Protocol Sobi.PEGCET-201
Version 3.0 (including Protocol Amendment 2), 17 September 2024

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

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)

Brief Title:

A Study of Pegcetacoplan for Patients with Transplant-associated Thrombotic Microangiopathy After Hematopoietic Stem Cell Transplantation

Final Protocol Number: **Sobi.PEGCET-201**

EU CT Number: 2023-510443-37-00

EudraCT Number: **2021-003157-27**

IND Number: **156294**

Type of Study: **Therapeutic Exploratory**

Original Protocol: **07 July 2021**

Protocol version 3.0 (including Protocol Amendment 2): **17 September 2024**

Sponsor: **Swedish Orphan Biovitrum AB, SE-112 76 Stockholm, Sweden**

Sponsor's Medical Director		Principal Coordinating Investigator	
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Medical Director Swedish Orphan Biovitrum AB SE-112 76 Stockholm, Sweden		[redacted]	
[redacted]			
Signature	Date	Signature	Date

Confidential

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Investigator statement

I have read the protocol entitled "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)" and the accompanying current Investigator's Brochure. I agree to conduct the clinical investigation in compliance with the Final Protocol, Version 3.0, 17 September 2024, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Independent Ethics Committee/Institutional Review Board/Research Ethics Board and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB (publ).

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

Table of contents

Table of tables

Table of figures

Appendices

1 Synopsis

STUDY IDENTIFIERS

Title of study:	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)
Clinical study number:	Sobi.PEGCET-201
Type of study:	Therapeutic exploratory

STUDY OBJECTIVES

Primary objective:

To evaluate the pharmacokinetics (PK), safety and tolerability of pegcetacoplan in patients with TA-TMA.

Secondary objectives:

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

STUDY ENDPOINTS

Primary PK endpoints:

- Pegcetacoplan PK parameters:
  - $AUC_{0\text{-}tau}$, C_{max}, T_{max} and C_{trough}.

Safety endpoints:

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

Secondary endpoints:

- PD endpoints:
  - Absolute levels, change from baseline, and % change from baseline to Week 24 in biomarkers of complement activation: sC5b-9, C3a, C3, Bb, 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) less than 1.5 x upper limit of normal (ULN) **and**
  - Platelet count ≥ 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/nonresponders.

- **TMA response** at Week 24, defined as improvement in laboratory markers as follows:
  - LDH < 1.5 x ULN **and**
  - Platelet count ≥ 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.

[redacted]

STUDY DESIGN AND METHODS

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 indicated below (see Test product; dose and mode of administration).

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

1) Screening period (up to 2 weeks)

Informed consent will be obtained at screening before any study-related procedures being conducted. Patients will be screened to confirm that the patient selection criteria for the study have been met. Key inclusion and exclusion criteria will be reviewed by the study medical monitor and eligibility will be confirmed prior to the enrollment.

2) Treatment period (up to 16 weeks)

[redacted]

At Week 12, if a clinical and/or TMA response according to the protocol definition is not reached, the investigator may decide to continue treatment, according to his/her judgment, for a total 16 weeks of treatment. If at Week 12 the patient has reached a partial clinical response (defined as improvement in signs/symptoms in 1 or more affected organs without meeting the protocol definition of 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 below), 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.

Clinical worsening will be defined as active laboratory TA-TMA as per Inclusion Criterion #3 **and** 3 of the 5 organ injuries listed below:

a. Kidney: requirement of renal replacement therapy after initial TA-TMA control, sustained (> 7 days) and attributable to TA-TMA.
b. Lungs: requirement of sustained (> 7 days) positive pressure ventilation, and attributable to TA-TMA.
c. Cardiovascular: uncontrolled severe hypertension with > 2 medications (excluding diuretics), and attributable to TA-TMA.
d. Central nervous system (CNS): uncontrolled seizures under medication attributable to posterior reversible encephalopathy syndrome or to hypertension resulting from TA-TMA.
e. GI tract: clinically significant GI bleeding requiring ≥ 20 mL/kg/day of PRBC transfusion daily for at least 7 days.

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

3) Follow-up period (up to 12 weeks)

After completion of the treatment period, all patients will enter in the follow-up period until Week 24. This includes an End of treatment visit 4 weeks after the last IMP dose and 1 or 2 more follow-up visits every 4 weeks for patients who have completed 16 or 12 weeks of treatment, respectively. The main analysis will be performed after all patients have completed their Week 24 visit.

