STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Cold Agglutinin Disease (CAD)
PROTOCOL (Version, Date):	Sobi.PEGCET-101 Version 5.0 13MAR2023
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STUDY PHASE:	Phase 3
SPONSOR:	Sobi
AUTHOR:	[redacted]
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Signature Page

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LIST OF ABBREVIATIONS

Abbreviation	Description
Ab	Antibodies
AE	Adverse Event
AIHA	Autoimmune Hemolytic Anemia
AR(1)	First order autoregressive
ARC	Absolute Reticulocyte Count
ATC	Anatomical Therapeutic Chemical
CAD	Cold Agglutinin Disease
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CM	Concomitant Medication
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DRM	Data Review Meeting
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	5-Level EuroQol 5-Dimension Score
FACT-An	Functional Assessment of Cancer Therapy – Anemia/Fatigue
Hb	Hemoglobin
ICE	Intercurrent Event
ICH	International Council for Harmonization
IgM	Cold antibodies
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology

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Abbreviation	Description
ITT	Intent to Treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat Set
MMRM	Mixed Model Repeated Measures
MNAR	Missing not at Random
NCS	Not Clinically Significant
PRBC	Packed Red Blood Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PP Set	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S.C.	Subcutaneous
SF-12	12-Item Short Form Survey
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
TLFs	Tables, Listings, and Figures
ULN	Upper Limit of Normal
WHO	World Health Organization

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1 PURPOSE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Sobi Study Sobi.PEGCET-101 and is based on protocol Version .0 (13 March 2023) and electronic case report form (eCRF) version 6.0 (15 August 2023).

The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

In the event of future amendments to the protocol, this SAP may need to be modified as necessary to account for changes relevant to the statistical analysis.

1.1 EARLY TERMINATION OF STUDY

A decision was made (effective on 10 January 2024) to terminate patient enrollment prior to reaching the planned number of patients. Patients already randomized and treated will continue treatment may continue until 10th of July 2024 Because of the early termination, the scope of analysis will be reduced. In general, all analyses of primary and secondary efficacy endpoints will be performed for Part A with the exception of supportive and sensitivity analyses.

- *Subgroup analyses will only be done for transfusions (≥1; 0) received during the 6 months prior to randomization (strata) and prior treatment with rituximab (yes/no) defined subgroups and only for primary and key secondary endpoints.*
- *Only the ITT population will be analysed – no PP or other populations as supportive/sensitivity analyses.*
- *No specific tables for Part B and C as previously planned – all visits in one table (descriptive for B and C as planned).*
- *Endpoints consisting of normalization and durability of response will not be analyzed beyond Part A.*

All safety data will be summarized as planned. The rest of this SAP reflects the full analysis which was planned prior to decision to terminate enrollment early. A detailed description of planned analyses which were not conducted will be contained in the clinical study report.

On FDA review of the SAP (submitted to the Agency on June 28, 2022 for IND 156993) comments were received including requests for additional sensitivity analyses. Because of the early termination, no sensitivity analyses will be performed.

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1.2 RESPONSIBLITIES

Allucent will perform the statistical analyses and is responsible for the production and quality control of all derived datasets and tables, listings, and figures (TLFs).

2 INTRODUCTION

Primary chronic CAD is an uncommon form of Autoimmune Hemolytic Anemia (AIHA) in which hemolysis is thought to be entirely complement-dependent. CAD accounts for about 15 % of AIHAs and is defined as an AIHA mediated by cold agglutinins, without any obvious underlying disease such as aggressive lymphoma, other overt malignancies or specific infections. Cold agglutinins are autoantibodies that can agglutinate red blood cells (RBCs) at an optimum temperature of 3 to 4 ºC.

Cold antibodies (IgM) temporarily bind to the RBC membrane, which in turn activates complement, and leads to the deposition of C3b on the cell surface. These C3b-coated RBCs are cleared slowly by the macrophages of the liver through extravascular hemolysis. To a lesser extent, the complete complement cascade may be activated at the cell surface, ultimately resulting in the insertion of membrane attack complex C5b to C9 and intravascular hemolysis.

Various therapeutic approaches have been used in treating these patients, including RBC transfusions, off-label use of rituximab, rituximab-based combination therapy or bortezomib. However, a substantial unmet medical need still exists.

2.1 STUDY OBJECTIVES

Primary objective: To demonstrate the efficacy of twice-weekly subcutaneous (s.c.) 1080-mg infusions of pegcetacoplan compared with that of placebo in patients with CAD.

Secondary objectives: *Key secondary objectives:*

- To demonstrate the effect of pegcetacoplan on the number of packed red blood cell (PRBC) transfusions in patients with CAD.
- To demonstrate the effect of pegcetacoplan on health-related quality of life in patients with CAD.

Other secondary objectives:

- To assess the effect of pegcetacoplan on clinical laboratory markers of hemolysis and transfusion dependence in patients with CAD.
- To determine the durability of response in patients with CAD receiving pegcetacoplan.
- To assess tolerability, safety and immunogenicity of pegcetacoplan in patients with CAD.

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- To describe long-term effect of pegcetacoplan in patients with CAD.

Exploratory objectives:

- To evaluate the pharmacokinetics (PK) of pegcetacoplan following twice-weekly s.c. infusions.
- To evaluate the effect of pegcetacoplan on complement biomarkers.

2.2 TRIAL DESCRIPTION

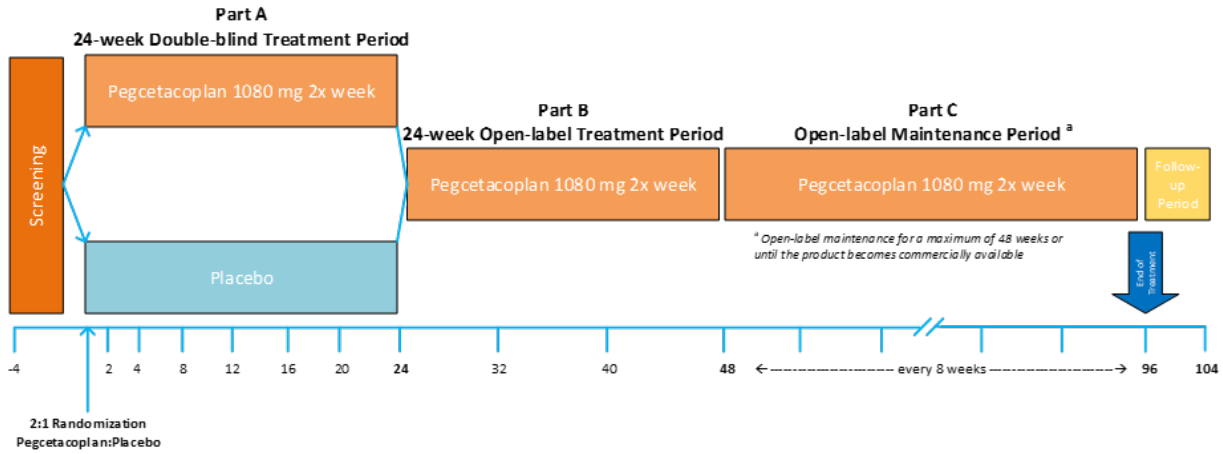
This is a phase 3, randomized, double-blind, placebo-controlled multicenter study of s.c. pegcetacoplan 1080 mg twice weekly or placebo conducted in 57 patients with CAD.

