Statistical Analysis Plan
Version 3.0, 27 February 2025

Protocol Sobi.PEGCET-201

Protocol Title: An Open-label, Single-arm, Multicenter Pilot Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Pegcetacoplan in Patients with Transplant-associated Thrombotic Microangiopathy (TA-TMA) After Hematopoietic Stem Cell Transplantation (HSCT)

National Clinical Trial number: NCT05148299

Swedish Orphan Biovitrum AB

STATISTICAL ANALYSIS PLAN

PROTOCOL Sobi.PEGCET-201

An Open-label, Single-arm, Multicenter Pilot Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Pegcetacoplan in Patients with Transplant-associated Thrombotic Microangiopathy (TA-TMA) After Hematopoietic Stem Cell Transplantation (HSCT)

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DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
Final 1.0	25 October 2021
Final 2.0	2 September 2022
Final 3.0	27 February 2025

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
2.0	NA	SAP author and reviewers were updated	To reflect updates in the study team
	NA	Title page updated	To reflect changes in the protocol's title
	1	List of abbreviations updated	To reflect updates to SAP text
	2	Study protocol and eCRF version updated	To reflect latest study documents
	3, 4, 5, 6, 7.4	Sections updated	To reflect changes to the study objectives in the protocol
	7.2, 7.3, 8.5, 8.6	Meaning of abbreviations added	To make content clearer and unambiguous
	8.3	Section added	To provide analysis visits details
	8.4 to 8.9	Sections have been renumbered	To reflect updates to SAP text due to Section 8.3 added.
	8.5	Number of patients enrolled by country has been added	To ensure consistency with Mock TLFs.
	8.7.1	Frequency of drinking alcohol/smoking were removed	To ensure consistency with Mock TLFs.
	8.7.2	Section updated	To reflect latest study documents
	8.7.3	Section updated	To reflect latest study documents
	8.7.4	Section updated	To make content clearer and unambiguous
	8.7.2	Meaning of abbreviations added and new items of Baseline TA-TMA data added in summary	To reflect last study documents and to make content clearer and unambiguous

	8.7.3	Dictionary used for coding medications added and sort ordering expected for summaries added	To make content clearer and unambiguous
	8.8.1	Meaning of abbreviations added	To make content clearer and unambiguous
	8.8.2, 8.8.3	Study endpoints updated	To reflect changes to the study endpoints in the protocol
	8.8.2, 8.8.3	Details have been added	To make content clearer and unambiguous
	8.9.1	Coding dictionary details added and new categories of TEAEs added	To provide more details on AEs
	8.9.1	Section updated	To align the AE section to another PEGCET study to align presentation of Aes.
	9	Administrative interim analysis added	To reflect changes in the protocol
	10	All deviations from protocol previously mentioned have been removed as now clearly stated in the protocol. Only TEAE of Special Interest item has been kept.	To reflect changes in the protocol
	13.1	Clinical response derivation updated	To reflect changes in the protocol
	13.2	Section added	To make content clearer and unambiguous
	13.3	Section renumbered	To reflect updates to SAP text due to Section 13.2 added.
3.0	NA	SAP reviewers were updated and co-author for PK section was added.	To reflect updates in the study team
	NA	The unit of platelet count has been updated from /mm^3 to 10^9/L	To ensure consistency with SDTM datasets
	1	List of abbreviations updated	To reflect updates to SAP text
	2	Study protocol and eCRF version updated	To reflect latest study documents
	4.1, 4.2	Section updated	To reflect latest study documents

	5	Section updated	To correct typographical issues
	6.1, 6.2, 6.3	Section updated	To make content clearer and unambiguous
	8.1	Section updated	To make content clearer and unambiguous
	8.2	Section updated	To make content clearer and unambiguous and to update the derivation of baseline.
	8.3	Section updated	To correct typographical issues and to update the derivation of baseline.
	8.4	Section updated for procedure	To make content clearer and unambiguous
	8.5	“Completion and reasons for premature discontinuation from treatment phase and from follow-up” has been updated to “completion and reasons for premature discontinuation from treatment and study”	To reflect changes in the eCRF as End of Study (EOS) form has been added
	8.5	Enrollment by country is now tabulated and listed.	To provide further information.
	8.6	Section updated	To correct typographical issues
	8.7.1	Frequency of drinking alcohol/smoking were added back and age in categories was added too.	To provide further information on study population.
	8.7.2	Section updated	To make content clearer and unambiguous
	8.7.3	Section updated	To make content clearer and unambiguous
	8.7.4	Section updated	To make content clearer and unambiguous
	8.7.5	A new category for infusion-level and volume-level compliances has been added and details about calculation of compliance has been added.	To ensure clarity in the reporting of data related to study drug administration
	8.8.1	Section updated	To make content clearer and unambiguous
	8.8.2.2	List of prohibited medications updated.	To reflect latest study documents

	8.8.2.3	Section updated	To correct typographical issues and hyperlink to the appropriate section.
	8.8.2.4	Section updated	To correct typographical issues
	8.8.2.5	Section updated	To correct typographical issues and hyperlink to the appropriate section.
	8.8.2.6 8.8.2.7	Section updated to clarify the protocol wording. The event is the first occurrence of response. If a patient has no response at any visit up to week 24, then he/she will be censored. But the two sets mentioned above are for patients achieving response and so we are not able to have such censored events. Then we rephrase the two sets by sustained or not sustained response	To make content clearer and unambiguous hyperlink to the appropriate section.
	8.8.2.8 8.8.2.9	Section updated to clarify the fact that reported TA-TMA relapse is from Survival Status eCRF form	To make content clearer and unambiguous
	8.8.2.8 8.8.2.9	The start date is defined as the date of the earliest clinical (TA-TMA) response. The loss of clinical (TA-TMA) response, the reported TA-TMA relapse as per Survival Status eCRF form and death from any cause are considered as events. So, a patient could have a clinical (TA-TMA) response and then could die. This should be considered as an event, and this is contradictory to the sentence “patients who died had no relapse will be censored at the date of death”. This sentence has been removed	To make content clearer and unambiguous
	8.8.2.9	Section updated	To hyperlink to the appropriate section.
	8.8.2.10	Section updated to have confidence interval for proportion of patients with TA-TMA relapse and not	To correct typographical issues

		responders	
	8.8.2.11 8.8.2.12	Section updated	To hyperlink to the appropriate section.
	8.8.3.1	Section updated	To make content clearer and unambiguous
	8.8.3.8	Section updated by adding a restriction that subgroup analyses will only be presented if we have at least 3 patients in a subgroup category	To ensure that the presented subgroup analyses are meaningful
	8.9.1	Section updated	To make content clearer and unambiguous
	8.9.1	Sort ordering of AE summaries has been updated	To ensure consistency with other SOBI studies of the same program.
	8.9.1	Category of Adverse Events of Special Interest modified to “Target Medical Events” and definition including a Table in Appendix IV added	The use of “Adverse Events of Special Interest” usually is reserved for AEs prospectively captured following a definition provided in the Protocol, thus this term should be avoided for clarity as this definition is not provided in the Protocol. The opportunity was taken to update the definitions for new product safety knowledge
	8.9.2	Section updated	To provide further information about the shift tables.
	8.9.5	Section updated by adding a summary for the proportion of patients with ADA results by category (treatment-emergent ADA and treatment-boosted ADA	To provide further information on ADA data.
	8.9.6	Section added	To provide further information on deaths
	9	Administrative interim analysis removed	The interim analysis has become unnecessary due to the fast recruitment of the last 5 study patients
	10	Adverse Events of Special Interest reworded as Target Medical Events and administrative interim analysis	To provide rationale of these changes from the protocol

		removed	
	11	Section updated	To make content clearer and unambiguous
	13.1	Section updated to add the derivation of the derived clinical response onset date, clarify what we are expecting behind 'Any blood transfusions at baseline" and update the cardiovascular response	To make content clearer and unambiguous
	13.2 13.3	Section updated	To correct typographical issues
	13.4	Section added	To provide further details about the Target Medical Events