The end of the study is defined as when all enrolled patients have completed the follow-up period and performed the End of study visit at Week 24 or the Early Termination visit in case of early discontinuation.

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

Number of patients planned:	12 patients.
Diagnosis and main criteria for inclusion:	Patients with TA-TMA after HSCT. Inclusion criteria:

1. Male and female patients aged ≥ 18 years at the time of informed consent form (ICF) signature.
2. Received allogeneic HSCT from a related or unrelated, human leukocyte antigen-matched or mismatched donor. Patients having received any of the following stem cell sources are eligible: granulocyte colony stimulating factor mobilized peripheral blood stem cells, bone marrow, umbilical cord blood.
3. Diagnosis of TA-TMA established as per the laboratory markers below, indicating TMA:
   a. De novo or progressing thrombocytopenia (platelet count < 50 x 10^9/L or > 50 % decrease in platelet count from the highest value achieved after transplantation). AND
   b. Elevated LDH (> 1.5 x ULN).

   AND at least 2 additional laboratory/clinical criteria among the following:

c. Presence of schistocytes on the peripheral blood smear (≥ 2 per hpf) or histologic evidence of microangiopathy in any biopsied organ. OR
d. De novo anemia (hemoglobin < LLN or anemia requiring PRBC transfusion support as per local institutional standard). OR
e. Proteinuria (random urinalysis protein concentration ≥ 30 mg/dL). OR
f. Elevated plasma concentration of sC5b-9 above ULN. OR
g. Arterial hypertension, defined by systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg.

4. Have a diagnosis of TA-TMA that persists despite initial management of any triggering condition.
5. Have rUPCR ≥ 1 mg/mg.
6. Women of childbearing potential, defined as any women who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative serum pregnancy test at screening and agree to use protocol-defined methods of contraception for the duration of the study and 8 weeks after their last IMP dose.

   Note: Postmenopausal is defined as having had 12 consecutive months with no menses without an alternative medical cause.
7. Men must agree to the following for the duration of the study and 8 weeks after their last dose of IMP:
   a. Avoid fathering a child.
   b. Use protocol-defined methods of contraception.
   c. Refrain from donating sperm.
8. Patient and/or legally authorized representative must be capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF.

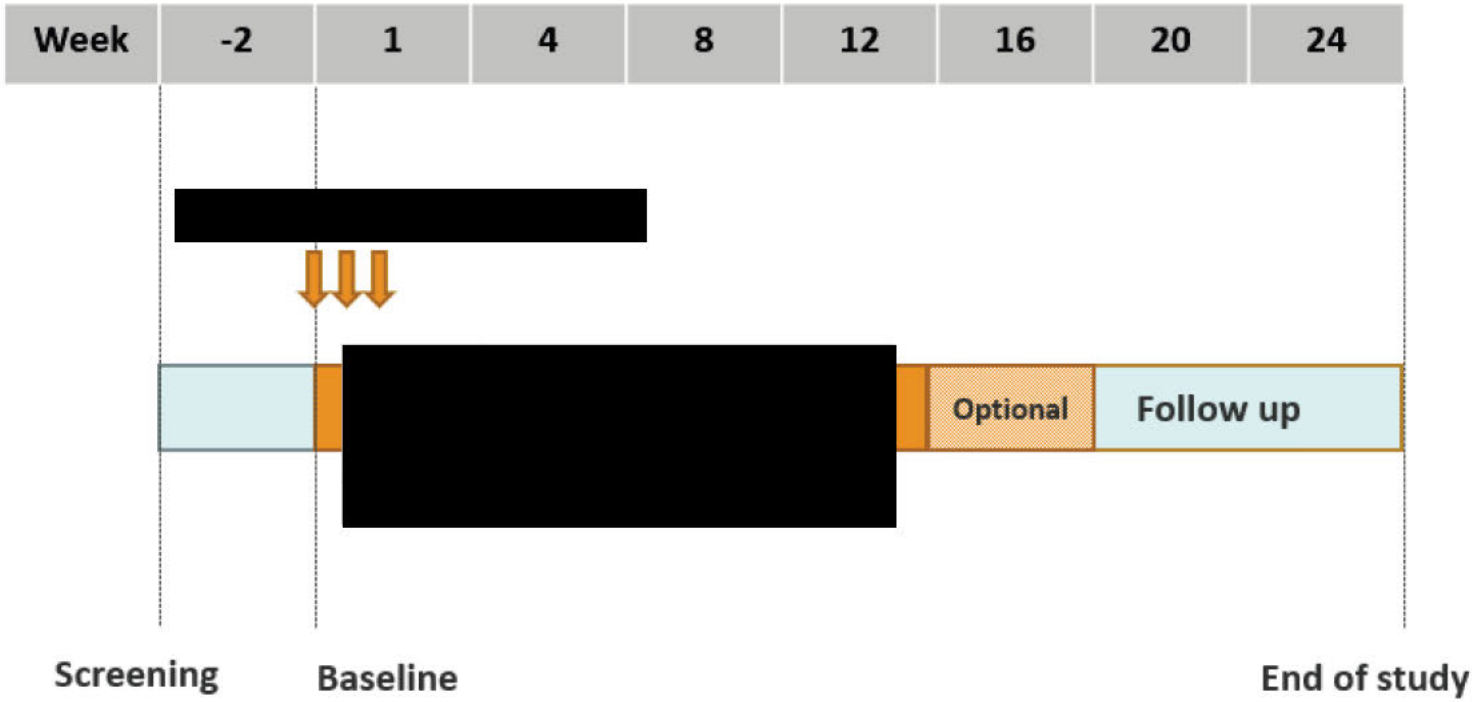
Exclusion criteria:

