procedure/conditions Time relationship to drug intake makes a relationship unreasonable Other obvious causes for event or laboratory test abnormality exist

13.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Mild	Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (eg, insomnia, mild headache).
Moderate	Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (eg, febrile illness requiring oral medication).
Severe	Event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention (eg, anemia resulting in blood transfusion).

13.4. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical/surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

**Life-threatening* is defined as an AE or suspected adverse reaction, which, in the view of either the investigator or sponsor, places the subject at immediate risk of death as it occurred. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected Adverse Event

An AE is considered "unexpected" if it is **not listed** in the Reference Safety Information section of the investigator brochure (IB) in effect at the time of event onset.

13.5. Pregnancy

Although pregnancy is not an AE, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female subject or the female partner of a male subject, must be followed to conclusion to determine their outcome and are considered immediately reportable events.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety within 24 hours of the investigator's awareness using the paper Pregnancy Report form. The Pregnancy Report Form shall be signed and dated by the investigator and submitted via email to CCI [redacted]

The investigator must follow the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc) and neonatal status up to 12 months postdelivery. An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE Report Form will be required.

13.6. Drug Abuse, Misuse, Overdose, and Medication Error

Occurrences of events of drug abuse, drug misuse, drug overdose, and medication error must be reported to Apellis Safety.

Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects.

Misuse: intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration and/or the indication(s) or not within the legal status of its supply.

Overdose: administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

Medication Error: an error made in prescribing, dispensing, administration and/or use of the study drug. Medication errors are reportable to the sponsor as defined below:

- The dispensing, administration, and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.

All AEs or SAEs associated with drug abuse, drug misuse, drug overdose, or medication error must be reported as appropriate.

14. DATA MANAGEMENT AND STATISTICAL METHODS

14.1. Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy.

Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

14.2. Clinical Data Management

Data are to be entered into a clinical database, as specified in the study-specific data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

14.3. Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. All statistical analyses will be performed using SAS (SAS Institute, Cary, NC, USA), version 9.3 or higher.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP for the final analysis will be finalized prior to final database lock and performing analyses to preserve the integrity of the statistical analysis and study conclusions.

14.4. Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

No interim analysis is planned. An external, independent data monitoring committee (DMC) will assess the safety/tolerability data of the study periodically.

14.5. Sample Size Justification

A total of 48 randomized subjects (32 subjects to pegcetacoplan and 16 subjects to SOC) are required to achieve 90% power, at the 5% significance level (2-sided), using a 2-group Fisher's exact test with unequal allocation 2:1 to treatment groups (pegcetacoplan and SOC). Calculation

assumes an increase of 45% in the proportion of subjects achieving Hb stabilization with pegcetacoplan, compared to SOC (ie, a change from 5% [no treatment] to 50% [pegcetacoplan]). With the same number of subjects and assuming an effect size of at least 1.2, the study will be at 96% for the LDH reduction endpoint.

To account for loss of power due to discontinuations, the study will attempt to randomize 54 subjects.

14.6. Preservation of Type 1 Error

To preserve the Type 1 error, a fixed sequence testing strategy will be used; hence, statistical significance with the first secondary endpoint (Week 26 Hb response in the absence of transfusion [Yes/No]) will only be concluded if statistical significance is achieved with the primary analysis of the co-primary endpoints.

The ordering of the secondary endpoints in this testing strategy will match the order in which they are presented in Secondary Efficacy Endpoints (see Section 7.2).

14.7. Statistical Analysis Methodology

A formal SAP will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses (other than those described in this section) may be performed, if deemed appropriate and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the final study report.

All endpoints will be summarized by treatment group and, where appropriate, by visit. Continuous data will be summarized using descriptive statistics (eg, mean and standard deviation), and categorical data will be summarized using frequency tables (counts and percentages).

14.7.1. Analysis Sets

14.7.1.1. Screened Set

The screened set will include all subjects who signed the ICF. This set will be used only for the purpose of describing subject disposition.

14.7.1.2. Safety Set

The safety set will include all subjects who receive at least 1 dose of study medication (pegcetacoplan), and subjects who are randomized to SOC (excluding complement inhibitors). Subjects will be analyzed according to the treatment they received.

14.7.1.3. Intent-to-Treat (ITT) Set

The ITT set will include all randomized subjects. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

14.7.1.4. Modified Intent-To-Treat (mITT) Set

The mITT set will include all subjects in the ITT set who continue study treatment beyond Visit 4 (Week 4).

14.7.1.5. Per-Protocol Set

The PP set will include all subjects in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from the PP analysis set will be made and documented prior to database lock.

14.7.1.6. Pharmacokinetic (PK) Set

The PK population will include all subjects in the ITT set who receive pegcetacoplan and have at least 1 evaluable post-dose PK measurement.

14.7.1.7. Pharmacodynamic (PD) Set

The PD population will include all subjects in the ITT set who have at least 1 evaluable post-dose PD measurement.

14.7.1.8. Data Review for Analysis Sets

After all of the data have been verified/coded/entered into the database, a review will be performed. The purpose of this review will be to define the analysis sets. The review will also check the quality of the data, identifying outliers, and make decisions on how to deal with any data issues (eg, missing values, withdrawals, protocol deviations). After the preanalysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

14.7.2. Efficacy Analyses

The efficacy endpoints will primarily be evaluated with the ITT set. All statistical testing will be at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups will be accompanied by 2-sided 95% confidence intervals (CIs).

All possible efforts will be made to ensure that subjects complete all the required assessments. As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, different strategies will be applied to provide a balanced assessment of treatment efficacy.

Endpoints will be summarized and, where appropriate, plotted over time for each treatment group.

Baseline will be taken at Day 1 prior to the start of study treatment for subjects randomized to pegcetacoplan and at Day 1 for subjects randomized to SOC.

14.7.2.1. Primary Endpoints

The co-primary efficacy endpoints will be analyzed, based on the ITT set.

The co-primary efficacy endpoints are:

- Hemoglobin stabilization defined as avoidance of a > 1 g/dl decrease in Hb levels from baseline in the absence of transfusion through Week 26 (Yes/No)

AND

- Reduction in lactate dehydrogenase (LDH) level from baseline to Week 26

For the first co-primary endpoint, the number and percentage of subjects who achieve Hb stabilization will be computed for treatment groups and compared between treatment groups using a stratified Cochran-Mantel-Haenszel (CMH) chi-square test. The treatment difference in percentages and 95% CI for the difference will be presented using the stratified Miettinen-Nurminen method.

Subjects who receive a transfusion through Week 26 or withdraw from the study before providing primary efficacy assessment will be categorized as failing to achieve Hb stabilization.

The second co-primary endpoint, change from baseline to Week 26 in LDH, will be analyzed using mixed model for repeated measures (MMRM) with: the effects of treatment; stratification randomization; visit, visit-by-treatment interaction; baseline LDH level; and baseline LDH level-by-visit interaction using an unstructured covariance matrix. The difference between treatment groups will be estimated, along with its 95% CI and p-value.