Patients will be randomized in a ratio of 2:1 to receive either pegcetacoplan or placebo, respectively. The randomization will be stratified by transfusion history (number of transfusions during the 6-month period prior to randomization ≥ 1; 0).

The planned length of participation in the study for each patient is a maximum of 110 weeks. This study will consist of 5 periods:

- Screening period: up to 4 weeks (may be extended by up to 2 additional weeks).
- Double-blind treatment period: 24 weeks (Part A).
- Open-label treatment period: 24 weeks (Part B).
- Open-label maintenance period: up to additional 48 weeks or until the product becomes commercially available (Part C).
- Follow-up period: 8 weeks.

Additional details about the study procedures for each study period can be found in the protocol. The overall study design is illustrated in the figure below.



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2.3 STUDY SAMPLE SIZE DETERMINATION

The primary endpoint is response to treatment at Week 24. Under the assumption that the response rate is 55% for pegcetacoplan and 10 % in placebo, 54 patients (36 treated with pegcetacoplan and 18 with placebo) are required to reject the null hypothesis of no difference between the treatment groups at a significance level of 5 % and a power of 90 % using a 2-sided Fisher's exact test with a 2:1 allocation to treatment groups. To account for a maximum of 5% non-evaluable patients (i.e., potential missing assessments and drop out prior to first dose of investigational medicinal product (IMP), 57 patients will be randomized.

2.4 TREATMENT ASSIGNMENT AND BLINDING

Randomization will occur through the interactive response technology (IRT) system.

All patients who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study after eligibility review by the study medical monitor, until 57 patients have been enrolled in the study. Patients will be randomly assigned through the IRT system to either pegcetacoplan or placebo in a 2:1 ratio. The randomization will be stratified by transfusion history (number of transfusions during the 6-month period prior to randomization >=1;0).

Blinded IMP supplies labeled with kit numbers and other information as per Master Label and in line with regulatory requirements will be provided to each study site. IMP dosing will be initiated at the site after randomization. At each visit when IMP is administered and dispensed, the study staff will contact the IRT to obtain appropriate kit numbers.

3 ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary endpoint is response to treatment at Week 24.

Response is defined as:

- An increase in hemoglobin (Hb) of ≥ 1.5 g/dL from Baseline or Hb normalization at Week 16; AND
- Maintenance of this effect from Week 16 to Week 24; AND
- The absence of PRBC transfusions (between Week 5 and Week 24).

Note: Hb normalization is defined as within normal range (between the defined upper and lower limits of normal [ULN and LLN]), as set by the testing laboratory.

Maintenance of effect is defined as the average change from Baseline in Hb of Week 16, Week 20 and Week 24 ≥ 1.5 g/dL or the average Hb at these time points within normal range.

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3.2 SECONDARY ENDPOINTS

3.2.1 Key Secondary Efficacy Endpoints

The key secondary endpoints are as follows.

- Change from Baseline to Week 24 in Hb level.
- Transfusion avoidance (Yes/No) from Week 5 to Week 24.
- Change from Baseline to Week 24 in the Functional Assessment of Cancer Therapy–Anemia/Fatigue (FACT-An) score.

3.2.2 Secondary Efficacy Endpoints

The secondary endpoints are as follows.

Part A:

- Number of PRBC transfusions from Week 5 to Week 24.
- Change from Baseline to Week 24 in the following:
  - Lactate dehydrogenase (LDH) level.
  - Haptoglobin level.
  - Indirect bilirubin level.
  - Absolute reticulocyte counts (ARC).
  - D-dimer level.
- Normalization of markers of hemolysis at Week 24, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Time to first normalization from Baseline to Week 24 for the following:
  - Hb level.
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Number of PRBC units transfused from Week 5 to Week 24.
- Change from Baseline to Week 24 in the following:
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale score of the FACT-An scale.
  - 12-Item Short Form Survey (SF-12) score.
  - 5-Level EuroQol 5-Dimension (EQ-5D-5L) score.

Part B:

- Change from Baseline to Week 48 in the following:
  - Hb level.
  - LDH level.
  - Haptoglobin level.

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  - Indirect bilirubin level.
  - ARC.
  - D-dimer level.
- Normalization of markers of hemolysis at Week 48, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Durability of response for patients randomized to pegcetacoplan who achieve the primary endpoint at Week 24.
- Change from Baseline to Week 48 in the following:
  - FACT-An score.
  - FACIT-F subscale score of the FACT-An scale.
  - SF-12 score.
  - EQ-5D-5L score.

3.3 TERTIARY EFFICACY ENDPOINTS

The tertiary efficacy endpoints are as presented below.

Part C:

- Change from Baseline to Week 96 in the following:
  - Hb level.
  - LDH level.
  - Haptoglobin level.
  - Indirect bilirubin level.
  - ARC.
  - D-dimer level.
- Normalization of markers of hemolysis at Week 96, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Change from Baseline to Week 96 in the following:
  - FACT-An score.
  - FACIT-F subscale score of the FACT-An scale.
  - SF-12 score.
  - EQ-5D-5L score.

3.4 SAFETY ENDPOINTS

The safety endpoints are as shown below.

- Adverse events (AEs) up to 8 weeks after end of treatment (EOT).
- Serious adverse events (SAEs) up to 8 weeks after EOT.

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- AEs leading to premature discontinuation of the IMP.
- Clinically meaningful laboratory abnormalities up to 8 weeks after EOT.
- Changes from Baseline in laboratory parameters markers.
- Clinically meaningful electrocardiogram (ECG) abnormalities up to 8 weeks after EOT.
- Clinically meaningful changes in vital signs from Baseline up to 8 weeks after EOT.
- Immunogenicity: presence of antibodies (Ab) to polyethylene glycol and pegcetacoplan peptide throughout treatment and follow-up periods.

3.5 EXPLORATORY ENDPOINTS

The exploratory endpoints are as shown below.

- Pegcetacoplan pharmacokinetic concentrations at Week 24 and Week 48.
- Changes from Baseline to Week 24 and Week 48 in complement biomarkers (C3 levels, functional assays for classical and alternative complement pathways).
- Changes from Baseline through Week 24 and Week 48 in C3 deposition on RBCs by flow cytometry
- Changes from Baseline to Week 24 and Week 48 in inflammatory biomarkers: TNFα, IL-6, IL-10, IFNγ and IL-1β.
- Normalization of haptoglobin level at Week 24, Week 48 and Week 96.
- Time to first normalization from Baseline to Week 24 for haptoglobin level.