1. Positive direct Coombs test.
2. Known familial or acquired ADAMTS13 deficiency.
3. Known Shiga toxin-related hemolytic uremic syndrome.
4. Known bone marrow or graft failure.
5. Diagnosis of disseminated intravascular coagulation.
6. Diagnosis of veno-occlusive disease (VOD).
7. Active GI bleeding (hematemesis or hematochezia) at baseline.
8. Body weight < 30 kg and > 100 kg.
9. Uncontrolled systemic bacterial or fungal infection, presence or suspicion of sepsis.
10. Previously or currently treated with a complement inhibitor (approved or investigational).
11. Pregnancy or breastfeeding.
12. Positive human immunodeficiency virus antibody at screening or documented in pre-HSCT medical record.
13. Hepatitis C virus detectable by polymerase chain reaction at screening or documented in pre-HSCT medical record.
14. Chronic inactive hepatitis B virus with viral loads > 1000 IU/mL (> 5000 copies/mL) at screening or documented in pre-HSCT medical record. Eligible patients who are chronic active carriers (≤ 1000 IU/mL)

	must receive prophylactic antiviral treatment (e.g., entecavir, tenofovir, lamivudine) according to local country guidelines. 15. Known or suspected hereditary fructose intolerance. 16. Hypersensitivity to pegcetacoplan or any of its excipients. 17. Inability to cooperate with study procedures or any condition that, in the opinion of the investigator, could increase the patient's risk by participating in the study or confound the outcome of the study.
Assessments:	Refer to Table 1.
Test product; dose and mode of administration:	Pegcetacoplan is a 54-mg/mL solution for injection/infusion for [redacted] or s.c. use. Each vial contains 1080 mg pegcetacoplan in a 20-mL volume. Pegcetacoplan will be administered using a syringe pump. [redacted] No dose modification is foreseen in this study. Treatment interruption or discontinuation necessary to manage toxicities will be decided upon investigator's judgment and should be discussed with the study medical monitor.
Reference product; dose and mode of administration:	Not applicable.
Duration of treatment(s):	Up to maximum 16 weeks.
Determination of sample size:	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 %).
Statistical methods:	All endpoints will be evaluated with descriptive statistics. PK and PD may also be presented graphically.