All the subjects LDH levels prior to transfusion and/or switch to pegcetacoplan will included in the model.

As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, the following sensitivity and supportive analyses will be performed to evaluate the robustness of the results from the primary analysis methods:

- The first co-primary efficacy endpoint will also be analyzed using a logistic regression with the effects of treatment group and stratification factors included. The odds ratio of being an Hb stabilization achiever the pegcetacoplan versus SOC group and associated 95% CI will be estimated from the final model.
- The second co-primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model (ITT set) with a last observation carried forward (LOCF) approach for handling missing data. The ANCOVA model will include terms for treatment, stratification factors, and baseline LDH level.
- The second co-primary endpoint will be analyzed using an ANCOVA model (ITT set) with a best observation carried forward (BOCF) approach for handling missing data. The ANCOVA model will include terms for treatment, stratification factors, and baseline LDH level.
- Analyses will be repeated using the mITT and PP sets.

14.7.2.2. Secondary Endpoints

The secondary endpoints will be analyzed using the ITT set and will be repeated using the PP set.

Summary statistics by randomization strata and by treatment groups will presented at each assessment visit during the 26-week randomized treatment period.

Continuous endpoints will be analyzed using MMRM with the effects of: treatment; stratification factors; visit; visit-by-treatment interaction; the relevant baseline level; and the baseline level-by-visit interaction using an unstructured covariance matrix. The difference between treatment groups will be estimated, along with its 95% CI and p-value. If a subject receives a transfusion during his/her treatment period, the pretransfusion Hb values, reticulocyte values, and FACIT-Fatigue Scale score will be used in the model.

For categorical endpoints, the number and percentage of subjects will be tabulated by treatment group and compared between treatment groups using a stratified CMH chi-square test.

Kaplan-Meier plots will be presented for time-to-event endpoints for each treatment group, and survival estimates will be provided.

The number of units of PRBCs transfused will be compared between the treatment groups using a Wilcoxon rank-sum test. The difference between the medians will be estimated along with its 95% CI (stratified). Subjects who withdraw before Week 26 will have the number of units estimated from the duration that they were in the study (ie, number per week × 12). This equates to an analysis of the frequency of transfusions.

14.7.3. Safety Analyses

Safety analyses will be based on the safety set.

Safety measures assessed at study visits, including vital signs (temperature, systolic and diastolic blood pressures, pulse, and respiratory rate), clinical laboratory results, ECGs and anti-pegcetacoplan antibodies will be descriptively summarized by treatment group at baseline and for each postbaseline visit. Absolute values and changes from baseline will be summarized.

14.7.3.1. Adverse Events

Treatment-emergent adverse events are defined as those AEs that develop or worsen after the first dose of study medication and for up to 30 days beyond the last dose of study medication. The current version of MedDRA will be used to classify all AEs.

Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term, in accordance with MedDRA. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as possibly related to study treatment by the investigator. The number of subjects reporting SAEs will also be tabulated. Adverse-event summaries will be presented for each period of the study (randomized treatment and after early escape) separately, within each treatment group.

The number of subjects reporting thromboembolic events will be tabulated for each period of the study, separately, within each treatment group.

14.7.3.2. Clinical Laboratory Tests

Changes from baseline in laboratory will be summarized using descriptive statistics by treatment, visit, and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of pegcetacoplan.

Out-of-range values will be flagged in the data listings.

14.7.3.3. Vital Signs and ECGs

Changes from baseline in vital signs and ECG parameters will be summarized using descriptive statistics by treatment, visit, and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of pegcetacoplan.

Values of potential clinical significance (eg, increase in QTcF ≥30 ms from baseline) will be flagged in listings and summarized by treatment.

Electrocardiogram parameters will be analyzed using concentration effect models.

14.7.4. Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK set.

Concentrations will be summarized using descriptive statistics over time for the run-in period (all subjects) and the randomized treatment period (pegcetacoplan group).

Individual subject concentration-time data will be plotted against actual sampling time. Median profiles of the concentration-time data, using nominal sampling times, will also be presented. Both linear-linear and linear-log plots will be presented.

Population PK and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan Population PK/PD Analysis Plan. The methods will be based on the FDA Guidances for both Exposure-Response and Population Pharmacokinetics (FDA 1999; FDA 2003).

14.7.5. Pharmacodynamic Analyses

The PD endpoints will be evaluated using the PD set.

Absolute values, changes from baseline, and percent changes from baseline will be summarized using descriptive statistics over time for the run-in period (all subjects) and the randomized treatment period by treatment group.

Individual subject-time profiles will be plotted against actual sampling time. Median profiles over time, using nominal sampling time, will also be presented.

The PD endpoints will be compared between treatment groups using mixed effect repeated measures analyses.

14.7.6. Other Data Analyses

Demographic data, baseline characteristics, physical examination, concomitant medication, medical history data, and study medication exposure will be summarized by treatment group.

World Health Organization (WHO) and MedDRA coding dictionaries will be used for the concomitant medications and medical histories, respectively.

14.8. Direct Access to Source Data/Documents

The PI must maintain, at all times, the primary records (ie, source documents) of each subject's data for data verification. Examples of source documents are: medical records, laboratory reports, study drug records, and eCRFs that are used as the source.

The PI will permit study-related monitoring, audits, and inspections by the sponsor and/or its designee, IRB/IEC, and the regulatory agencies at any time during the study. The PI will ensure that the auditor is allowed direct access to the source data, medical records, eCRFs, and the Site's regulatory file for the study and any other pertinent information.

14.9. Quality Control and Quality Assurance

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. The PI, sponsor, and/or designee(s) are responsible for ensuring that the study staff receive appropriate training on the protocol, study procedures, and any other relevant information.

Quality assurance and quality control systems are implemented and maintained using written Investigative site, sponsor and/or designee 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, applicable regulatory requirement(s), and national and local laws, rules, and regulations.

Quality control checks will be applied at each stage of data handling (eg, edit checks) to ensure that all data are reliable and have been processed correctly.

14.9.1. Monitoring

On-site monitoring will be performed by the sponsor's designee for the duration of the study. The monitor will ensure that the study is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and applicable regulatory requirements. The monitor will verify the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The PI will provide direct access to source data/documents for study-related monitoring. It is important that the PI and the staff are available at these visits. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be documented in writing to the PI.

15. ETHICS

15.1. Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline (Guideline for Good Clinical Practice), E6, R2 (ICH GCP).

15.2. Institutional Review Board/Ethics Committee

The study protocol, any amendments to the protocol, the ICF, the IB, and other study-specific information will be reviewed and approved by the IRB/IEC. The study will not be initiated until the IRB/IEC has approved the protocol or a modification, thereof. All records pertaining to IRB/IEC submission and approval should be kept in the site's regulatory files and the sponsor's trial master file.

The IRB/IEC must be constituted and operate in accordance with the all applicable regulatory requirements.

15.3. Subject Information and Consent

The PI or appropriate designee is responsible for obtaining an informed consent. A written informed consent, in compliance with ICH Guideline E6, must be obtained from each subject prior to screening and enrollment or performing any study-related procedures.