Population PK and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan Population PK/pharmacodynamic (PD) Analysis Plan and reported in a separate population PK report.

4 ANALYSIS POPULATIONS

4.1 SCREENED SET

The screened set will include all patients who provide written informed consent. This set will be used only for the purpose of describing patient disposition.

4.2 SAFETY SET

The safety set will include all patients who receive at least 1 dose of IMP. Patients will be analyzed according to the treatment they received. This set will be used for all safety analysis.

4.3 INTENT-TO-TREAT SET

The intent-to-treat (ITT) set will include all randomized patients. Patients will be analyzed according to their assigned treatment, regardless of the treatment actually received. The ITT set will be used for all efficacy analysis.

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4.4 PER-PROTOCOL SET

The per-protocol (PP) set will include all patients 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 patients from the PP analysis set will be made and documented prior to database lock at a blinded data review meeting.

4.5 PHARMACOKINETIC SET

The PK set will include all patients in the ITT set who receive IMP and have at least 1 evaluable post dose PK measurement.

4.6 PHARMACODYNAMIC SET

The PD set will include all patients in the ITT set who receive IMP and have at least 1 evaluable post dose PD measurement.

5 GENERAL ASPECTS FOR STATISTICAL ANALYSES

5.1 GENERAL METHODS

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).
- Categorical variables will be summarized using the number of observations (n), frequency and percentage of patients. All percentages will be presented as 1-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100 % and percentages will not be presented for zero frequencies.
- Continuous variables and ordered categorical data will be summarized using the number of patients with evaluable data, mean, standard deviation (SD), geometric mean (where appropriate), median, first and third quartiles, minimum and maximum. The same precision as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD. For ordered categorical data and nominal data, absolute counts and relative frequencies (in %) will be calculated.
- Lower and upper bound values for the CIs will be reported to 2 more decimal places than the raw data.
- All statistical hypothesis tests and confidence intervals will be 2-sided, using a type I error rate of 0.050.
- Unless stated otherwise, the percentages will be based on the number of non-missing observations. The column header will still contain the number of patients in the treatment group. There will be a row for the number of non-missing observations in the table (at each time point, if required) for each variable being summarized.
- Any calculated p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as ‘p<0.001’ and p-values greater than 0.999 will be presented as ‘p>0.999’.
- All collected patient data and relevant summaries and derivations will be included in listings and sorted by treatment group, Subject ID, and visit, as applicable, for all randomized patients.

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- All TLFs will include footers that identify the name of the program that created the output, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

5.2 KEY DEFINITIONS AND CONVENTIONS

5.2.1 Baseline values

The baseline value for any parameter will be defined as the last measurement prior to dosing on Day 1 of Part A of the study. If there are both central and local laboratory results available from samples collected at the same date and time, the central laboratory result will be selected for baseline. Baseline values can be obtained during screening or at visit 2 (before first dose). For ePRO questionnaires (FACT-An, SF-12, and EQ-5D-5L), baseline is collected prior to dosing but there are no times collected. When these assessments are performed on the date of first dose, the assessment will be considered as pre-dose for identification of a baseline.

5.2.2 Missing data

In general, missing values will not be imputed for the analysis unless otherwise stated in the SAP or dataset specifications. Missing dates will not be imputed. However, if there is a missing start date for an AE, the AE will be considered treatment emergent. For concomitant medications (CM), the CM will be regarded as concomitant if the start date is missing. In the case of missing end dates for AEs and CMs, the events will be considered as ongoing at study end/end of Parts A, B, or C.

5.2.3 Visit Windowing

Data will be summarized and analyzed based on the list of visits specified in table below. The relative day of each assessment [(date of assessment) – (date of first dose) +1] will be calculated for post randomization while the relative day of each assessment will be calculated as [(date of assessment) – (date of first dose)] for prior to dosing. The relative day will be used to assign analysis visits following the table below.

Planned or nominal visits as recorded in the eCRF data will be considered first. Only if there is no planned visit or nominal visit recorded in the eCRF (or a planned visit contains missing data) unscheduled visits will be considered. Early termination visits will be treated like unscheduled visits and assigned to scheduled visits based on windows.

If more than 1 record is within the same analysis visit window, the record closest to the target day (the day of the planned visit according to protocol schedule of assessments) will be used in the analysis. If 2 records are tied for being closest to the target day, the earlier record will be used in the analysis. If there are both central and local laboratory results available from samples collected at the same date and time, the central laboratory result will be selected for the visit. If more than one assessment falls within the same defined window, the assessment closest to the target day with non-missing data will be considered for analysis.

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If no planned, unscheduled, or early termination visit is within the analysis window the data for the visit will remain as missing.

NOTE: Visits can only be assigned within periods. A visit in the double-blind treatment period (Part A) can only be assigned to Part A and a visit in the open-label treatment period (Part B) can never be assigned to Part A. However, visits in Part B can be mapped to Part C and visits in Part C can be mapped to Part B as these periods are both open label. Since Week 24 visit is both the end of Part A and the start of dosing in Part B, assessments prior to OLE dosing at the Week 24 visit will be mapped to Part A. Assessments after the start of dosing during OLE will be mapped to Part B.

Period	**Visit**	**Target Day**	**Analysis Window**	**Interval**
Screening	Screening	-28 – - 1	< 1	NA
Double-blind treatment period (Part A)	Day 1	1	1	1
	Week 1	8	2–11	10
	Week 2	15	12–21	10
	Week 4	29	22* – 43	22
	Week 8	57	44 – 71	28
	Week 12	85	72 – 99	28
	Week 16	113	100 – 127	28
	Week 20	141	128 - 155	28
	Week 24	169	156 - 197	42
Open label treatment period (Part B)	Week 32	225	198 - 253	84
	Week 40	281	254 - 309	84
	Week 48	337	310 - 365	84
Open label maintenance period (Part C)	Week 56	393	366 - 421	84
	Week 64	449	422 - 477	84
	Week 72	505	478 - 533	84
	Week 80	561	534 - 589	84
	Week 88	617	590 - 645	84
EOT	Week 96	673	N/A	N/A
EOS	Week 104	729	N/A	N/A
	* Manually adjusted to allow +/-7 at Week 4 visit as allowed in protocol			

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6 STUDY SUMMARIES

6.1 DISPOSITION OF PATIENTS

Summary statistics will tabulate the number and percentage of patients who are screened, screen failures, randomized, received at least 1 dose of study treatment, who completed the study, who prematurely discontinued the study treatment along with associated reasons and who prematurely terminated the study along with associated reasons. This table will also show the number of patients who completed and discontinued each part of the study. The number and percentage of patients included in each of the analysis populations will be presented. The number of randomized patients in each group will be used as the denominator to calculate percentages. The disposition table will be based on all screened patients.