APPROVAL SIGNATURES

STUDY TITLE:
An Open-label, Single-arm, Multicenter Pilot Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Pegcetacoplan in Patients with Transplant-associated Thrombotic Microangiopathy (TA-TMA) After Hematopoietic Stem Cell Transplantation (HSCT)

PROTOCOL NUMBER: Sobi.PEGCET-201

PROTOCOL VERSION: Version 3.0, 17 September 2024

SAP Version 3.0, 27 February 2025

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1. LIST OF ABBREVIATIONS

ADAs	Anti-drug antibodies
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}taud1\text{-}d3}$	Area under the concentration-time curve over the dosing interval on days 1 to 3
$AUC_{0\text{-}taud3\text{-}d5}$	Area under the concentration-time curve over the dosing interval on days 3 to 5
$AUC_{0\text{-}taud5\text{-}d8}$	Area under the concentration-time curve over the dosing interval on days 5 to 8
BATAP	Bilirubin, Age, Thrombocytopenia, Anemia, Proteinuria
Bb	Activated factor B
BLQ	Below Limit of Quantification
C3	Complement component 3
C3a	Complement component 3a
C4a	Complement component 4a
C_{max}	Maximum observed serum concentration
CI	Confidence interval
CNS	Central Nervous System
COVID-19	Coronavirus disease 19
C_{trough}	Observed serum concentration predose
CV	Coefficient of variation
[redacted]	[redacted]
DBL	Database lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
[redacted]	[redacted]
EOT	End of Treatment
ET	Early Termination
[redacted]	[redacted]
[redacted]	[redacted]
GCV	Geometric coefficient of variation
GI	Gastrointestinal
GVHD	Graft-versus-host disease
Hb	Hemoglobin
HSCT	Hematopoietic stem cell transplantation
ICE	Intercurrent event
ICF	Informed Consent Form
[redacted]	[redacted]
IMP	Investigational medicinal product
[redacted]	[redacted]
ITT	Intent-to-treat
[redacted]	[redacted]
LDH	Lactate dehydrogenase
LOQ	Limit of Quantification
MAGIC	Mount Sinai Acute Graft-versus-host disease International Consortium
MedDRA	Medical Dictionary for Regulatory Activities

PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PRBC	Packed red blood cells
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Preferred Term
QOL	Quality of life
rUPCR	Random urine protein/creatinine ratio
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
sC5b-9	Terminal complement complex (soluble)
SD	Standard deviation
[redacted]	[redacted]
SOC	System Organ Class
SRC	Safety Review Committee
TA-TMA	Transplant-associated thrombotic microangiopathy
TBI	Total-body irradiation
TEAE	Treatment-emergent adverse event
TFLs	Tables, listings, and figures
T_{max}	Time to the maximum observed serum concentration
[redacted]	[redacted]
TOI	Trial Outcome Index
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO-DD	World Health Organization-Drug Dictionary

2. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analyses and reporting plans for the protocol Sobi.PEGCET-201 Version 3.0 dated 17 September 2024 and for the final electronic Case Report Form (eCRF) dated 21 September 2023.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

The primary objective of this study is to evaluate the pharmacokinetics (PK), safety and tolerability of pegcetacoplan in patients with TA-TMA.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate the pharmacodynamics (PD) of pegcetacoplan in patients with TA-TMA
- To evaluate the efficacy of pegcetacoplan in patients with TA-TMA

3.3 [redacted]

[redacted]

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

This is a prospective, open-label, multicenter, single-arm, pilot study to evaluate the PK, PD, efficacy, and safety of pegcetacoplan in patients with TA-TMA after HSCT.

The study will enroll 12 patients with TA-TMA, who will receive treatment with open-label pegcetacoplan at the planned dose regimen presented in Section §4.2.

The planned study duration for each patient is up to 24 weeks. The study will consist of the following periods:

- Screening period (up to 2 weeks),
- Treatment period (up to 16 weeks) and
- Follow-up period (up to 12 weeks).

The main analysis will be performed after all enrolled patients have completed the follow-up period and performed the End of study visit at the Week 24 visit or the Early Termination visit in case of early discontinuation.

A Safety Review Committee (SRC) will assess the progress and cumulative PK, PD, safety and efficacy data of the study.

4.2 STUDY TREATMENT

All patients will receive [redacted] pegcetacoplan [redacted] (see Section §6.4.1 of the protocol).

At Week 12, if a clinical and/or TMA response according to the protocol definition is not reached, the investigator may decide according to his/her judgment to continue treatment for additional 4 weeks until a total of 16 weeks of treatment. If at Week 12 the patient has reached a partial clinical response, 4 additional weeks of pegcetacoplan every 3 days will be administered to complete 16 weeks of treatment.

At any time after the first 3 weeks of treatment, in the event of significant clinical worsening associated with active laboratory TMA (as defined in Section §6.1.2.1 of the protocol), the patient may be discontinued from study treatment and receive rescue therapy. In case of earlier clinical worsening, it is recommended to wait until at least 3 weeks of treatment are completed to allow pegcetacoplan to reach the target exposure and exert a clinical effect; however, if deemed by the investigator that the patient's safety is at risk, the patient can be discontinued from study treatment at any time. Discontinued patients will remain on study and will be followed for survival until the end of the study.

Any concomitant TA-TMA directed therapy will be prohibited for the entire treatment period, including plasma-exchange, defibrotide and any other complement inhibitor.

5. SAMPLE SIZE AND POWER CALCULATION

This is a pilot study, and the sample size is based on practical rather than statistical aspects.

A total of 12 patients will be included and treated in the study. With 12 patients included, it is estimated that 9 patients will complete at least 4 weeks of treatment, which is deemed sufficient to characterize the PK of pegcetacoplan in patients with TA-TMA to an appropriate precision. In addition, 12 patients will provide a 72% probability to observe a response rate of at least 8 responders of the 12 patients recruited (assuming the true response rate is 70%).

6. ANALYSIS ENDPOINTS

6.1 PRIMARY ENDPOINTS

The primary PK endpoints of this study are PK parameters for pegcetacoplan on Day 1, 3, and 5: Area under the concentration-time curve over the dosing interval on days 1 to 3 ($AUC_{0\text{-}taud1\text{-}d3}$), 3 to 5 ($AUC_{0\text{-}taud3\text{-}d5}$) and 5 to 8 ($AUC_{0\text{-}taud5\text{-}d8}$). Maximum observed serum concentration (C_{max}), Time to the maximum observed serum concentration (T_{max}) and Observed serum trough concentration pre-dose (C_{trough}) at all visits.

The primary safety endpoints are as follows:

- Occurrence of treatment-emergent adverse events (TEAEs)
- Changes from baseline in laboratory parameters and vital signs
- Occurrence of clinically significant abnormal electrocardiogram (ECG) findings
- Presence of antibodies to polyethylene glycol (PEG) and pegcetacoplan throughout treatment and follow-up periods

6.2 SECONDARY ENDPOINTS

Secondary endpoints are as follows:

- PD endpoints:

  - Absolute levels, change from baseline, and % change from baseline to Week 24 in biomarkers of complement activation: terminal complement complex (soluble) (sC5b-9), complement component 3a (C3a), complement component 3 (C3), activated factor B (Bb), complement component 4a (C4a), functional assays for classical and alternative complement pathways.
- **Clinical response** at Week 24, defined as improvement in laboratory markers **and** improvement in clinical status as follows:
  Improvement in laboratory markers:
  - Lactate dehydrogenase (LDH) < 1.5 x upper limit of normal (ULN) **and**
  - Platelet count ≥ 50*10^9/L (50 000/ mm^3) without transfusion support during the prior 7 days.