The purpose of the study, the procedures to be carried out, and the potential hazards will be described to the subjects in nontechnical terms. The subject will be given sufficient time to consider the study's implications before deciding to participate in the study. The subject and/or legal guardian will be required to sign and date an ICF and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. The PI shall retain the original, signed informed consent for study participation in the subject's medical record and shall provide the subject and/or legal guardian with a copy of the signed consent.

If there are any changes/amendments to the approved protocol that may directly affect the subject's decision to continue participation in the study, the ICF shall be amended to incorporate the changes to the protocol and the subject must re-sign the IRB-/IEC-approved, amended ICF.

15.4. Confidentiality

Confidentiality of subject's information must be maintained in accordance with national and local privacy laws.

15.5. ClinicalTrials.gov

This study has been listed with ClinicalTrials.gov, as required.

15.6. Termination of Study

The sponsor reserves the right to suspend or discontinue this study for administrative and/or safety reasons, at any time. The PI reserves the right to discontinue dosing subjects, at any time,

for safety reasons, but should contact the sponsor prior to discontinuing a subject from pegcetacoplan.

15.7. Data Handling and Record Keeping

The PI must maintain all documentation related to this study. All essential documents (as defined in the ICH Guideline E6) and the data generated in connection with this study, together with the original copy of the final report, will be retained for at least 5 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor.

It is the responsibility of the sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

15.8. Protocol Amendments

Any amendments to the study protocol deemed necessary as the study progresses will be discussed between sponsor and the PI. The PI will not implement any changes to the protocol without an agreement by the sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazards to study subject or when the changes involve only logistical or administrative aspects of the study (eg, change in staff, telephone numbers).

Amendment(s) will be approved and signed off in the same way as the protocol.

15.9. Report Format

According to the ICH Harmonised Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.10. Finance and Insurance

Finance and insurance will be addressed in a Clinical Trial Agreement between the PI/Institution and the sponsor.

15.11. Publication Policy

The data generated for this study are considered confidential information and are the property of the sponsor. All study information provided to the PI and site personnel by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

Apellis will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner, regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Apellis adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is

done for large, multicenter Phase 2-4 and certain other studies, as determined by Apellis. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Apellis products or projects must undergo appropriate technical and intellectual property review, with Apellis agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the PI will own (or share with other authors) the copyright on his/her publications. To the extent that the PI has such sole, joint, or shared rights, the PI grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure, including: original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Apellis, the institution and PI shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

16. REFERENCES

DeZern AE, Dorr D, Brodsky RA. Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria. *Eur J Haematol*. 2013;90(1):16–24.

[FDA] Food and Drug Administration. Guidance for industry: population pharmacokinetics. Available at: https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf. 1999. Accessed 20 September 2018.

[FDA] Food and Drug Administration. Guidance for industry: exposure-response relationships – study design, data analysis, and regulatory applications. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf. 2003. Accessed: 20 September 2018.

[FDA] Food and Drug Administration. Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies. Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm227351.pdf. 2012. Accessed: 09 November 2018.

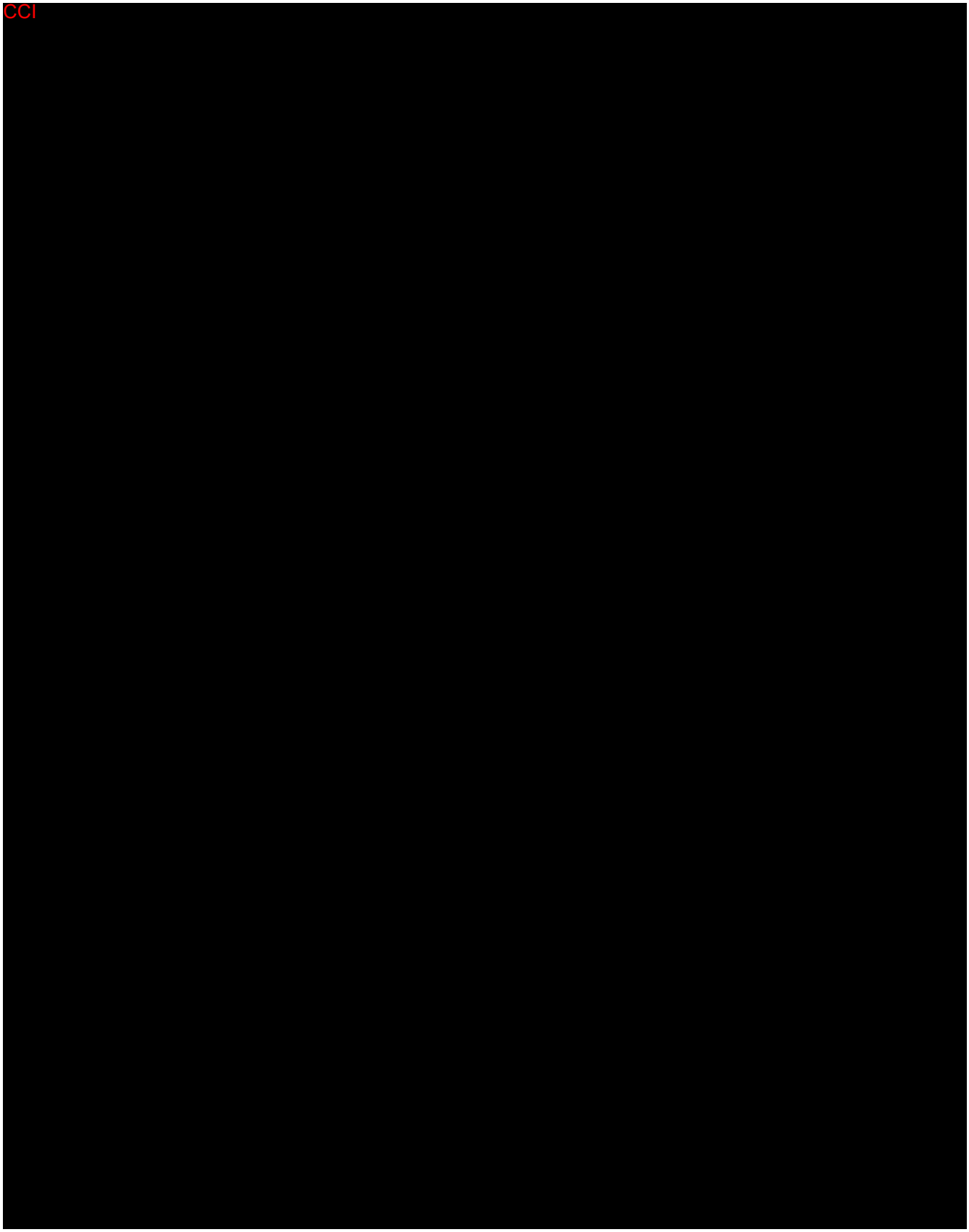
Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinet Pharmacodyn*. 2001;28(6):507-532.

Risitano AM, Notaro R, Marando L, et al. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. *Blood*. 2009;113(17):4094-4100.