Patient disposition data listings will be presented.

6.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data as collected on the demographics eCRF page will be summarized. The demographic summary table is expected to present information such as age, race, ethnicity, sex, and other baseline characteristics.

The demographic and baseline characteristics table will be based on the safety set. Patient demographic data listings will be presented.

6.3 MEDICAL HISTORY

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the patient's preexisting conditions, including all prior significant illnesses, up to and including 1 year before screening.

6.3.1 Targeted Medical History

A summary table will be shown to present data from the targeted medical history eCRF page. This will include the following.

- Time since diagnosis (missing month and day will be imputed to July 1, missing day only will be imputed to first of the month)
- Diagnostic criteria
- Presence of Symptoms
- Prior hospitalization due to CAD
- Prior hematological malignancy history
- Prior non-malignant hematological disease
- Prior thromboembolic history
- Prior rituximab-based regimen
- Prior transfusions in the 6 months prior to randomization

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6.3.2 Medical History other than CAD

A summary table of medical history on the medical history eCRF page will be shown.

Medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Summary tables of the number and percentage of patients with medical history by system organ class (SOC) and preferred term (PT) will be produced for patients in the safety set. Medical history will be sorted in descending order of frequency in the pegcetacoplan group. For the summary tables, a patient may appear more than once if they have more than 1 medical history finding coded under different SOC terms or more than 1 medical history finding with a different PT under the same SOC term. However, the patient will be counted only once in each SOC.

A patient medical history listing with coded SOC and PT along with verbatim eCRF term will also be provided.

6.3.3 Alcohol Consumption and Smoking History

A summary table will be shown to present data from the alcohol consumption and smoking history eCRF page.

6.3.4 Bone Marrow Biopsy History

A summary table will be shown to present data from the bone marrow biopsy eCRF page including MYD88 mutation test result and presented in a listing.

6.4 PRIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

6.4.1 PRIOR AND CONCOMITANT MEDICATIONS

Separate summary tables will be provided for prior and concomitant medications in the safety set, presenting the number and percentage of patients by each treatment group.

All prior and concomitant medications will be coded using the latest version of World Health Organization drug dictionary (WHO Drug Global).

Medications will be presented by ATC level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with numbers and percentages by treatment group and overall. A patient who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification.

In the summary tables, prior medications and concomitant medications will be presented by decreasing frequency of patients overall within each ATC level 2 class and then similarly by decreasing frequency of patients overall within each ATC level 5 class. In cases of ATC level 2 classes or ATC level 5 classes with equal frequencies, medications will be sorted alphabetically.

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Prior medications will be defined as those medications administered within 12 weeks prior to the time of informed consent. Concomitant medications will be defined as those medications taken following the time of informed consent.

Hence medications started before informed consent but continuing after will be considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

For the purposes of identifying prohibited medications, medical judgment will be involved in interpreting partial dates, if any.
All prior and concomitant medications will be listed.

6.4.2 CONCOMITANT PROCEDURES

Prior and concomitant procedures will be presented in a summary table with numbers and percentages of patients by procedure.

Prior procedures will be defined as those procedures performed within 12 weeks prior to the time of informed consent. Concomitant procedures will be defined as those procedures performed following the time of informed consent.

All prior and concomitant procedures will be listed.

6.5 PROPHYLATIC ANTIBIOTICS, PRIOR VACCINES AND PRIOR CAD THERAPY

Prophylactic antibiotics taken after first dose of study drug as captured on the prophylactic eCRF page will be summarized in a table and listed.

Prior vaccines, as recorded on the prior vaccination eCRF page, will be summarized in a table and listed.

Prior CAD therapy, as recorded on the prior CAD therapy eCRF page, will be summarized in a table and listed.

6.6 PROTOCOL DEVIATIONS

A summary table of protocol deviations will be provided and a listing of all protocol deviations by patient will be provided.

Protocol deviations that may significantly impact the quality (i.e., completeness, accuracy, and reliability) or integrity of key trial data will lead to exclusion of the patient from the PP set. Final decisions about protocol deviations that may lead to exclusion from the PP set will be made prior to database lock at a blinded data review meeting.

Examples of such protocol deviations include but is not limited to:

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- Non-compliance with study drug (less than 80 % of planned infusions)
- Not fulfilling the CAD diagnostic criteria at study entry
- Use of medication that can influence the efficacy endpoints (for example medications used outside of the definition of permitted concomitant medication as in the protocol)
    - Note: Prohibited medication as defined in the protocol is not to be considered a protocol deviation to exclude a patient from the PP, these are handled as intercurrent events (ICEs)

6.7 PHYSICAL EXAMINATIONS

Physical examinations will be described in a data listing.

6.8 TREATMENT COMPLIANCE AND EXPOSURE

Definitions of exposure variables are provided below.

Variables	**Definitions**
Duration of treatment (days)	Date of last dose of treatment – date of first dose of treatment +1
Study treatment compliance (%)	100 * (total number of infusions) / (total number of infusions planned to be taken). The total number of infusions planned to be taken will be calculated as 2 times the number of weeks a patient is on treatment. It is noted that the number of weeks a patient is on treatment will be estimated as (date of EOT visit– date of first treatment +1)/7 rounded up to next integer.

A compliance and exposure summary table will be presented that summarizes duration of treatment, study treatment compliance, and number of infusions received for patients in the safety set.

The number and percentage of patients who had a percentage of drug compliance range by increment of 10 % (≥ 80 % to 90 % and ≥ 90 % to ≤ 100 %) will be presented in a table by treatment group.

The following parameters will be calculated and presented using the safety set:

- Total dose administered (mg)
- Duration of treatment (days)
- Number and percentage of patients who received infusions
    - Number and percentage of patients with all infusions completed

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  - Number and percentage of patients with any infusion interrupted
- Total number of infusions
- Number and percentage of infusions completed
- Number and percentage of infusions interrupted

Duration of treatment, study treatment compliance, and number of infusions will also be presented in a listing.

7 STUDY ENDPOINT ANALYSES

7.1 PRIMARY ENDPOINT ANALYSIS

The primary endpoint is response to treatment at Week 24, with response defined as:

- An increase in Hb of ≥ 1.5 g/dL from Baseline or Hb normalization at Week 16; AND
- Maintenance of this effect from Week 16 to Week 24; AND
- The absence of PRBC transfusions (between Week 5 and Week 24)

Note: Hb normalization is defined as within normal range (≤ the ULN and ≥ the LLN, as set by the testing laboratory reference ranges. Hb will be assessed locally.
Maintenance of effect is defined as the average change from Baseline in Hb of Week 16, Week 20 and Week 24 ≥ 1.5 g/dL or the average Hb at these time points within normal range.