  AND **in patients with signs or symptoms of organ dysfunction at baseline**, in addition to the above laboratory markers, **at least 1** of the following clinical criteria needs to be fulfilled, **depending on the organ/system involved at baseline** (without appearance of new signs or symptoms of organ dysfunction in other organs not present at baseline):

  - **Renal response** – requires > 40 % reduction in creatinine, or normalization of creatinine, or discontinuation of renal replacement therapy, or ≥ 50 % reduction from baseline in random urine protein/creatinine ratio (rUPCR)
  - **Pulmonary response** – requires extubation and discontinuation of positive pressure ventilation
  - **Gastrointestinal (GI) response** – applicable only to patients with biopsy-proven GI TA-TMA and requires improvement in GI function as determined by the Mount Sinai Acute Graft-versus-host disease International Consortium (MAGIC) criteria (no or intermittent nausea, vomiting or anorexia attributed to TA-TMA for upper GI; stool output/day for lower GI as follows: < 500 mL/day or < 3 episodes/day)
  - **Neurological response** – requires improvement in reversible neurological conditions (e.g., cessation of seizures or controlled under medication, resolution of mental alteration; residual radiologic signs are acceptable without clinical symptomatology), or stabilization of irreversible. neurological conditions (e.g., stability of neurological deficits following stroke without further deterioration or subsequent strokes)
  - **Freedom from transfusion** – requires absence of platelet or packed red blood cells (PRBC) transfusions attributed to TA-TMA during the prior 7 days (only applicable if patient was undergoing platelet or PRBC transfusion at baseline)
  - **Cardiovascular response** – requires resolution of pulmonary hypertension (may receive anti-pulmonary hypertension medications if still on maintenance therapy), or hypertension control on no more than 2 medications excluding diuretics (applicable only to patients with severe hypertension at baseline)
  - **Serositis response** – requires no evidence of clinically significant pericardial or pleural effusion requiring surgical therapy (e.g., pericardiocentesis/thoracocentesis)

Patients meeting intercurrent events, including use of prohibited medication or study withdrawal before Week 24 will be considered as failures/non-responders.

The exact rules to be used for the derivation of the clinical response are described in Appendix I (Section 13.1).

- TMA response at Week 24, defined as improvement of laboratory markers as follows:
  - LDH < 1.5 x ULN **and**
  - Platelet count ≥ 50*10^9/L (50 000/ mm^3) without transfusion support during the prior 7 days **and**
  - ≥ 50 % reduction from baseline in rUPCR.
- Overall survival at Day 100 from date of TA-TMA diagnosis
- Overall survival at Week 24 from treatment start

- Time to clinical response
- Time to TMA response
- Duration of clinical response
- Duration of TMA response
- TA-TMA relapse at Week 24
- Clinical response at Week 12
- TMA response at Week 12

6.3 [redacted]

[redacted]

7. ANALYSIS SETS

7.1 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.

7.2 SAFETY SET

The safety set will include all patients who receive at least 1 dose of investigational medicinal product (IMP). This analysis set will be used for all safety analyses.

7.3 INTENT-TO-TREAT SET

The intent-to-treat (ITT) set will include all patients enrolled. This analysis set will be used for efficacy endpoints. ITT should be identical to the Safety set, i.e. all enrolled patients who received at least one dose of IMP. Enrolled patients are defined as Informed Consent Form (ICF) signed and all eligibility criteria are met.

7.4 PHARMACOKINETIC SET

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

7.5 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.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be performed, and outputs (TFLs) will be created using the SAS system version 9.4 or higher.

Data collected in this study will be presented in patient data listings and summary tables.

Descriptive statistics (number of patients with non-missing values, arithmetic mean, standard deviation (SD), median, first quartile [Q1], third quartile [Q3], minimum, and maximum) will be presented for continuous variables. For all PK parameters, the coefficient of variation (CV), geometric mean, and corresponding 95% confidence interval (CI) and geometric CV will be added to the summaries. All raw data will be presented to the original number of decimal places. Means and medians will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data.

- Geometric mean is calculated as follows:

$$\mu_g = \exp\left(\frac{\sum_{i=1}^{n} \ln x_i}{n}\right)$$

  Where x_i is the value of interest for each patient.
- CV is calculated using SD and mean using the following formula:

$$CV\ (\%) = \frac{SD}{Mean} x100$$

- Geometric CV is calculated as follows:

$$GCV\ (\%) = \sqrt{\exp(SD^2) - 1}\ x100$$

  Where SD is the standard deviation of the log-transformed value of interest for each patient.

Frequency distributions (counts and percentages) will be presented for categorical variables. Percentages will be suppressed when the count is zero, however the category will still be displayed. If not specified otherwise, the number of observations with non-missing values will be the denominator for percentage calculation. Percentages will be presented to 1 decimal place. Further details on the handling of missing observations are given in Section §8.4.

Safety laboratory results reported as below or above limits of quantification, e.g., “<x.x”, “<=x.x”, “>x.x” or “>=x.x”, will be summarized in the tables using the reported limit of quantification (LOQ). The listings will show the result as reported.

Calculations using dates (e.g., relative day after the first dose of the study drug) will adhere to the following conventions:

- Study days on or after the start day of study treatment will be calculated as the difference between the date of interest (TARGET DATE) and the first date of dosing of study treatment (TSTART) plus 1 day. The generalized calculation algorithm for the relative day is the following:
  - If TARGET DATE ≥ TSTART then STUDY DAY = (TARGET DATE – TSTART) + 1.
  - Else use STUDY DAY = TARGET DATE – TSTART.

  Note that Study Day 1 is the first day of study treatment. Study days on or before Day 1 are reflective of observations obtained during the baseline/Screening period.

- Intervals that are presented in weeks will be transformed from days to weeks by using (with rounding

to 4 decimal places) the following conversion formula:

$$WEEKS = DAYS / 7$$

- Intervals that are presented in months will be transformed from days to months by using (with rounding to 4 decimal places) the following conversion formula:

$$MONTHS = DAYS / 30.4375$$

- Intervals that are presented in years will be transformed from days to years by using (with rounding to 4 decimal places) the following conversion formula:

$$YEARS = DAYS / 365.25$$

All data collected will be presented in the data listings.

All the analyses will be descriptive, no hypothesis testing will be performed.

8.2 Definition of Baseline, and Change From Baseline

Baseline will be defined as the value at Baseline visit (i.e., visit 2). For TA-TMA related variables, the value reported on the baseline TA-TMA form will be considered as baseline. If no assessment is available at the Baseline visit, then the last assessment during the screening period will be used. As a general rule, the last assessment prior to the first dose of the study treatment will be considered as baseline. On study day 1, if assessment time is available and before the first infusion, then it will be considered as baseline. Assessments of height and weight and questionnaires completed at study day 1 will be considered as baseline if no time stamp of the assessment is available. If assessment time is available and after the infusion, then it will be presented as study day 1 of the treatment period and not as baseline.

Change from Baseline will be calculated using the following formula:

$$Change\ from\ Baseline = \text{Post baseline value} - \text{Baseline value}$$

8.3 Study Visits and Analysis Windows

Data will be summarized and analyzed based on the list of visits specified in Table 1 – Study Visits and Analysis Windows.