17. APPENDICES

CCI

[redacted]


CCI

CCI

[redacted]

CCI

[redacted]

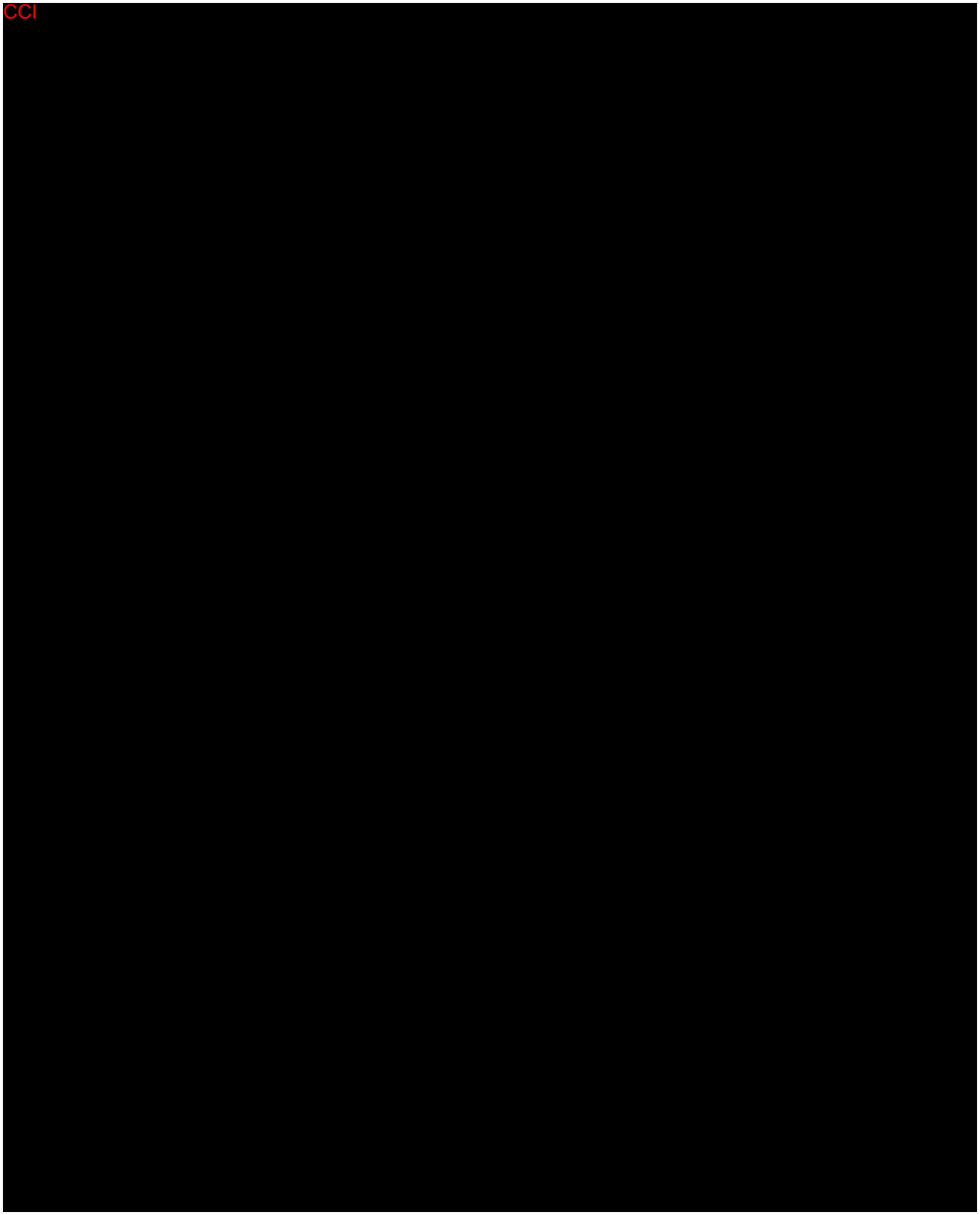
CCI

[redacted]

CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

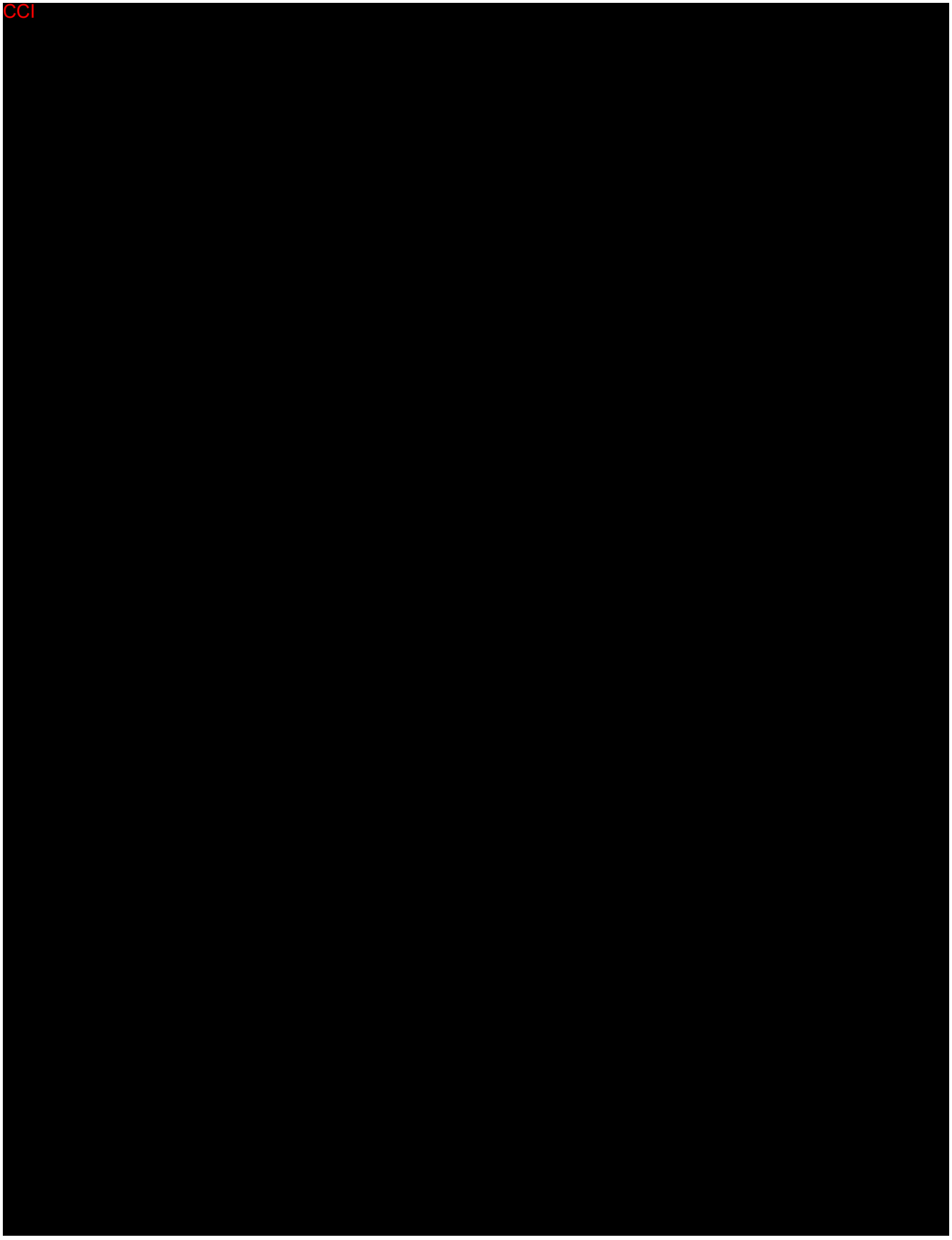
CCI

[redacted]