Study schematic

Figure 1 Study schematic



Abbreviations: s.c., Subcutaneous; [redacted]

Schedule of assessments

Table 1 Schedule of Assessments

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
Informed consent	X														
Demographics	X														
Medical history	X														
Inclusion/ Exclusion criteria	X	X													
Vaccination [a]	X														
Mandatory anti-infective prophylaxis [b]			----------→												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height	X														

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
12-lead ECG (prior to venipuncture)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pegcetacoplan administration [c]		----------→													
Infusion-site assessment [d]		----------→													
Concomitant medications/ treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs measurements [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, serum chemistry, coagulation profile [g]	X	X [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [g]	X	X [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers of complement activation		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibodies to PEG and pegcetacoplan [h]	X	X		X		X				X		X	X	X	X
HIV, HCV-RNA, HBV-DNA [i]	X														
Serum pregnancy (β-HCG and FSH) [k]	X														
Urine pregnancy [k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs [m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Platelet and PRBC transfusions collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear for schistocytes evaluation	X														

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
Biopsy collection of any affected organ (if performed)	X														
Direct Coomb's test	X														
ADAMTS13 activity test	X														
[redacted]	X	*X*													
rUPCR	X	X [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical response evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X				X		X		X			X		X
[redacted]		X								X					X
[redacted]															X

Study period	Screening	Treatment period									Optional treatment		Follow-up period		
Study Week	-2	Baseline 0	1	2	3	4	6	8	10	12	*14*	*16*	EOT/ET [o] 16	20 [o]	EOS 24
Study Day	-14	1	8	15	22	29	43	57	71	85	*99*	*113*	113	141	169
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Visit window (± days)			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 3)	(± 3)	(± 3)
Survival status and evidence of TA-TMA relapse													X	X	X

Abbreviations: AE, Adverse event; β-hCG, Human chorionic gonadotropin-beta; [redacted] ECG, Electrocardiogram; eCRF, Electronic case report form; EOS, End of study; EOT, End of treatment; [redacted] ET, Early Termination; [redacted] FSH, Follicle stimulating hormone; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HSCT, Hematopoietic stem cell transplantation; ICF, Informed consent form; [redacted] PEG, Polyethylene glycols; [redacted] PK, Pharmacokinetic; PRBC, Packed red blood cells; rUPCR, Random urine protein:creatine ratio SAE, Serious adverse event; s.c., Subcutaneously; [redacted] TA-TMA, Transplant-associated thrombotic microangiopathy; [redacted].

[a] Patients should be vaccinated against *Neisseria meningitidis* (Types A, C, W, Y, and B) either within 2 years prior to Day 1 or if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. Patients should be re-vaccinated against *Haemophilus influenzae* Type B and *Streptococcus pneumoniae* if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT.

[b] All patients must continue to be administered coverage with prophylactic antibiotics and antifungals according to institutional posttransplant infection prophylaxis guidance, including coverage against *N. meningitidis*, for the entire treatment period and for 8 weeks following the final dose of pegcetacoplan.

[c] [redacted] If deemed by the investigator that a patient can be discharged from hospital upon the clinical improvement, pegcetacoplan administration will occur at home. Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. Patients will self-administer pegcetacoplan, after receiving appropriate training by research personnel. When the patient's pegcetacoplan dosing schedule aligns with study visit days, pegcetacoplan should be administered at the study site and complete the study procedures as outlined in this schedule of assessments. In some instances, however, a patient may not be

able to align the date of a study visit with his/her pegcetacoplan administration schedule (e.g., if the patient has to utilize the visit window in order to be able to attend a study visit). In such instances it is important that pegcetacoplan dosing occurs according to the dosing schedule and not the visit schedule.

[d] On the days of clinic visits, if pegcetacoplan is administered at the visit site, an assessment of the pegcetacoplan infusion site will be made as a part of the AE assessment. If pegcetacoplan is administered at the visit, the site staff will observe the dosing and pump use safety will be assessed. The infusion site will be checked again within 30 minutes after each study drug administration. The infusion-site assessments will be performed by an appropriately trained staff, as delegated by the investigator. The infusion site and surrounding area will be inspected for redness, swelling, induration and bruising. The patient will be asked about the presence of pain and/or tenderness, and any issue related to pump use. Patients will be instructed to notify the investigator or other study personnel if an infusion-site reaction occurs after self-administration of pegcetacoplan.

[e] Vital signs (body temperature, respiration rate, heart rate, systolic and diastolic blood pressure measurements) will be evaluated per institutional practices. When pegcetacoplan is administered at the study site, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 min) postdose.

[f] On dosing Days 1, 3 and 5, PK samples will be taken up to 30 minutes predose and at 15 minutes (± 5 min), 30 minutes (± 5 min), 1 hour (± 10 min), 4 hours (± 10 min), 8 hours (± 30 min), and 24 hours (± 30 min) postdose. From Day 8 and onwards, PK samples will be taken predose at all other visits.