If response can't be evaluated (Hb at Week 16 and/or at Week 24 is missing) the patient will be considered to be a non-responder. If data at Week 20 is missing, the average of Week 16 and Week 24 will be used to calculate maintenance of effect.
The absence of PRBC transfusions will be assessed from Day 29 and until the end of the double-blind period (Week 24 or early withdrawal).

The primary analysis will be conducted on the ITT.

The estimand will be a composite where patients having an ICE will be considered as non-responders. The ICEs of interest are:

- Withdrawal from treatment or lost to follow-up before end of the double-blind period
- Use of prohibited medications (rituximab alone or in combination, any other complement inhibitor, any other investigational drug and plasma exchange.).

The number and percentage of patients who respond will be tabulated by treatment group and compared between treatment groups using an exact Cochran-Mantel-Haenszel (CMH) test stratified for the criterion used for stratification of randomization (>=1/0 transfusions during the 6-month period prior to randomization). The odds ratio of being a responder for the pegcetacoplan treatment group versus the placebo group and associated exact 95% CI and p-

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value will be provided. The responder rate, difference between treatment groups and 95% CI will also be reported.

As supportive analyses, the above will be repeated using the PP set and mITT set.

7.1.1 Subgroup analyses

Subgroup analyses on the primary endpoint will be conducted for:

- The strata with ≥ 1 / 0 transfusions during the 6 months prior to randomization. Fisher's exact test will be used for this subgroup analysis.
- The subgroups of patients previously treated with rituximab / rituximab-naïve patients.

Baseline will be taken as the last measurement prior to the first dose of IMP. All efficacy data will be listed.

7.2 KEY SECONDARY EFFICACY ENDPOINT ANALYSES

The key secondary efficacy analyses in this section will be analyzed based on the ITT.

To preserve the Type 1 error, a fixed-sequence testing strategy will be used; hence, statistical significance with the first key secondary endpoint will only be concluded if statistical significance is achieved with the primary analysis of the primary endpoint. The ordering of the key secondary endpoints in this testing strategy will be in the following order:

- Change from Baseline to Week 24 in Hb level
- Transfusion avoidance (Yes/No) from Week 5 to Week 24
- Change from Baseline to Week 24 in the FACT-An score

The hierarchical testing will be applied to the primary and key secondary endpoints, no further multiplicity control will be applied.

7.2.1 Subgroup analyses

For all key secondary endpoints, subgroup analyses will be presented for the following subgroups:

- The strata with ≥ 1 / 0 transfusions during the 6 months prior to randomization.
- The subgroups of patients previously treated with rituximab /rituximab-naïve patients.

For continuous endpoints the same MMRM model will be used for analysis except for omitting strata from the model. For transfusion avoidance Fisher's exact test will be used.

7.2.2 Change from Baseline to Week 24 in Hb level

The ICEs for the change from Baseline to Week 24 in Hb analysis, and their associated strategies to handle them, will be as follows:

- Withdrawal from treatment or lost to follow-up before end of the double-blind period (all measurements after withdrawal or lost to follow up will be set to missing);
- Use of prohibited medications (all measurements after prohibited medication start date will be set to missing)

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- Transfusion from week 5 to week 24 (all measurements after transfusion will be set to missing)

The change from Baseline to Week 24 in Hb will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and Hb level at Baseline as covariate using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom.

This MMRM analysis will implicitly impute data that was set to missing after an ICE resulting in a hypothetical strategy for handling the ICEs. Additional summary tables of change from baseline irrespective of ICEs will be created for hemoglobin with no MMRM.

Should the model fail to converge with an unstructured covariance matrix, other covariance structures will be explored (unstructured will be attempted first, followed by compound symmetry, followed by AR(1) if needed). The difference between treatment groups will be estimated, along with its 95% CI and p-value.

7.2.3 Transfusion avoidance (Yes/No) from Week 5 to Week 24

Transfusion avoidance (Yes/No) from Week 5 to Week 24 (Day 29 until end of double-blind period, which is Week 24 or early withdrawal) will be tabulated by treatment group and compared between treatment groups using an exact CMH test stratified for the criterion used for randomization stratification (>=1/0 transfusions during the 6-month period prior to randomization). The odds ratio of showing transfusion avoidance from Week 5 to Week 24 for the pegcetacoplan treatment group versus the placebo group and associated 95% CI will be provided.

The composite strategy will be used as the estimand where patients meeting any of the ICEs will be considered as non-responders (transfusion avoidance=No).

- Withdrawal from treatment or lost to follow-up before end of the double-blind period.
- Use of prohibited medications (rituximab alone or in combination, any other complement inhibitor, any other investigational drug and plasma exchange. Phlebotomy/venesection is not included) during the double-blind period.
- Transfusion from week 5 to week 24 (Day 29 until end of double-blind period).

Transfusions before Week 5 (Day 29) are not counted and not considered an ICE but patients who withdraw or use prohibited medication before Week 5 will be considered non-responders (transfusion avoidance=No).

7.2.4 Change from Baseline to Week 24 in the FACT-An score

The change from Baseline at Week 24 in the FACT-An scores will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and the FACT-An score at Baseline as covariate using an unstructured covariance matrix and the Kenward rogers

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method for calculating the degrees of freedom. Should the model fail to converge with an unstructured covariance matrix other covariance structures will be explored (unstructured will be attempted first, followed by compound symmetry, followed by AR(1) if needed). The difference between treatment groups will be estimated, along with its 95% CI and p-value.

The FACT-An total score is a key secondary endpoint. Additional FACT-An scores that will be summarized include the physical subscore, social subscore, emotional subscore, functional subscore, and anemia subscore.

Reference documents for quality of life scores may be used as needed. These include the FACT-An Scoring Guidelines, FACIT Fatigue Scale (Version 4) guidelines, and the EQ-5D-5L (Version 3.0 SEP2019) User Guide.

The ICEs and their associated strategies to handle them, will be the same as for the key secondary endpoint Change from Baseline to Week 24 in Hb level in section 7.2.2. An additional (descriptive only) summary table of change from baseline irrespective of ICEs will be created for FACT-An.

7.3 SECONDARY EFFICACY ENDPOINT ANALYSIS FOR PART A

All secondary efficacy analyses will be analyzed with the ITT set.

7.3.1 Number of PRBC transfusions from Week 5 to Week 24.

The number of PRBC transfusions from Week 5 to Week 24 in each treatment group will be compared using a stratified Wilcoxon rank-sum test-p-value will be calculated. Crude rates of transfusions will be calculated for the double-blind period (Part A). Patients who withdraw from randomized treatment or receive prohibited medication before Week 24 will have the number of transfusions estimated from the duration that they were in the study until withdrawal or initiation of prohibited medication.