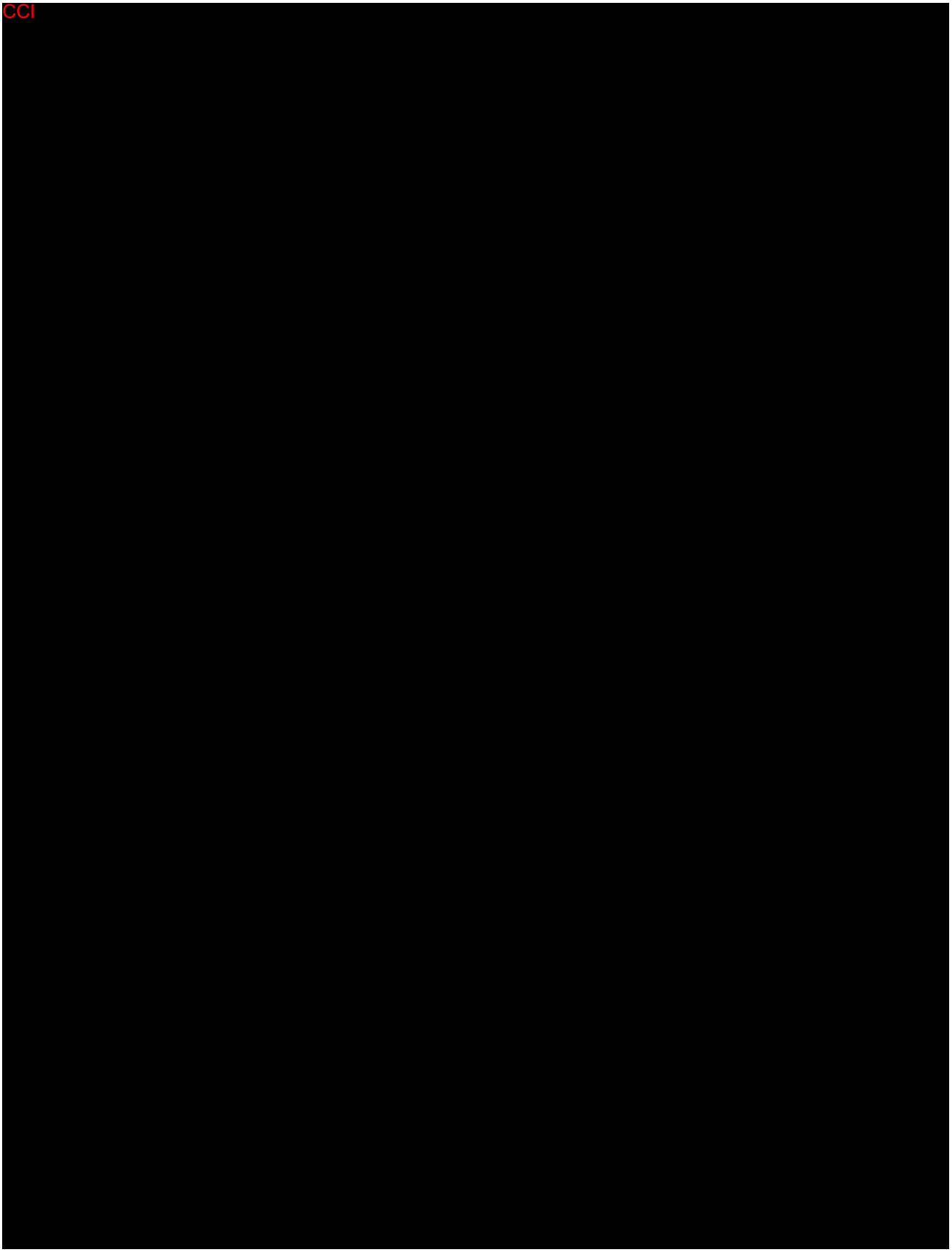
CCI

[redacted]

CCI



CCI



CCI

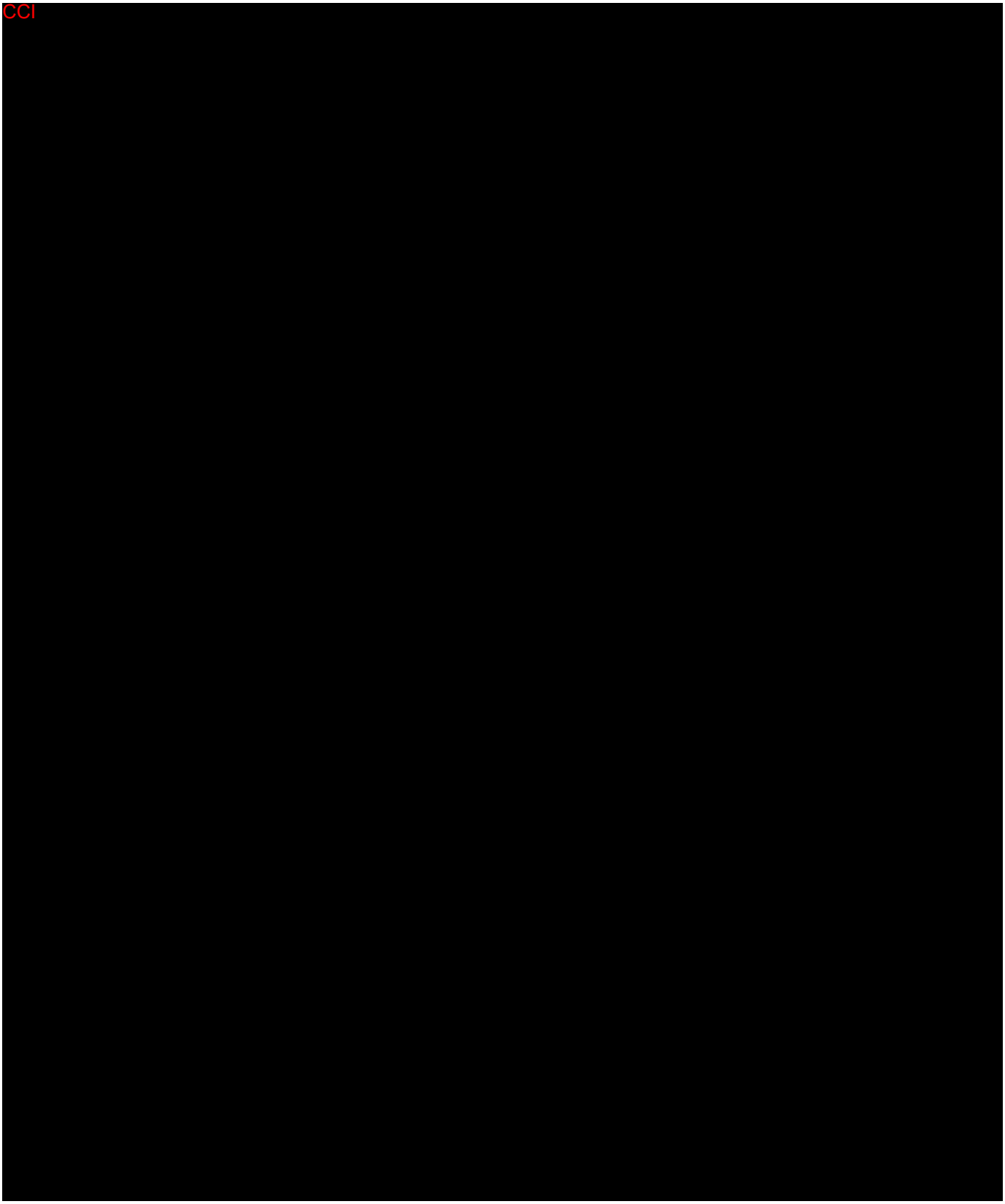
[redacted]