[g] Laboratory tests: refer to Table 3. Blood and urine samples will be analyzed at a central unless a local laboratory facility is necessary, as defined in the laboratory manual. Urine samples will be analyzed by dipstick and microscopic analysis. The use of silica agents should be avoided in patients treated with pegcetacoplan.

[h] Samples that are confirmed positive for anti-pegcetacoplan peptide or anti-PEG antibodies will be characterized with an antibody titer for that specific antibody. Any samples that are confirmed positive for anti-pegcetacoplan peptide antibody will be further characterized with a neutralizing antibody assay. If a clinic visit is on a dosing day, the sample should be taken predose but otherwise a sample is still required.

[i] Pre-HSCT evaluations will be accepted as screening tests.

[k] β-HCG for women of childbearing potential and FSH for postmenopausal women. For women of childbearing potential, a serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all subsequent site visits. Patients with positive results will be excluded or discontinued from the study.

[m] All AEs occurring upon receiving the first IMP dose up to 8 weeks after last IMP administration must be recorded in the eCRF. SAEs will be reported from signing of the ICF up to 8 weeks after last IMP administration. New SAEs occurring at any time after the 8-week AE follow-up period up to EOS should be reported only if considered causally related to previous exposure to the IMP by the investigator.

[redacted]

[o] An 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. The main analysis will be performed after all patients have completed their Week 24 visit.

[p] Blood collection for safety laboratory tests at Day 1 can be omitted if screening samples were collected on Day -1.Note: On dosing days, all blood samples will be collected predose. The date and time of the sample and the date and time of the previous dose of pegcetacoplan must be recorded in the eCRF.

Note: Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.

2 Abbreviations and definition of terms

2.1 List of Abbreviations and definitions

Term	Definition
AE	Adverse event
aPTT	Activated partial thromboplastin time
AUC	Area under the concentration-time curve
$AUC_{0\text{-}tau}$	Area under the concentration-time curve over the dosing interval
BATAP	Bilirubin, Age, Thrombocytopenia, Anemia, Proteinuria
Bb	Activated factor B
BP	Blood pressure
C3	Complement component 3
C3a	Complement component 3a
C4a	Complement component 4a
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 19
CSR	Clinical study report
C_{trough}	Observed serum concentration predose
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good clinical practice
GI	Gastrointestinal
GVHD	Graft-versus-host disease
hpf	High power field
HSCT	Hematopoietic stem cell transplantation

[redacted]	[redacted]
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
[redacted]	[redacted]
[redacted]	[redacted]
IMP	Investigational medicinal product
IRB	Independent review board
IRT	Interactive response technology
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MAGIC	Mount Sinai Acute Graft-versus-host disease International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PRBC	Packed red blood cells
rUPCR	Random urine protein/creatinine ratio
s.c.	Subcutaneous(ly)
SAE	Serious adverse event
SAP	Statistical analysis plan
sC5b-9	Terminal complement complex (soluble)

[redacted]	[redacted]
Sobi	Swedish Orphan Biovitrum AB (publ)
SOC	System organ class
SRC	Safety Review Committee
TA-TMA	Transplant-associated thrombotic microangiopathy
TEAE	Treatment-emergent adverse event
TMA	Thrombotic microangiopathy
T_{max}	Time of the maximum measured serum concentration
[redacted]	[redacted]
ULN	Upper limit of normal
VOD	Veno-occlusive disease
WHO-DD	World Health Organization-Drug Dictionary

3 Ethics

3.1 Independent ethics committee and/or institutional review board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written patient information and ICF from the IEC/IRB. The investigator should file all correspondence with the IEC/IRB. Copies of IEC/IRB correspondence and approvals should be forwarded to Swedish Orphan Biovitrum (Sobi).

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the ICH GCP [1], applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki) [2].

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient (or patient's acceptable representative) prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. The written patient information and/or ICF must not be changed without prior discussion with Sobi. Before any revisions are implemented, the revised written patient information and/or ICF must be approved by the IEC/IRB.

It is the responsibility of the investigator to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed ICF.

4 Introduction

4.1 Background

TA-TMA is a life-threatening complication of HSCT characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ damage most commonly affecting the kidneys, lungs, CNS and the GI tract due to platelet clumping in the microcirculation [3].