Table 1 – Study Visits and Analysis Windows

Period	Visit	Target Study Day	Analysis Window (study day)	Interval (days)
Screening	Screening	-14	-14 to -1	NA
	Baseline	Last assessment prior to first dose of the study treatment. On study day 1, If assessment time is available and before the first infusion or if assessment of height and weight, and questionnaires then it will be considered as baseline.		
Treatment	Day 1	1	1	1

	Week 1	8	2-11	10
	Week 2	15	12-18	7
	Week 3	22	19-25	7
	Week 4	29	26-35	10
	Week 6	43	36-50	14
	Week 8	57	51-64	14
	Week 10	71	65-78	14
	Week 12	85	79-92	14
	Week 12**	85	79-99	21
Optional Treatment	Week 14	99	93-106	14
	Week 16	113	107-127	21
Follow-up	Week 16**	113	100-127	28
	Week 20	141	128-155	28
	Week 24	169	156-183	28

* Study day 1 is the day of the first dose of pegcetacoplan.
** This is for patients who complete 12 weeks of treatments. An End of Treatment/Early termination (EOT/ET) visit will be performed 4 weeks after the last dose of pegcetacoplan. For patients who complete 12 weeks of treatment, the EOT visit will be at Week 16, and there will be further follow-up visits at Weeks 20 and 24. For patients who complete 16 weeks of treatment, the EOT visit will be at Week 20, and there will be a further follow-up visit at Week 24.

Planned visits, as recorded in the eCRF, will be considered first. Only if there is no planned visit recorded in the eCRF (or a planned visit which contains missing data) unscheduled visits will be considered.

If more than 1 record is within the same analysis visit window, the record closest to the target day with non-missing data (the day of the planned visit according to protocol schedule of assessments) will be used in the analysis.

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

8.4 HANDLING OF MISSING DATA

Unless specified otherwise, no imputation of missing data will be performed.

Adverse Event (AE) start dates will not be imputed. In case of an incomplete or missing start date, AEs will be classified as treatment-emergent unless sufficient information is available to conclude that the event started or worsened before the first study treatment (e.g., if only the year is available and it matches the year of the first study treatment date, the event will be considered treatment-emergent).

In order to distinguish prior and concomitant medications/procedures, the end date will be compared to the start date of the study medication/procedure. Incomplete end dates will not be imputed. Medications/procedures will be flagged as both prior and concomitant if there is uncertainty (e.g., missing end date, while month and year are equal to study treatment start and start date is before the date of study treatment start).

8.5 PATIENT DISPOSITION

Patient screening data (informed consent, screening failures, and their reasons, enrollment) will be tabulated for Screened set. Enrollment by country will be tabulated and listed. Numbers of patients in all the study populations will also be presented. Completion and reasons for premature discontinuation from treatment and study will be summarized for Safety and PK sets. Time on study (weeks) will also be summarized. It will be defined as the time between the first dose of the study drug and study completion/discontinuation.

Patients who discontinued due to a coronavirus disease 19 (COVID-19)-related reason will have their reason for discontinuation classified and summarized as such.

8.6 PROTOCOL DEVIATIONS

Study-specific protocol deviations considering the operational aspect of the study conduct, including deviations as a result of the COVID-19 pandemic, will be classified as Minor or Major at database lock (DBL).

Major protocol deviations will be tabulated for the ITT and PK sets.

Major protocol deviations due to COVID-19 will be identified and summarized separately.

The monitoring of Quality Tolerance Limits was not implemented due to study sample size. Risk control measures that were used to protect data integrity and subject safety will be described in the clinical study report.

8.7 PATIENT CHARACTERISTICS

Patient characteristics will be summarized for ITT and PK sets.

8.7.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Demographics (age, age in categories, sex, race, ethnicity, child-bearing potential, and method of contraception) and baseline characteristics (weight, height) will be summarized.

Age categories: age is defined as 2 categories:

- Adults (18 to 64 years)
- From 65 to 84 years

Alcohol consumption and smoking habits (presence or absence of each habit and frequency) will be summarized.

8.7.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Medical history (conditions that ended before the date of enrollment) and current medical conditions (those that started before and were ongoing at the date of enrollment) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version current at the time of DBL and tabulated by System Organ Class (SOC) and Preferred Term (PT).

Baseline TA-TMA data will be summarized using the following variables:

- The platelet value at the diagnosis (10^9/L),
- The highest platelet value achieved after transplant (10^9/L),
- The LDH value at diagnosis (U/L),
- Diagnosis of TA-TMA established as per laboratory/clinical markers indicating TMA,
    - Presence of schistocytes in the peripheral blood smear (yes or no),
        - Absolute number of schistocytes per high power field in the peripheral blood smear (per hpf),
    - Was any biopsy performed to confirm the histologic diagnosis of TA-TMA (yes or no),
        - If yes, sample location,
    - De novo anemia at diagnosis (yes or no)
        - The most recent pre-transfusion hemoglobin (Hb) level at diagnosis (g/dL),
    - Proteinuria at diagnosis (yes or no),

    - The most recent rUPCR value at diagnosis (mg/mg),
    - The most recent proteinuria value at diagnosis (mg/dL),
  - Elevated plasma concentration of Sc5b-9 above ULN (yes or no),
    - Sc5b-9 level at diagnosis (ng/mL),
  - Arterial hypertension defined by systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg (yes or no),
    - The pre-antihypertensive therapy systolic blood pressure (mmHg),
    - The pre-antihypertensive therapy diastolic blood pressure (mmHg),
    - Patients taking any antihypertension medication (yes or no),
    - Number of ongoing medications, excluding diuretics,
      - 0 medication,
      - ≤ 2 medications,
      - > 2 medications,
  - Time between HSCT and TA-TMA diagnosis (days),
  - Time between TA-TMA diagnosis and study enrollment (days),
  - TA-TMA persisting despite initial management of any triggering condition (yes or no),
  - Any sign/symptom of kidney dysfunction (yes or no),
    - The most recent serum creatinine value (mg/dL),
    - The last serum creatinine value pre-transplant (mg/dL),
    - Patients requiring renal replacement therapy (yes or no),
  - Any sign/symptom of lungs dysfunction (yes or no),
    - The lowest oxygen level in the blood (%),
    - Patients receiving noninvasive positive pressure ventilation (yes or no),
    - Patients receiving invasive positive pressure ventilation (yes or no),
  - Any sign/symptom of cardiovascular dysfunction (yes or no),
    - Patients with pulmonary hypertension diagnosis (yes or no),
      - If yes, the diagnostic method,
  - Any sign/symptom of serositis (yes or no),
    - Patients with pleural effusion,
    - Patients with pericardial effusion,
    - Patients requiring pericardiocentesis,
    - Patients requiring thoracocentesis,
  - Any sign/symptom of central nervous system (CNS) dysfunction (yes or no),
    - Patients with diagnosis of posterior reversible encephalopathy syndrome (PRES) (yes or no),
  - Any biopsy-proven GI involvement of TA-TMA (yes or no).

HSCT disease history data will be summarized. The following HSCT variables will be assessed:

- Underlying disease diagnosis,
- Donor type,
- Stem cell source,
- Transplant manipulation (yes or no),
- Type of conditioning regimen,
- Total-body irradiation (TBI) (yes or no),
- Time from start of conditioning regiment until TA-TMA diagnosis (days),
- Donor chimerism (%),
- Time from confirmed engraftment until TA-TMA diagnosis (days),
- Graft-versus-host disease (GVHD) prophylaxis (pre TA-TMA diagnosis) (yes or no),
- If yes, name of GVHD prophylaxis,
- GVHD Diagnosis (yes or no),
- Time from GVHD onset until TA-TMA diagnosis (days),

- GVHD grade according to the International Bone Marrow Transplant Registry Severity Index,
- Presence of infection (yes or no),
- Presence of donor-specific antibodies (yes or no),
- Post-transplant treatments (yes or no),
- Post-transplant treatment type.