CCI

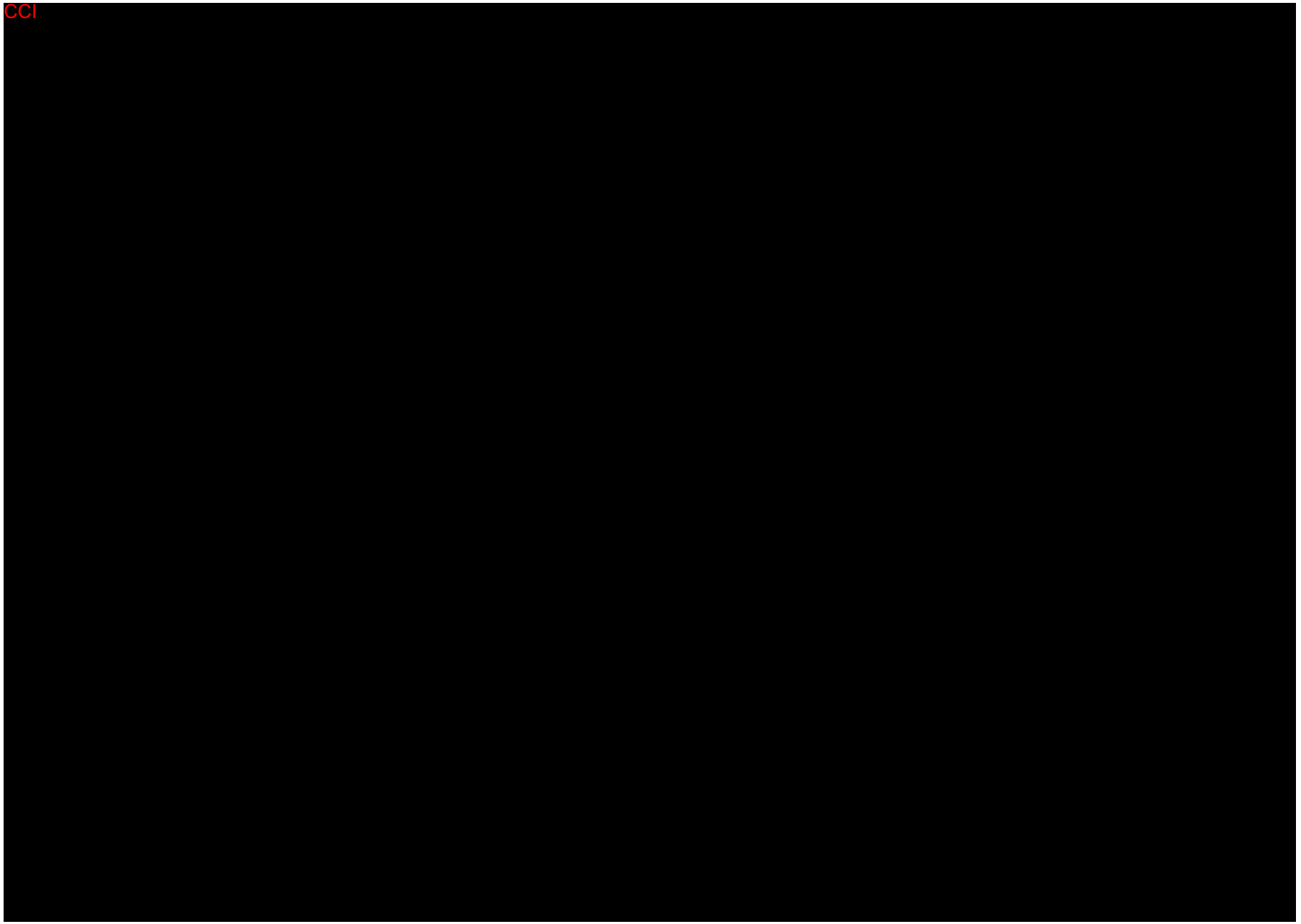
[redacted]