7.3.2 Change from Baseline at Week 24 in LDH, haptoglobin, indirect bilirubin, ARC and D-dimer

The change from Baseline at Week 24 in LDH, haptoglobin, indirect bilirubin, ARC and D-dimer will be analyzed using MMRM analysis with the fixed effects of treatment, strata, visit, visit-by-treatment interaction, and the respective Baseline level as covariate, using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom. Should the model fail to converge with an unstructured covariance matrix, other covariance structures may be explored (unstructured will be attempted first, followed by compound symmetry, followed by AR(1), if needed). The difference between treatment groups will be estimated, along with its 95% CI and p-value

The ICEs and their associated strategies to handle data following the ICEs, will be the same as for the key secondary endpoint Change from Baseline to Week 24 in Hb level in section 7.2.1. Additional (descriptive only) summary tables of change from baseline irrespective of ICEs will be

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created for LDH, Haptoglobin, ARC, and indirect bilirubin. No MMRM modeling will be included.

Central laboratory values will be used for the endpoint assessments above except ARC which will be assessed locally.

7.3.3 Normalization of markers of hemolysis (LDH, indirect bilirubin and ARC) at Week 24

For the normalization of markers of hemolysis (LDH, indirect bilirubin and ARC) at Week 24, the number and percentage of patients who achieve normalization will be tabulated by treatment group and compared between treatment groups using an exact CMH test stratified for the criterion used for randomization strata (>=1/0 transfusions during the 6-month period prior to randomization). The strategy for handling ICEs will be the same as for the primary endpoint where patients meeting an ICE will be considered not normalized. A parameter is considered to have met the normalization response criteria if the patient has a non-normal result at baseline and then has a lab value for that parameter which is in the normal range post-baseline, as defined in the laboratory data.

If data at Week 24 is missing the patient will be considered not normalized.

A composite strategy for handling of ICEs will be used for these endpoints, if any of the ICEs as listed below occurs, the patient is not considered normalized at Week 24 and will be set to non-responder.

- Withdrawal from treatment or lost to follow-up before end of the double-blind period
- Use of prohibited medications (rituximab alone or in combination, any other complement inhibitor, any other investigational drug and plasma exchange. Phlebotomy/venesection is not included).
- Transfusion from Week 5 to Week 24.

Kaplan-Meier plots will be presented for the time-to-event endpoints of time to first normalization from Baseline to Week 24 for LDH, Hb, indirect bilirubin and ARC for each treatment group at Week 24, and Kaplan-Meier estimates will be provided.

Central laboratory values will be used for the endpoint assessments above except ARC which will be assessed locally.

7.3.4 Number of units of PRBCs transfused from Week 5 to Week 24

The number of units of PRBCs transfused from Week 5 to Week 24 in each treatment group will be compared using a stratified Wilcoxon rank-sum test (i.e., the Van Elteren test). Patients who withdraw before Week 24 will have the number of units estimated from the duration that they were in the study until withdrawal or initiation of prohibited medication.

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The average number of units transfused for the duration where a patient has evaluable data for PRBC transfusions will be used to estimate the total number of transfused units that would have been used through Week 24 had they not withdrawn from the study.

If the number of PRBC is reported in units and mL in the database the mL will be converted to units using the following formula:

Number of PRBC units = Round (PRBC (mL) / 300),1).

7.3.5 Change from Baseline at Week 24 in SF-12, EQ-5D-5L and the FACIT-F subscale score of the FACT-An scale.

The change from Baseline at Week 24 in SF-12, EQ-5D-5L and FACIT-F subscale score of the FACT-An scale will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and the respective baseline level as covariate, using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom. Should the model fail to converge with an unstructured covariance matrix, other covariance structures such as autoregressive (1) will be attempted first followed by compound symmetry after that if needed. The difference between treatment groups will be estimated, along with its 95% CI and p-value.
The ICEs and their associated strategies to handle them, will be the same as for the key secondary endpoint Change from Baseline to Week 24 in Hb level. Additional (descriptive only) summary tables of change from baseline irrespective of ICEs will be created for SF-12, EQ-5D-5L and the FACIT-F subscale score of the FACT-An scale.

Summary statistics by treatment groups will be presented at each assessment visit during the 24-week double-blind treatment period.

SF-12 summary will show two separate composite scores (MCS and PCS) as provided by QualityMetrics.

For EQ-5D-5L, the visual analogue score and each of the 5 dimensions will be summarized.

For the FACIT-F score, the total score will be summarized as well as the percentage of patients with at least a 4-point improvement from Baseline at Week 24 and Week 48.

The FACT-An scores that will be summarized are the total score, physical subscore, social subscore, emotional subscore, functional subscore, and anemia subscore.

Reference documents for quality of life scores may be used as needed. These include the FACT-An Scoring Guidelines, FACIT Fatigue Scale (Version 4) guidelines, and the EQ-5D-5L (Version 3.0 SEP2019) User Guide.

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7.4 SECONDARY EFFICACY ENDPOINT ANALYSIS FOR PART B

All Part B secondary efficacy analyses will be analyzed with the ITT set, and data presentations will be by visit and by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 48 in Hb, LDH, haptoglobin level, indirect bilirubin, ARC and D-dimer will be analyzed using descriptive statistics.

For the endpoint regarding the normalization of markers of hemolysis (LDH, indirect bilirubin and ARC) at Week 48, the number and percentage of patients who respond will be tabulated in frequency tables by randomized treatment group in Part A as well as combined. All data will be used as collected (no ICEs will be considered) and no imputations will be done.

Durability of response is the time until response is lost; response is lost at the first time point when the average change from baseline in Hb is < 1.5 g/dL (the average of all time points starting from Week 24), or the patient receives a transfusion, or the patient discontinues treatment or the study or the patient receives prohibited medication. Durability of response will be analyzed as a time to event variable with Kaplan-Meier statistics provided. Only patients randomized to pegcetacoplan in Part A who achieved the primary endpoint at Week 24 will be included in this analysis. The time to event will be defined as the time the patient achieved the primary endpoint at Week 24 until the earliest time durability of response (as defined above) is lost. Due to the termination of the study, durability of response will not be included in the analysis.

The change from Baseline at Week 48 in FACT-An, SF-12, EQ-5D-5L and FACIT-F subscale score of the FACT-An scale will be analyzed using descriptive statistics.

All data will be used as collected (no ICEs will be considered) and no imputations will be done.

7.5 TERTIARY EFFICACY ENDPOINT ANALYSIS FOR PART C

All tertiary efficacy analyses will be analyzed with the ITT set and data presentations will be by visit and by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 96 in Hb, LDH, haptoglobin, indirect bilirubin, ARC and D-dimer will be analyzed using descriptive statistics.

For the endpoint regarding the normalization of markers of hemolysis (LDH, indirect bilirubin and ARC), at Week 96, the number and percentage of patients who respond will be tabulated in frequency tables by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 96 in FACT-An, SF-12, EQ-5D-5L and FACIT-F subscale score of the FACT-An scale will be analyzed using descriptive statistics.