8.7.3 Prior and Concomitant Medications and Procedures

Use of prior medications (stopped before treatment started) and concomitant medications (ongoing at treatment start or started after the first study treatment) will be coded using the latest World Health Organization-Drug Dictionary (WHO-DD) and tabulated on the Anatomical Therapeutic Chemical (ATC) 2, ATC 4, and PT levels.

Medications will be sorted in descending order of frequency of ATC 2 category based on the total. Patients may have more than 1 medication per ATC class and PT. At each level of summarization, a patient is counted once if he/she reported & or more medications at that level. Within each ATC 2 category, the ATC 4 category will be sorted in descending order of frequency based on the total. Within each ATC 4 category, PTs will be sorted in descending order of frequency based on the total. In case of identical frequencies, ATC2, ATC4, or PT will be sorted alphabetically.

Surgeries and other procedures will also be coded using MedDRA and summarized by SOC and PT. They will be classified as pre-treatment or on-treatment, similar to the medications described above.

8.7.4 Exposure to Study Treatment

Overall exposure to pegcetacoplan will be summarized using the following parameters:

- Total dose administered (mg) per patient throughout the study,
- Total time on study treatment (days) calculated as the time in days from the first study drug infusion date until the last study drug infusion date,
- Number and percentage of patients receiving treatment for exactly 12 weeks or exactly 16 weeks,
- Number and percentage of patients receiving infusions,
    - Number and percentage of patients with all infusions completed (Infusion is considered complete if volume administered [at least equals] ≥ 80 % of volume prepared),
    - Number and percentage of patients with any infusions missed (i.e., planned infusion not done),
    - Number and percentage of patients with any infusions permanently interrupted,
    - Number and percentage of patients with any infusions interrupted and restarted,
    - Number and percentage of patients receiving exactly 1, exactly 2, etc. infusions.
- Number of started infusions,
- Number and percentage of started infusions completed (Infusion is considered complete if volume administered [at least equals] ≥ 80 % of volume prepared) based on all started infusions,
- Number and percentage of interrupted infusions based on all started infusions,
- Number and percentage of permanently interrupted infusions based on all started infusions,
- Number and percentage of interrupted and restarted infusions based on all started infusions,
- Number and percentage of patients having exactly 1, exactly 2, etc., interrupted infusions,
- Number and percentage of patients having exactly 1, exactly 2, etc., interrupted, and restarted infusions,
- Number and percentage of patients having exactly 1, exactly 2, etc. permanently interrupted infusions.

[redacted]

[redacted]

8.7.5 Study Treatment Compliance

All the details related to the IMP administration originate from the "Pegcetacoplan administration" eCRF form, regardless of the infusion site. The clinic and non-clinic administrations will be included in the calculation of compliance.

Two measures of compliance will be calculated in the study: infusion-level compliance and volume-level compliance.

Infusion-level compliance is defined as the total number of study infusions administered from the first infusion to the last infusion, multiplied by 100 and divided by the expected number of infusions. In case of premature treatment discontinuation, the expected number of infusions will be calculated for the period up to treatment discontinuation. The exact number of expected infusions will be calculated based on the total number of days from the date of the first study drug infusion till the date of treatment discontinuation. The rules are as follows:

- If time on treatment is less than 7 days, then expected number of infusions = floor ((time on treatment (days)+1)/2)
- If time on treatment is 7 days or more, then expected number of infusions = 3 + floor ((time on treatment (days) – 5)/3)

Floor in the above derivations refers to rounding down to the closest integer.

Volume-level compliance will be defined as the total volume of study drug administered divided by the total volume that had to be administered (based on the total amount of infusions expected, calculated as described above).

Both compliance measures will be summarized as numeric values. In addition, the number and percentage of subjects who had treatment compliance in the three categories [80%; 90%], [90%; 100%] and [80%, 100%] will be presented.

8.8 Pharmacokinetic and Efficacy Endpoints and Analyses

Unless otherwise specified, all PK and efficacy analyses will be done on ITT set.

8.8.1 Analysis of Primary Endpoints

Individual serum pegcetacoplan concentrations, actual sampling times, and deviations from nominal sampling times will be presented in a data listing for all subjects included in the PK Set. Pegcetacoplan concentrations will be summarized with descriptive statistics at each scheduled time point (day and time post-dose). The number of subjects with a below limit of quantification (BLQ) value will also be tabulated. Concentrations that are BLQ will be treated as zero for the computation of descriptive statistics, except geometric mean. For the calculation of the geometric mean, they will be treated as equal to the LOQ. Missing values will be omitted from the calculation of descriptive statistics. Individual and median serum pegcetacoplan concentrations across time will be presented graphically on both linear and semi-logarithmic concentration scales. Actual sampling times will be used for the graphical presentation of individual concentration-time data, and nominal sampling times will be used for mean (SD) concentration-time plots.

For linear concentration scale plots of individual concentration-time data, BLQ will be set to 0. For semi-logarithmic concentration scale plots, BLQ values will be set equal to the LOQ. If a BLQ value falls between two quantifiable concentrations, the value will be set equal to the LOQ, unless its exclusion can be justified (e.g., implausibility given the profile observed and known PK properties).

The PK analysis is performed by noncompartmental analysis using the WinNonlin software by Amador Biosciences, according to Amador's SOPs. PSI Biostats will only present the derived PK parameters as calculated by Amador Biosciences. For the estimation of PK parameters, concentrations that are recorded as BLQ prior to the first quantifiable value will be set to 0. Concentrations that are recorded at the end of the sampling period (i.e., no further quantifiable concentrations) will be set to missing and will not be used for the estimation of parameter values. If a BLQ value falls between two quantifiable concentrations, the value will be set to LLOQ/2, unless its exclusion can be justified, based on implausibility of the observed PK profile (e.g., if pivotal concentration values around C_{max} or several values are missing). In these cases when the AUC cannot be reliably determined, PK parameters will not be calculated. Furthermore, such cases will be described in the CSR.

Actual sampling time from start of infusion will be used for parameter estimation except for predose data points, which will be set to 0. If actual sampling time is missing, the planned time should be used. If a predose sample is taken after dosing, it will be taken as missing. AUC is calculated using the linear-log trapezoidal rule.

The following PK parameters will be calculated:

Day 1 (induction phase):

- $AUC_{0\text{-}tau}$: area under the concentration-time curve over the dosing interval, as calculated by the linear-log trapezoidal method.
- C_{max}: maximum observed serum concentration.
- T_{max}: time to the maximum observed serum concentration. If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.

Day 3 (induction phase):

- $AUC_{0\text{-}tau}$:
- C_{max}
- T_{max}: If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.

Day 5 (induction phase):

- $AUC_{0\text{-}tau}$:
- C_{max}
- T_{max}: If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.

Day 8 and onwards (s.c. maintenance phase):

- C_{trough}: observed serum concentration predose.

Serum PK parameters C_{max}, AUC_{tau}, and T_{max} and C_{trough} concentrations will be summarized including N,

arithmetic mean, standard deviation, coefficient of variation, minimum, maximum, Q1, Q3, and median. In addition, geometric means and corresponding 95% confidence intervals will be calculated for AUC parameters, and C_{max}. For t_{max}, the geometric mean and its 95% CI, SD are not calculated. Figures: individual pegcetacoplan concentration-time curves and mean (SD) concentration-time profiles will be created to present the repeated-dose profile obtained from Day 1 to Day 8.