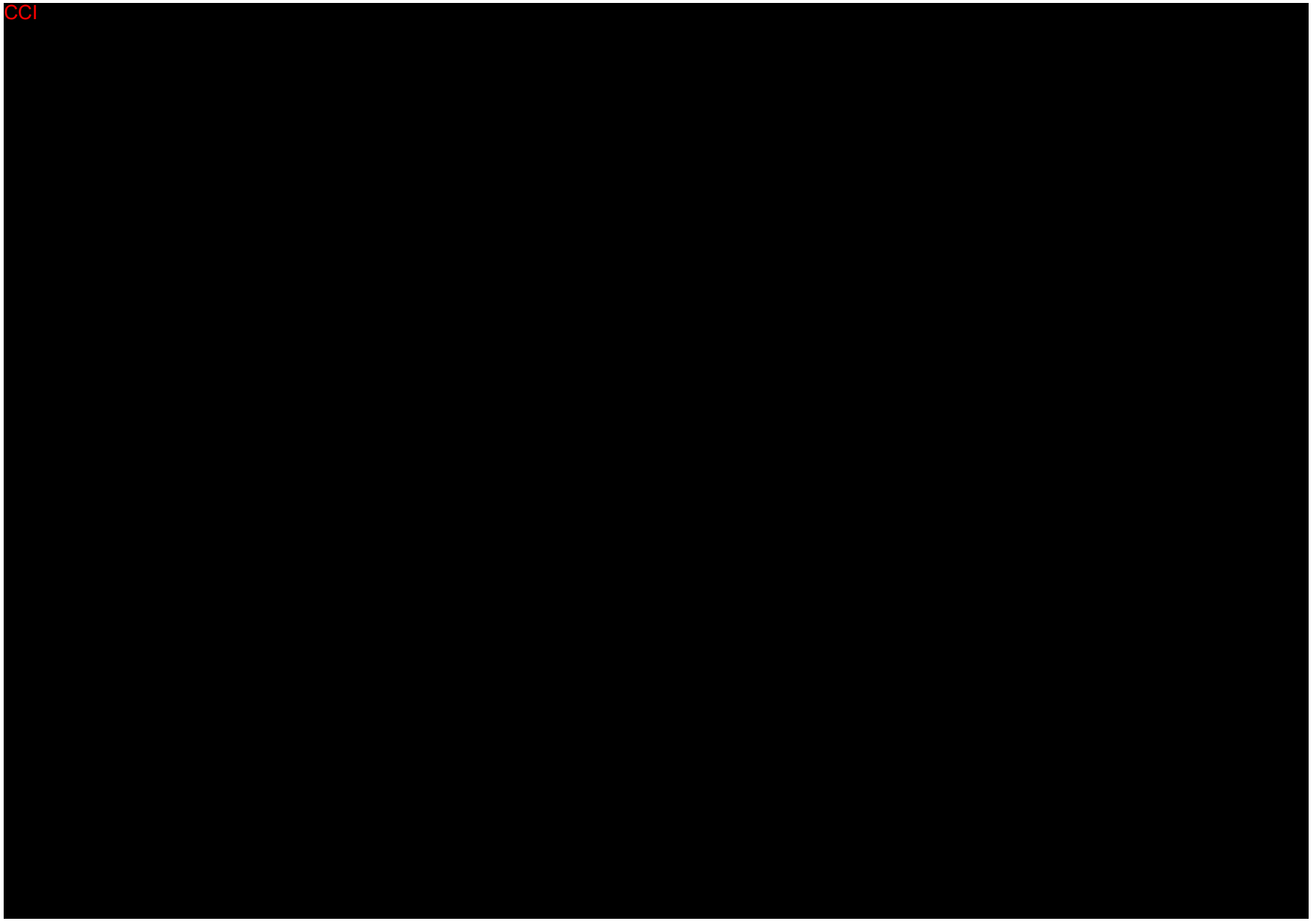
CCI

[redacted]