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All data will be used as collected (no ICEs will be considered) and no imputations will be done.

7.6 SAFETY ENDPOINT ANALYSIS

All safety analyses will be carried out descriptively on the safety set and presented by randomization sequence. For each output summary, all data will be presented as it becomes available. For example, data for Part A will be presented when Part A is reported. When Part B data are available, all cumulative data from Parts A and B will be reported together. When Part C data are available, all cumulative data from Parts A, B, and C will be reported.

7.6.1 Adverse events

Pretreatment AEs are those occurring between ICF signature and the first IMP administration. Treatment-emergent Adverse Events (TEAEs) are defined as those AEs that start on or after the first dose of IMP and up to 8 weeks after the last dose of study medication.

An overall summary table will summarize the following information by treatment group.

- Treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Non-serious adverse events
- TEAEs leading to premature discontinuation of IMP.
- TEAEs leading to death
- Device related TEAEs
- TEAEs by severity

Separate tables will be presented with the following summaries:

- TEAEs of special interest will be summarized: infections (defined as any AE with SOC "Infections and Infestations"), and injection site reactions (from eCRF)
- Pretreatment AEs by PT
- TEAEs by SOC and PT, including incidence rates.
- TEAEs by PT, including incidence rates.
- Non-serious TEAEs by SOC and PT, including incidence rates.
- Non-serious TEAEs PT, including incidence rates.
- Treatment-emergent SAEs PT, including incidence rates.
- TEAEs leading to premature discontinuation of IMP by PT, including incidence rates.
- TEAEs related to the IMP by PT, including incidence rates.
- Treatment-emergent SAEs related to the IMP by PT, including incidence rates.
- TEAEs by severity (mild/moderate/severe) and PT, including incidence rates.
- TEAEs that were injection site reactions, by PT.

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The time at risk per patient is defined as time from first dose of study drug to last dose of study drug + 56 days (treatment-emergent), or death, if earlier, for those patients without a respective TEAE. For patients with an TEAE, time at risk is defined as the time from first dose of study drug to TEAE start date. Exposure adjusted incidence rates will be calculated as (number of patients with AE/total person-years at risk)*100.

All AE data will be presented in a listing and include at least onset date, duration, relationship to IMP, severity, action taken with IMP, treatment of event, and outcome.

7.6.2 Laboratory data

Laboratory data will be graded for severity using the CTCAE v5.0 and all results of grade ≥ 3 will be considered clinically meaningful.

A frequency table will be presented to summarize patients with CTCAE grading >= 3 from Baseline until 8 weeks after end of treatment for each laboratory parameter for hematology, chemistry, and urinalysis.

Concentrations below the lower limit of quantification (LLOQ) (e.g., <0.20) or upper limit of quantification (ULOQ) will be replaced with LLOQ (e.g., 0.20) or ULOQ in summary tables. In listings, the original value will be presented (e.g., “BLQ” or “<0.20”). When an imputation is made in a summary table, a footnote will be added with the imputation approach.

A summary table will be presented with descriptive statistics and change from baseline for all laboratory parameters. Baseline will be taken as the last measurement prior to the first dose of IMP. For urinalysis parameters that are categorical (e.g., “None”, “Trace”, “1+”), a categorical summary of urinalysis results may be created to complement quantitative results.

All laboratory data will be presented in a listing and values outside normal range values will be flagged.

7.6.3 ECG data

A frequency table will be presented to summarize the normal, abnormal but not clinically significant, and abnormal clinically significant ECGs recorded at each visit.

All ECG data will be presented in a listing.

7.6.4 Vital sign data

Vital signs will be graded for severity using the CTCAE v5.0 and all results of grade ≥ 3 will be considered clinically meaningful. A frequency table will be presented to summarize the clinically meaningful abnormalities as recorded from treatment start date until 8 weeks after end of treatment for each parameter.

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A summary table will be presented with descriptive statistics and change from baseline for all parameters.

All vital sign data including the overall interpretation (normal and if abnormal CS/NCS, Not Evaluable / Not done, etc.) a s assessed by the will be presented in a listing. Reference ranges for heart rate, respiratory rate, blood pressure and body temperature will be added and values will be flagged as High/Low according to the reference ranges.

7.6.5 Immunogenicity data

Frequency tables will be presented to summarize the presence of anti-drug antibodies (ADA) to polyethylene glycol and to pegcetacoplan peptide. ADA evaluable patients are defined as:

- For baseline ADA: having at least one evaluable ADA sample at baseline.
- For treatment-emergent ADA and treatment-boosted ADA: having at least one evaluable ADA sample at baseline and at least one evaluable post dose sample.

Baseline ADA prevalence is defined as the number of patients with ADA positive at baseline divided by the number of patients with evaluable ADA at baseline.

Post-baseline ADA incidence is defined as the proportion of patients developing treatment-emergent ADA among those negative for ADA at baseline, or treatment-boosted ADA, among those positive for ADA at baseline.

Treatment-emergent ADA is defined as ADA that are present at a post-dose visit in a patient who had negative ADA at baseline.

Transient treatment-emergent ADA is defined as treatment emergent ADA detected in a single post dose sample (that was not the last assessment) or in more than 1 ADA sample where the first post dose and last ADA positive samples were separated by a period of less than 112 days (16 weeks), irrespective of any negative and positive samples in between. Persistent treatment emergent ADA is defined as more than 1 positive post dose ADA sample ≥112 days (16 weeks) apart or a positive ADA sample at the last time point with no further results available. Treatment-emergent ADA can only be defined if baseline ADA result is obtained.

Treatment-boosted ADA is defined as positive ADA at a titer more than 4-fold the baseline titer found in a patient with positive ADA at baseline. Treatment-boosted ADA can only be defined if baseline ADA titer result is obtained.

Testing for neutralizing antibodies will be performed for all samples with positive ADA. Definitions for baseline Nab prevalence, post-baseline Nab incidence, and treatment-emergent Nab are the same as for ADA but with Nab.

A summary table of baseline ADA prevalence, post-baseline ADA incidence, treatment-emergent/boosted ADA, maximum titers for patients with treatment-emergent/boosted ADA,

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time to treatment-emergent/boosted ADA, duration of treatment-emergent ADA, the proportion of patients with transient and persistent treatment-emergent ADA, baseline Nab prevalence, post-baseline Nab incidence, and prevalence of treatment-emergent/boosted Nab will be presented for pegcetacoplan peptide and polyethylene glycol.

Spaghetti plots of individual ADA titers will be presented for pegcetacoplan peptide and polyethylene glycol in semi-logarithmic format. Negative ADA results will be imputed as 0.1 to display on the log-scale.

All immunogenicity data will be presented in a listing.