Additional PK analyses may be performed if deemed appropriate.

8.8.2 Analysis of Secondary Efficacy Endpoints

8.8.2.1 Biomarkers of Complement Activation

Biomarkers of complement activation: sC5b-9, C3a, C3, Bb, C4a, functional assays for classical and alternative complement pathways will be summarized by visit. Absolute values, changes from baseline, and percent changes from baseline will be summarized. The summaries will be done on PD set. Plots over time for biomarker results for individual patients will be prepared.

8.8.2.2 Clinical Response at Week 24

Clinical response at Week 24 will be summarized. Counts and proportions of clinical response will be reported. 95% Clopper-Pearson confidence interval (CI) for proportion of responders will also be presented. Additionally, clinical response results will be summarized for all visits similar to what was done for Week 24. Patients meeting intercurrent events (ICE), including use of prohibited medication (Plasma exchange – identified by manual review, Defibrotide – ATC code B01AX and manual review, , complement inhibitors – ATC code L04AJ) or withdraw from the study before Week 24 are considered as failures/non-responders at all the visits occurring after the medication/withdrawal. The number and percentage of patients who had an ICE and by ICE category will be presented as well. Medical review of the programmatically generated list of prohibited medications will be performed prior to interim analysis and final database lock.

In addition, investigator assessed response will be summarized per visit. Counts and proportions of response categories (clinical response, partial response, and clinical worsening) will be reported.

8.8.2.3 TMA response at Week 24

TMA response at Week 24 is defined as improvement in laboratory markers as follows:

- LDH < 1.5 x ULN **and**
- Platelet count ≥ 50*10^9/L (50 000/mm^3) without transfusion support during the prior 7 days **and**
- ≥ 50 % reduction from baseline in rUPCR

TMA response will be analyzed in the same way as Clinical Response at Week 24 (see Section §8.8.2.2 for details).

8.8.2.4 Overall Survival at Day 100

Overall survival at Day 100 (days) is defined as survival from the day of TA-TMA diagnosis and will be analyzed using Kaplan-Meier model. Kaplan-Meier survival estimate at Day 100 and its 95% CI will be presented. Counts and proportions of patients with events and censored will be presented, together with estimates of median and quartiles obtained from the model. Kaplan-Meier curves will also be presented. Death for any cause will be considered an event, with the date of death defining the event date. Patients alive on the date of last contact will be censored on this date. Pegcetacoplan-withdrawn patients for which survival at Day 100 is unknown will be censored at the date of last contact. If the event/censored date is more than 100 days from the start date, the patient will be considered censored at 100 days.

8.8.2.5 Overall Survival at Week 24

The start date for overall survival at Week 24 from treatment start will be defined as the date of first exposure

to the study drug. Death for any cause will be considered an event, with the date of death defining the event date. Patients alive at the end of the study visit will be considered censored at the date of the visit.

Overall survival at Week 24 (weeks) will be analyzed in the same way as Overall survival at Day 100 (see Section §8.8.2.4 for details).

8.8.2.6 TIME TO CLINICAL RESPONSE

Time to clinical response (weeks) will be defined as the date of first exposure to the study drug to the first occurrence of clinical response (derived as in Appendix I [Section 13.1]). Time to clinical response (weeks) will be evaluated for:

- Patients achieving clinical response (without a preceding ICE) at any time during the study. Note the patient in this case will be considered as a responder even if not any longer in clinical response at week 24 or not (sustained response not required)
- Patients achieving clinical response at Week 24 without meeting an ICE (response must be sustained until Week 24)

In sustained response, if the patient has a missing evaluation at Week 24, this patient will not be considered as a responder and will be censored on the day after the last previous assessment in which the response could be evaluated. Patients without clinical response at any visit up to Week 24 will be censored on the day after the last previous assessment in which response could be evaluated. Patients with no clinical response evaluation visits will be excluded from the analysis.

In case clinical response is lost, and redetected, the date of clinical response will be defined as the date when the most recent clinical response was detected. For sustained response, this date will be the event date if the patient is in clinical response at week 24.

The time to clinical response (weeks) will be analyzed in the same way as Overall survival at Day 100 (see Section §8.8.2.4 for details). Nevertheless, Kaplan-Meier curves will be presented as increasing curves as the event here is positive.

8.8.2.7 TIME TO TMA RESPONSE

Time to TMA response (weeks) will be defined as the date of first exposure to the study drug to first occurrence of TMA response (derived as in Appendix II [Section 13.2]). Time to TMA response (weeks) will be evaluated for:

- Patients achieving TMA response (without a preceding ICE) at any time during the study. Note the patient in this case will be considered as a responder even if not any longer in TMA response at week 24 or not (sustained response not required)
- Patients achieving TMA response at Week 24 without meeting an ICE (response must be sustained until Week 24)

The time to TMA response (weeks) will be analyzed in the same way as Time to Clinical Response (see Section §8.8.2.6 for details).

8.8.2.8 DURATION OF CLINICAL RESPONSE

Duration of clinical response (weeks) is defined as the time from the first observed clinical response until the response criteria is no longer fulfilled or until end of study. Duration of response will be defined for patients with clinical response without meeting an ICE. Mean and median duration of response, together with their 95% CI will be estimated using Kaplan-Meier method. Kaplan-Meier curves will also be presented. The start date will be defined as the date of the earliest clinical response. Loss of clinical response as per appendix I (Section 13.1) reported TA-TMA relapse (from Survival Status eCRF form), and death from any cause will be

considered events, with the date of loss of clinical response, date of first reported TA-TMA relapse or date of death, whichever occurs first, defining the event date. Patients without events (i.e., still in clinical response) up to Week 24 will be censored at the date of the last clinical response evaluation prior to end of study.

8.8.2.9 DURATION OF TMA RESPONSE

Duration of TMA response (weeks) is defined as the time from the first observed TMA response until the response criteria is no longer fulfilled or until end of study. Duration of response will be defined for patients with TMA response without meeting ICE. The start date will be defined as the date of the earliest TMA response. Loss of TMA response as per appendix II (Section 13.2), reported TA-TMA relapse (from Survival Status eCRF form), and death from any cause will be considered events, with date of loss of TMA response, date of first reported TA-TMA relapse or date of death, whichever occurs first, defining the event date. Patients without events (i.e., still in TMA response) up to Week 24 will be censored at the date of the last TMA response prior to end of study.

The duration of TMA response (weeks) will be analyzed in the same way as Duration of Clinical Response (see Section §8.8.2.8 for details).

8.8.2.10 PROPORTION OF PATIENTS WITH TA-TMA RELAPSE AT WEEK 24

Proportion of patients with TA-TMA relapse at week 24 will only be defined for patients reaching clinical response at some point of the study. TA-TMA relapse will be defined as reappearance of clinical/laboratory markers of TA-TMA as outlined in Inclusion Criterion #3. Counts and proportions of patients with and without relapse at Week 24 will be summarized. 95% Clopper-Pearson CI for proportion of patients with TA-TMA relapse will also be presented.

8.8.2.11 CLINICAL RESPONSE AT WEEK 12

Analysis of Clinical Response at Week 12 is covered in the Section §8.8.2.2.

8.8.2.12 TA-TMA RESPONSE AT WEEK 12

Analysis of TA-TMA Response at Week 12 is covered in the Section §8.8.2.3.