The incidence of TA-TMA varies widely, in part, due to the lack of standard diagnostic criteria. The reported incidence of TA-TMA following allogeneic transplant ranged from 0 % to 64 % in a review of 35 published case series, though 28 different diagnostic criteria were used [4,5]. Since 2005, several studies have proposed different algorithms to assist in the diagnosis of TA-TMA using various clinical and laboratory criteria [5,6,7,8]. However, frequently, TA-TMA

is clinically judged at an earlier stage before all these criteria are fulfilled, and most retrospective studies have been based on cases diagnosed by nonharmonized diagnostic criteria [9]. Diagnostic misjudgment may also be caused by the co-existence of other HSCT complications, such as infections, GVHD and VOD/sinusoidal obstruction syndrome, usually appearing in the acute phase after allo-HSCT when TA-TMA is most often observed [10]. The pathophysiology of TA-TMA differs substantially from that of idiopathic thrombotic thrombocytopenic purpura as evidenced by normal levels of ADAMTS13 [11] and a normal von Willebrand factor multimer pattern [12]. Endothelial injury is fundamental to the pathogenesis of TA-TMA, and the initiation of endothelial injury can be portrayed as a "2-hit" process consisting of generation of risk factors that create a procoagulant state during the preconditioning and an early aplastic phase post HSCT (infections, chemotherapy and radiotherapy, prolonged immobilization, human leukocyte antigen mismatch, unrelated donor), and subsequent exposure to conditions that facilitate injury during the recovery phase and beyond (calcineurin and mechanistic target of rapamycin inhibitors, acute GVHD, infections). The endothelial injury initiates the process of platelet aggregation and thrombus formation in the microvessels. These microthrombi lead to consumptive thrombocytopenia, affected organ failure and intravascular hemolysis [13].

Despite the broadened understanding of its pathogenesis and significant improvement in pre- and posttransplant supportive care, TA-TMA is still recognized as a devastating complication after allogeneic HSCT, exhibiting a mortality rate of up to 60 % to 75 % [6,14].

4.2 Study rationale

Significant effort was made in recent years by researchers and physicians to better understand the complement role in the pathophysiology of TA-TMA [3].

In 2015, the first prospective TA-TMA monitoring study was published by Jodele et al in 100 children and young adults demonstrating that complement activation plays a significant role in the pathogenesis and severity of TA-TMA. This prospective study showed that recipients with HSCT with both proteinuria and terminal complement activation as measured by elevated plasma C5b-9 level had very poor 1-year HSCT survival (< 20 %), whereas patients without complement activation (normal plasma C5b-9) survived without any targeted interventions [3]. This initial research was followed with several valuable studies dedicated to the understanding of the complement system in TA-TMA pathogenesis, and investigating complement system as a diagnostic and therapeutic target [15,16,17]. Jodele et al also examined the possibility of genetic predisposition to TA-TMA by analyzing 17 candidate genes known to play a role in complement activation by using gene expression profiling. Totally, 65 % of patients with TA-TMA had genetic variants in at least 1 gene compared with 9 % of patients without TA-TMA. Patients at risk of developing TA-TMA likely have complement genetic polymorphisms that would not be significant under normal life circumstances, but complement activation can be provoked under adequate stressors of the transplantation process like chemotherapy, radiation, infections and medications. The complement system is activated by the stressors in susceptible individuals leading to vascular endothelial injury due to an activated terminal complement complex resulting in end-organ injury. All these data together indicate that HSCT-associated TMA is driven by

complement-mediated tissue injury and that complement dysregulation is not simply a marker of tissue injury incurred during transplantation [18].

There are no universally agreed on care strategies for TA-TMA after HSCT [18]. Treatment of TA-TMA is mostly supportive, including withdrawal or minimization of medication insult to endothelium, treatment of co-existing conditions such as infections and GVHD that may aggravate TMA and aggressive hypertension management. However, these interventions are successful only in nonsevere TA-TMA cases where the end-organ damage is not yet established [3,13]. A few pharmacologic agents like rituximab, defibrotide and daclizumab have been explored in TA-TMA with limited efficacy, and there are currently no approved drugs for this indication. Recently, several case reports and small studies have reported successful use of the C5 inhibitor eculizumab in TA-TMA [8,19,20]. However, eculizumab therapy in TA-TMA has some challenges, including difficulty in achieving therapeutic levels in critically ill patients, longer periods of induction therapy needed in many patients and limited availability in many countries [13]. A substantial unmet medical need exists for patients with TA-TMA.