7.7 EXPLORATORY ENDPOINT ANALYSIS

The exploratory endpoints will be summarized with numerical descriptive statistics.

- Pegcetacoplan concentrations at Week 24 and Week 48.
- Changes from Baseline to Week 24 and Week 48 in complement biomarkers (C3 levels, functional assays for classical and alternative complement pathways).
- Changes from Baseline through Week 24 and Week 48 in C3 deposition on RBCs by flow cytometry.
- Changes from Baseline to Week 24 and Week 48 in inflammatory biomarkers: TNFα, IL-6, IL-10, IFNγ and IL-1β.
- Normalization of haptoglobin level at Week 24, Week 48 and Week 96
- Time to first normalization from Baseline to Week 24 for haptoglobin level

The following endpoint will be summarized with frequencies via counts and percentages.

- Normalization of haptoglobin level at Week 24, Week 48 and Week 96.

The following endpoint will be summarized with survival estimates in a table.

- Time to first normalization from Baseline to Week 24 for haptoglobin level.

7.8 PHARMACOKINETIC AND PHARMACODYNAMIC ENDPOINT ANALYSIS

PK/PD analyses will be described in the PK/PD Analysis Plan. All population modelling will be described and done in the PK/PD plan. Selected PK/PD summaries included in this analysis are described in this section.

7.8.1 PK Summaries

Pegcetacoplan concentration time results will be evaluated using the PK set. Concentrations will be summarized, using descriptive statistics, over time, in the randomized treatment groups. Individual patient concentration-time data will be plotted against actual sampling time. Individual patient concentration time data will also be plotted with patients who are positive for ADA are indicated with a different color. 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.

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Concentrations below the lower limit of quantification (LLOQ) will be replaced with LLOQ, except for <LLOQ pre-treatment concentrations, which will be replaced with zero.

7.8.2 PD Summaries

The PD endpoints will be evaluated using the PD set. Absolute values, changes from Baseline and percentage changes from Baseline will be summarized using descriptive statistics, over time by treatment group. Individual patient time profiles will be plotted against actual sampling time. Median profiles, over time, using nominal sampling time, will also be presented.

The PD endpoints in each treatment group will be compared using mixed effect repeated measures analyses.

- Changes from Baseline to Week 24 and Week 48 in complement biomarkers (C3 levels, functional assays for classical and alternative complement pathways).
- Changes from Baseline through Week 24 and Week 48 in C3 deposition on RBCs by flow cytometry.
- Changes from Baseline to Week 24 and Week 48 in inflammatory biomarkers: TNFα, IL-6, IL-10, IFNγ and IL-1β.

8 INTERIM ANALYSIS

No formal interim analyses are planned for the primary endpoint. Data will be reported for Part A (double-blind treatment period) once all patients have completed their Week 24 visits (or have early discontinued) and the database has been cleaned and verified for all visits up to and including Week 24. Similarly, data will be reported after Part B.

9 SOFTWARE AND PROGRAMMING SPECIFICATIONS

All datasets, TLFs, and statistical analyses will be generated using SAS, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated datasets, table, listing and figure output will adhere to the following specifications:

9.1 GENERAL PROGRAMMING SPECIFICATIONS

- One SAS program can create several outputs, or a separate SAS program can be created for each output at the statistical programmer's discretion.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format / rtf format.
- Numbering of TLFs will follow ICH E3 guidance

9.2 TABLE, LISTING, AND FIGURE FORMAT

9.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.

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- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape-orientated page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (e.g., m^2, C_{max}).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

9.2.2 Headers

- All outputs should have the following header at the top left of each page:

  Sobi
  Protocol: Sobi.PEGCET-101

- All outputs should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

9.2.3 Display Titles

Each TLF should be identified by the designation and a numeral. (e.g., Table 14.1.1). ICH E3 recommended numbering will be used. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title (if needed)
Analysis Set

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9.2.4 Column headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.

9.2.5 Body of the data display

9.2.5.1 General conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

9.2.5.2 Table conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
very severe	2
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values should be presented to 1 more significant digit than the original values, and standard deviations should be presented to 2 more significant digits than the original values. The minimum and maximum

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should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as < 0.001. If the p-value should be less than 0.0001 then present as < 0.0001. If the p-value is returned as > 0.999 then present as > 0.999
- Percentage values should be printed to 1 decimal place, in parentheses with no spaces, 1 space after the count (e.g., 7 [12.8%], 13 [5.4%]). Values that round down to 0.0 will be displayed as '< 0.1'. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100 % should be presented as 100 %.
- Unless otherwise specified, tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, drug class, or SOC in descending order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Details of this will be provided in footnotes in tables where appropriate.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than 1 category, a footnote will note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than 1 page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading will only be output on the first relevant page.

9.2.5.3 Listing conventions

- Listings will be sorted for presentation in order of treatment groups (as above), subject ID visit/collection day, and visit/collection time.
- Dates will be printed in SAS® DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates will be represented on patient listings as dashes (--JUL2000). Dates that are

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missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

9.2.5.4 Figure conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis.

9.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Patient specific footnotes will be avoided wherever possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than 6 lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last 2 lines of the footnote section will be a standard source that indicates the name of the program used to produce the data display, date the program was run, and the listing source (or data source for a listing) (e.g., 'Program: myprogram.sas Listing source: 16.x.y.z').

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10 QUALITY CONTROL

10.1 SPECIFICATIONS

Once the SAP is finalized, dataset and TLF specifications will be developed and reviewed by the study team. A review of draft specifications will be conducted by the Allucent Lead Programmer, Lead Statistician and Senior Reviewer.

The client will then review, comment and approve (via signature) this analysis plan and all dataset and TLF specifications as well as any subsequent amendments to any of these.

10.2 OUTPUTS

Validation of analysis datasets and tables will be conducted through independent parallel programming of the statistical output according to the agreed upon specifications defined in the protocol, this SAP, table and shells, and dataset specifications. In this process, 2 programmers working independently (i.e., without input from one another), will program the same output and compare results (via SAS PROC COMPARE). Any discrepancies will be discussed and resolved, and the validation cycle repeated until no further differences are noted between the 2 outputs.

All programs will be submitted in batch mode to document the results of the PROC COMPARE indicating no unequal observations. Additionally, tracking logs will be maintained which document all QC and validation findings and their resolution.

For CDISC datasets the Pinnacle 21 report will be used to validate the datasets for CDISC compliance.

Once the validation cycle is complete, the output (dataset or TLF) will be subjected to the lead statistician's review as well as an Allucent senior statistical review.

The client will review, comment and approve (via signature) all final datasets and TLFs.

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11 APPENDICES

11.1 CHANGES TO THE PROTOCOL SPECIFIED ANALYSES

In the event that there are discrepancies between the protocol and the SAP, the SAP will take precedence.

11.2 SCHEDULE OF EVENTS

See the protocol for a table of the planned schedule of events.

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