8.8.3 [redacted]

8.8.3.1 [redacted]

[redacted]

8.8.3.2 [redacted]

[redacted]

[redacted]

8.8.3.3 [redacted]

[redacted]

8.8.3.4 [redacted]

[redacted]

8.8.3.5 [redacted]

[redacted]

8.8.3.6 [redacted]

[redacted]

8.8.3.7 [redacted]

[redacted]

8.8.3.8 [redacted]

[redacted]

[redacted]

8.9 Safety Endpoints and Analyses

Safety analyses will be performed using the Safety set. All data relating to safety will be listed and summarized using descriptive statistics. No inferential statistical tests will be performed.

8.9.1 Adverse Events

All AEs will be coded using MedDRA version current at the time of the DBL.

Pre-treatment AEs are those occurring between the ICF signature and the first IMP administration. TEAEs are defined as those AEs that start or worsen after the first dose of IMP and up to 8 weeks after the last IMP dose. Events will be flagged as treatment-emergent unless sufficient data are available to conclude that the start/worsening occurred before the treatment was started.

If the severity or relationship is missing for one of the treatment-emergent occurrences of an adverse event for a patient, the maximal severity or relationship on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

An overall summary table of the number and percentages of patients within the following categories will be provided:

- Any TEAE,
- Any related TEAE,
- Any serious TEAE,
- Any related serious TEAE,
- Any non-serious TEAE,
- Any related non-serious TEAE,
- Any TEAE leading to withdrawal of pegcetacoplan,
- Any serious TEAE leading to withdrawal of pegcetacoplan,
- Any TEAE leading to drug interruption,
- Any TEAE that is considered as a Target Medical Event as defined in Table 2 - Definition of Target Medical Events,
- Any TEAE leading to death,
- Any TEAE that were infusion site reactions (as per eCRF, both injection and infusion site reactions

will be included),
- Any device related TEAEs (as per eCRF),
- Any TEAE by severity (mild, moderate and severe).

Pre-treatment AEs will be listed.

TEAEs, serious TEAEs, non-serious TEAEs, TEAEs by severity (mild, moderate, and severe), TEAEs related to pegcetacoplan, TEAEs leading to the withdrawal of pegcetacoplan, TEAEs leading to drug interruption, TEAEs that are considered as Target Medical Events, TEAEs that were infusion site reactions, device related TEAEs and AEs leading to death will be summarized by SOC and PT. Three categories of selected target TEAEs (Target Medical Events, defined in Table 2 - Definition of Target Medical Events) that are considered as Target medical Events will be summarized a posteriori. Summaries will include incidence of AEs, and number of events. The severity of AEs and the relationship to the IMP will be summarized for each SOC and PT.

Pre-treatment AEs, TEAEs, serious TEAEs, non-serious TEAEs, TEAEs by severity (mild, moderate and severe), TEAEs related to pegcetacoplan, serious TEAEs related to pegcetacoplan, TEAEs leading to withdrawal of pegcetacoplan, and target medical events will be summarized by PT.

At each level of summarization, a patient is counted once if he/she reported 1 or more events at that level. These summaries by SOC and PT will be sorted by decreasing order of overall incidence of SOC and decreasing order of overall incidence of PT within SOCs. In case of identical frequencies, SOC and PT will be sorted alphabetically. The summaries by PT will be sorted by decreasing frequency of overall incidence of PT.

All AE data will be listed including onset date, duration, relationship to IMP, severity, seriousness, action taken with IMP, treatment of event and outcome.

8.9.2 Hematology, Serum Chemistry and Coagulation

Summary statistics of quantitative laboratory results and changes from baseline will be summarized by visit. Shift tables of worst post-baseline assessments (including unscheduled observations) vs. baseline will be presented. For parameters with NCI-CTCAE toxicity grades for changes in both directions, the shift tables will be done using NCI-CTC toxicity grades, with separate parameters depending on the direction. For parameters with NCI-CTCAE toxicity grades for changes in only one direction, the shift tables will be done using the NCI-CTC toxicity grades and the normal ranges (Low, Normal, High, Missing). For parameters without NCI-CTCAE toxicity grades for changes, the shift tables will be done using the normal ranges. Out-of-range values will be flagged in data listings. In addition, scatterplots for lab parameters (baseline vs. post-baseline values) will be prepared.

8.9.3 Urinalysis

Continuous results will be summarized together with changes from baseline similarly to hematology per visit, and categorical results will be summarized in frequency tables by visit. Tests for which normal ranges are provided will also be summarized by means of frequency and shift tables in the same way as the hematology results.

8.9.4 Vital Signs, Physical Examination and ECG

Summary statistics of vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature) and their changes from baseline will be presented by visit and timepoint.

Physical examination data will be presented in a listing.

The incidence of clinically significant abnormal ECG findings will be summarized by visit and timepoint.

8.9.5 ANTI-PEGCETACOPLAN AND ANTI-PEG ANTIBODIES

The proportion of patients with positive anti-drug antibodies (ADA) results during the study will be summarized at each visit for the Safety and PK set. Neutralizing antibodies will also be summarized for patients from the Safety set who had positive ADA results.

The proportion of patients with ADA results by category (as outlined below) will be summarized.

- Patients with treatment emergent ADA: any patient negative for ADA at baseline and positive at any post-baseline samples.
- Patients with treatment boosted ADA: any patient positive for ADA at baseline and with a measurable titer at any post baseline sample if the baseline titer was not reportable or with an increase in titer by 4-fold if the baseline titer was reportable.

ADA titers and fold-increases overall and of the maximum titer of each patient will be summarized descriptively with medians, interquartile range (Q1 and Q3) for treatment-emergent, and treatment-boosted ADA, respectively.

ADA will also be listed.

8.9.6 DEATHS

The proportion of patients who died will be summarized by cause of death.

Deaths will also be listed.

9. INTERIM AND FINAL ANALYSIS

No interim analysis will be conducted.

The final analysis is planned to be performed when all patients have completed the End of Study visit (Week 24) or Early Termination visit in case of early discontinuation.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

- The analysis of target medical events has been introduced to the analysis. This is a new analysis not mentioned in the protocol. The Adverse Event of Special Interest is usually defined prospectively. The alternative term “Target Medical Event” is used to avoid any confusion created by the use of a term associated in normal terminology to a prospective definition.
- The administrative interim analysis required to be conducted by study Protocol Sobi.PEGCET-201 when at least 10 patients have completed 12 weeks of treatment (or have been withdrawn) for informing about future development program will not be conducted. The rationale is that its purpose is future planning of the TA-TMA development program. The Sponsor determined that the planned interim analysis would not provide sufficiently different information from those of the final analysis to provide extra guidance and that there was no need to obtain earlier information for development program planning. The underlying reason is that this provision was thought for the event of a slow recruitment creating a long lead time while the latest study patients were recruited during which development design and interactions with Authorities benefiting for the interim analysis results would need to be conducted. In the actual conduct of the study, the end of the study was a rapid recruitment period (last 5 patients recruited in 5.5 months, of which last 3 patients recruited in about 12 weeks) rendering futile the conduct of the interim analysis as compared to the expected date of the final analysis.

11. PROGRAMMING SPECIFICATIONS

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

The margins should be at least 1.50 inches for the binding (top) edge and 1.0 inches for all others. Courier New 8-point bold font will be used for all outputs. TLFs will be produced in “rtf”, “doc(x)” and “pdf” format in landscape layout. Outputs will be delivered as three files in PDF format: one for all the tables, one for all the listings, and one for all the figures.