Pegcetacoplan is formed by a pentadecapeptide (combining a bioactive cyclic tridecapeptide C3 inhibiting moiety and a 2–amino acid linker) covalently coupled to each end of a linear 40 kDa PEG chain, so that there are 2 active peptide moieties per molecule of pegcetacoplan. The peptide portion of the drug binds to complement C3 and is a broad modulator of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. The PEGylation of the molecule imparts slower elimination from mammalian systems following administration (see the pegcetacoplan IB). Pegcetacoplan has already proved to be effective in several clinical trials in complement-mediated hematological diseases (PNH, cold agglutinin disease). Pegcetacoplan received marketing approval in the US and EU for the treatment of adults with PNH in 2021, and further approvals have been obtained in Japan, Russia, Australia, and other countries in Europe, Asia, and Latin America. Moreover, on 06 May 2024, the indication in the EU was expanded to allow the treatment of adult patients with PNH who have hemolytic anemia.

On the basis of scientific and clinical evidence on the role of complement activation in TA-TMA, it can be anticipated that pegcetacoplan, which acts through modulation of the complement system, has the potential to prevent the C3-mediated overactivation of complement pathways leading to endothelial injury and may represent a valid treatment strategy for patients with TA-TMA.

4.3 Potential risks and benefits

Cumulatively, up to 13 May 2024, approximately 659 patients have been systematically exposed (via [redacted] and s.c. route) to pegcetacoplan in completed and ongoing studies across multiple indications (refer to the pegcetacoplan IB). The administration of pegcetacoplan was well tolerated and the safety data did not indicate any significant safety concern. Nonetheless, a number of safety monitoring practices are being employed by this protocol to ensure patient safety, including physical examination, vital signs monitoring, ECGs, hematology (including coagulation), serum chemistry, urinalysis, and prompt reporting of AEs.

The event of hypersensitivity was identified as having a strong causal association with systemic pegcetacoplan. Cumulatively, in the systemic clinical development program for pegcetacoplan, 3 SAEs were assessed as related by investigators and the sponsor. Two SAEs of hypersensitivity and one SAE of hypersensitivity pneumonitis have been reported. The SAEs occurred in Study APL2-PNH-204 (hypersensitivity), Study APL2-ALS-206 (hypersensitivity), and Study APL2-302 (hypersensitivity pneumonitis).

As with other complement-inhibiting drugs, there is a potential increased risk of infections with encapsulated pathogens including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* Type B. Cumulatively in the systemic clinical development program for pegcetacoplan, 4 SAEs of infections associated with encapsulated bacteria have been reported. The 4 SAEs are comprised of 2 events of pneumococcal infection (1 pneumonia and 1 upper respiratory infection/epiglottitis), 1 event of pneumonia pneumococcal in Study APL2-C3G-310, and 1 event of Klebsiella pneumoniae in Study APL2-C3G-308. Three events of pneumococcal infections occurred in participants with renal disease; 2 of 3 were participants who had had a kidney transplant and were on immunosuppressive treatment. One case of Klebsiella pneumoniae occurred in a participant with PNH who had a history of medullary aplasia and pancytopenia. All cases were assessed as unrelated to pegcetacoplan by the sponsor. These cases were observed over 913.75 patient years of cumulative exposure in clinical studies (data until 13 May 2024, inclusive). The serious infections that were observed across studies were manageable. Therefore, the sponsor believes that the data do not support an increased risk of serious infections attributable to pegcetacoplan treatment.

However, as a precautionary measure, to reduce the risk of infection, patients taking pegcetacoplan should be vaccinated against *N. meningitidis* (Types A, C, W, Y, and B) either within 2 years prior to Day 1 or if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. Patients should be re-vaccinated against *H. influenzae* Type B and *S. pneumoniae* if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. All patients must continue to be administered coverage with prophylactic antibiotics and antifungals according to institutional posttransplant infection prophylaxis guidance, including coverage against *N. meningitidis*, for the entire treatment period and for 8 weeks following the final dose of pegcetacoplan.