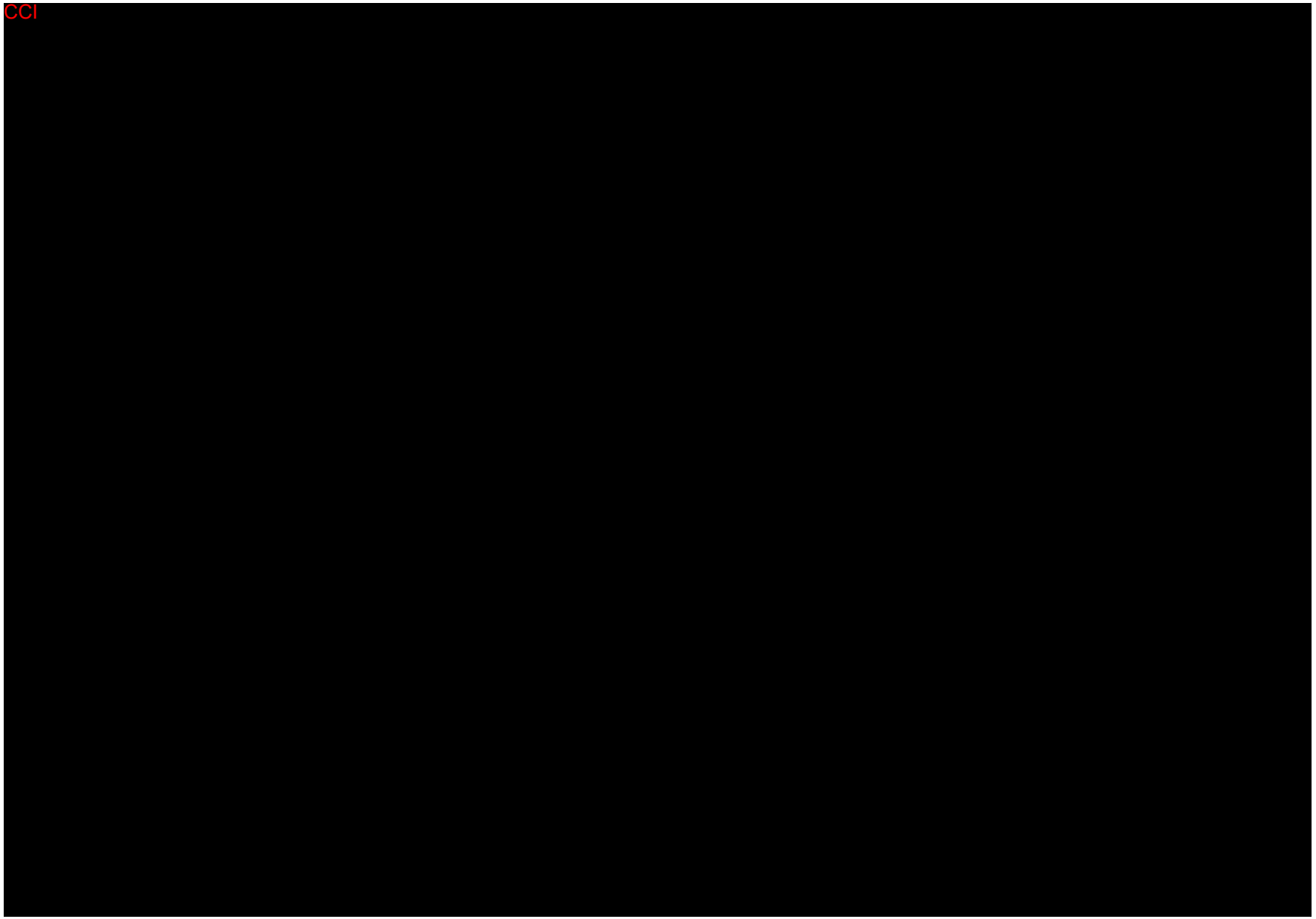

CCI

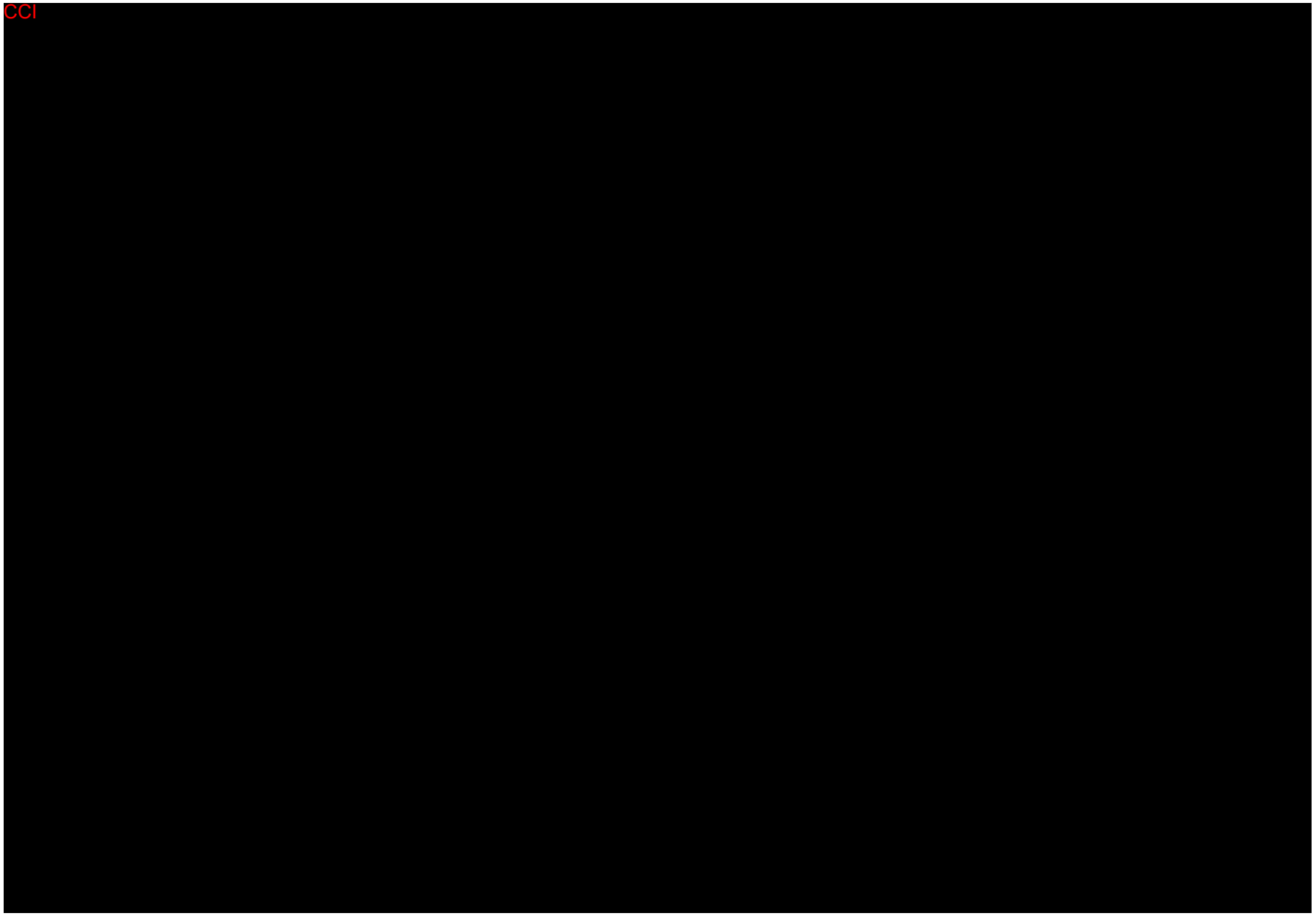

CCI


CCI

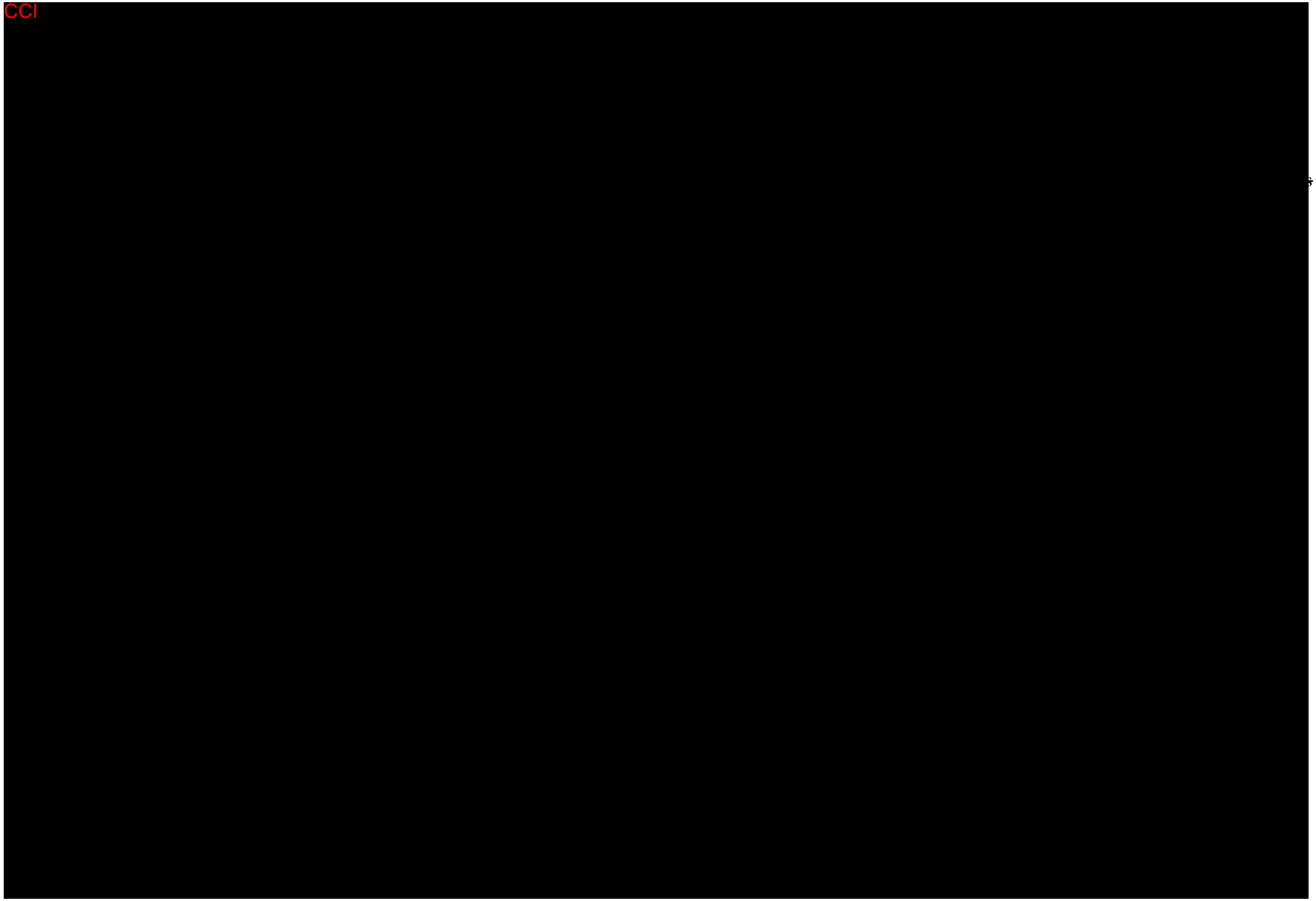

CCI

CCI




CCI

CCI



CCI