In the top left portion of each output, the protocol number will be presented. On the next line, an output number followed by the title of the output and population information will be displayed. Horizontal lines will appear after the column heading of the output. Footnotes will be put under the main body of text at the bottom of the page. All abbreviations used in the output will be given in the footnote. For all tables reporting percentages, the denominator used for percentage calculation will be described either in the body of the table or in a footnote. The source listing number will be displayed for all tables. The SAS program name and programmer ID will appear at the bottom left corner in a string, and the page number will appear in the bottom right corner of each output. The date and time of creation of the output will appear at the top right, just above the page number. Additionally, the following information should be produced by the SAS program and displayed in each output: the sponsor’s name, the database lock date or data snapshot date, the cut-off date for analysis (if applicable), and the name of the program output and its location.

Any date information in the listing will use the date9. Format, for example, 07MAY2002.

Example:

```
Swedish Orphan Biovitrum AB
Sobi.PEGCET-201                                                                                 01DEC2018 11:51
                                                                                                    Page X of Y
                                            Listing XXX
                                               Title
                                            (Population)

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Source: Listing Number        Data set: ADXX
Generated by: \\ PEGCET-201_XXX_XXX.sas (Programmer ID: XX)                          Final/Draft version
Output: \\ PEGCET-201_XXX_XXX_201812011437             Analysis Cut-off: 15SEP2018 Database Lock: 01OCT2018
```

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

12. LIST OF TABLES, LISTINGS, AND FIGURES

The TFLs for this study are presented in a separate document (PEGCET-201 Mock TFLs).

13. APPENDICES

13.1 APPENDIX I. DERIVATION RULES FOR CLINICAL RESPONSE

eCRF forms: Platelet or PRBC Transfusion form, Central laboratory sampling form, Baseline TA-TMA form, Clinical Response Evaluation form,
Programming note: If central lab values not available, use local lab values reported on the clinical response evaluation form

Improvement in laboratory markers
IF [(LDH < 1.5 x ULN) **AND** (Platelet count ≥ 50*10^9/L (50 000/mm^3)) **AND**
((Any blood transfusions performed=No) **OR**
((Any blood transfusions performed=Yes) **AND** (Type of blood transfusion=PRBC **OR**
Type of blood transfusion=Platelet) **AND** (Date of blood sample taken> Date of last platelet transfusion + 7 days)))**]**

THEN lab markers response =1 **ELSE** lab markers response=0

Renal response
IF *(Has the patient any sign/symptom of kidney dysfunction=Yes)* **THEN DO**
IF [(((*creatinine_baseline* – creatinine)/*creatinine_baseline*) > 0.4)
OR
((creatinine_baseline > ULN mg/dL (abnormal high)) **AND** (creatinine <= ULN mg/dL (normal))
OR
(discontinuation of renal replacement therapy=Yes)
OR
(((*rUPCR_baseline* – rUPCR)/ *rUPCR_baseline)* ≥ 0.5)]
THEN renal response =1 **ELSE** renal response=0
END
ELSE renal response=0

Pulmonary response
IF *(Has the patient any sign/symptom of lung dysfunction=Yes)* **THEN DO**
IF [(Absence of positive pressure ventilation =Yes)
AND
(Absence of invasive ventilator support=Yes)**]**
THEN pulmonary response =1 **ELSE** pulmonary response=0
END
ELSE Pulmonary response=0

Gastrointestinal (GI)
IF *(Has the patient a biopsy-proven GI involvement of TA-TMA=Yes)* **THEN DO**
IF [(Presence of nausea, vomiting or anorexia attributed to TA-TMA=No)
AND
((Stool output: in mL/day < 500 mL/day) **OR** (Stool output: number of episodes/day< 3 episodes/day))**]**
THEN GI response=1 **ELSE** GI response=0
END
ELSE Gastrointestinal response =0

Cardiovascular response
IF (*Has the patient any sign/symptom of Cardiovascular dysfunction=Yes)* **THEN DO**
IF [
((*Has the patient a diagnosis of pulmonary hypertension =Yes)* **AND** (Is pulmonary hypertension present=No))
OR
[((pre-antihypertensive therapy diastolic blood pressure ≥ 90 *mmHg)* **OR**
(pre-antihypertensive therapy systolic blood pressure ≥ 140 *mmHg)* **OR**
((Is the patient taking any antihypertension medication=Yes*)* **AND** *(the number of ongoing medications excluding diuretics* >2 *)))*
AND
((diastolic blood pressure< 90 mmHg) **AND**
(systolic blood pressure < 140 mmHg) **AND**
(Ongoing medications for arterial hypertension excluding diuretics < 2))]
]
THEN cardiovascular response=1 **ELSE** cardiovascular response=0
END
ELSE cardiovascular response=0

Serositis response

IF [*((Has the patient any sign/symptom of Serositis=Yes, Pericardial effusion)* **AND**
(was surgical therapy required =Yes, Pericardiocentesis) **AND**
(Presence of pericardial effusion requiring pericardiocentesis=No))
OR
((Has the patient any sign/symptom of Serositis=Yes, Pleural effusion) **AND**
(was surgical therapy required=Yes, Thoracocentesis) **AND**
(Presence of pleural effusion requiring thoracocentesis=No))]
THEN serositis response=1 **ELSE** serositis response=0

CNS response

IF *(Has the patient any sign/symptom of CNS dysfunction=Yes)* **THEN DO**
IF [(Irreversible neurological conditions=Stabilized)
OR
(Reversible neurological conditions: cessation of seizures or controlled seizures under medication, resolution of mental alteration=Yes)**]**
THEN CNS response=1 **ELSE** CNS response=0
END
ELSE CNS response=0

Freedom of transfusion

IF *(Any blood transfusions performed at Baseline =Yes)* **THEN DO**

IF [(Any blood transfusions performed=No)
OR
((Any blood transfusions performed=Yes) **AND** (Was the transfusion attributed to TA-TMA=Yes) **AND** (date of response assessment > Start date of transfusion + 7))**]**
THEN freedom of transfusion = 1 **ELSE** freedom of transfusion=0
END
ELSE freedom of transfusion=0

Please note that any blood transfusion with date before the first study drug administration should be identified as “Any blood transfusions performed at baseline”.

IF [(improvement of laboratory markers =1) **AND**
((renal response + pulmonary response + GI response + neurological response + freedom of transfusion + cardiovascular response + serositis response) >= 1) **AND (**deterioration in other organs attributable to TA-TMA=0) **AND**
(Prohibited medication as described in SAP= 0)**]**

THEN
Clinical response = Yes
ELSE Clinical response = No

Please note that the derived clinical response date is defined as the date on which all the individual response parameters fulfil the response criteria i.e., the latest date among the individual parameters.

13.2 APPENDIX II. DERIVATION RULES FOR TMA RESPONSE

eCRF forms: Platelet or PRBC Transfusion form, Central laboratory sampling form.

TMA response is defined as improvement in laboratory markers as follows:

IF [(LDH < 1.5 x ULN) **AND** (Platelet count ≥ 50*10^9/L (50 000/mm^3)) **AND** ≥ 50% reduction from baseline in rUPCR **AND**
((Any blood transfusions performed=No) **OR**
((Any blood transfusions performed=Yes) **AND** (Type of blood transfusion=PRBC **OR**
Type of blood transfusion=Platelet) **AND** (Date of blood sample taken> Date of last platelet transfusion + 7 days)))**]**

THEN TMA response =1 **ELSE** TMA response=0

13.3 APPENDIX III. [redacted]

[redacted]

[redacted]

13.4 APPENDIX IV. TARGET MEDICAL EVENT

Table 2 - Definition of Target Medical Events

Target Medical Event	**Search criteria in MedDRA**
Infections	SOC Infections and infestations
Serious hypersensitivity reactions	SMQ Anaphylactic reaction (narrow) and SMQ Hypersensitivity (narrow)
Infusion site reactions	HLT Injection site reactions and HLT Infusion site reactions