Body temperature and vital signs will be monitored at all clinic visits and relevant blood parameters will be monitored throughout the study to assess for signs of infection. In the event of a suspected infection, the principal investigator should provide guidance on appropriate action to be taken.

Infusion-site/pump safety will be assessed during clinical visits, and any significant finding from the assessment will be reported as an AE.

Whenever possible, the study medical monitor will be contacted before interrupting or discontinuing treatment with IMP.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with pegcetacoplan are justified by the anticipated

benefits that may be afforded to patients with TA-TMA for whom no valid alternative therapeutic options exist.

More detailed information about the known and expected benefits, and risks and reasonably expected adverse events (AEs) of pegcetacoplan may be found in the pegcetacoplan IB.

5 Study objectives and endpoints

5.1 Primary objective

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

5.1.1 Primary PK endpoints

The primary PK endpoints of this study are the following:

- Pegcetacoplan PK parameters:
  - $AUC_{0\text{-}tau}$, C_{max}, T_{max} and C_{trough}.

5.1.2 Safety endpoints

The safety endpoints are as follows:

- Occurrence of TEAEs.
- Changes from baseline in laboratory parameters and vital signs.
- Occurrence of clinically significant abnormal ECG findings.
- Presence of antibodies to PEG and pegcetacoplan throughout treatment and follow-up periods.

5.2 Secondary objectives

The following are the secondary objectives of this study:

- To evaluate the PD of pegcetacoplan in patients with TA-TMA.
- To evaluate the efficacy of pegcetacoplan in patients with TA-TMA.

5.2.1 Secondary endpoints supporting the secondary objectives

The secondary endpoints are as follows:

- PD endpoints:

- Absolute levels, change from baseline, and % change from baseline to Week 24 in biomarkers of complement activation: sC5b-9, C3a, C3, Bb, 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:

  - LDH < 1.5 x ULN **and**
  - Platelet count ≥ 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** as described in Section 6.5.1 (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 rUPCR.
  - **Pulmonary response** – requires extubation and discontinuation of positive pressure ventilation.
  - **GI response** – applicable only to patients with biopsy-proven GI TA-TMA and requires improvement in GI function as determined by the 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) [21].
  - **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 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/nonresponders.

- **TMA response** at Week 24, defined as improvement in laboratory markers as follows:

  - LDH < 1.5 x ULN **and**
  - Platelet count ≥ 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.

5.3 [redacted]

[redacted]

- [redacted]
- [redacted]

5.3.1 [redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6 Investigational plan

6.1 Overall study design and plan

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 indicated in Section 6.4.1.1.

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 patients have completed their Week 24 visit.

An SRC will assess the progress and cumulative PK and safety data of the study.

The study design is outlined in Figure 1, and the visit schedule and planned assessments at each visit are detailed in Table 1.

6.1.1 Screening period (up to 2 weeks)

Informed consent will be obtained at screening before any study-related procedures being conducted. Patients will be screened to confirm that the patient selection criteria for the study have been met. Key inclusion and exclusion criteria will be reviewed by the study medical monitor and eligibility will be confirmed prior to the enrollment.

6.1.1.1 Retesting and rescreening

Patients who fail to qualify for the study on the basis of certain laboratory parameters may be retested and/or rescreened at the discretion of the investigator.

6.1.1.1.1 Retesting

Retesting is defined as repeating laboratory tests within the same screening period.

Patients who initially fail to qualify for the study on the basis of laboratory test results not meeting inclusion criteria or due to technical issues (e.g., hemolysis, clotting) may have, at the discretion of the investigator, any individual laboratory parameter retested 1 time within the 2-week screening period. Retesting within the 2-week screening period does not constitute rescreening; however, if retesting falls outside of the 2-week screening period, it should be considered rescreening (see below).

6.1.1.1.2 Rescreening

Rescreening is permitted for patients who consent to participate in the study but who do not initially meet all the requirements as outlined in the inclusion and exclusion criteria. In this case,

additional screening visits and/or repeat screening assessments may be conducted, as needed, to establish eligibility.

Screening is limited to 3 attempts (screening and 2 additional rescreening attempts).

In the event that rescreening occurs and the patient has not remained in the screening period, the individual is required to reconsent and must be assigned a new identification number.

6.1.1.2 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but who do not meet 1 or more criterion required for participation and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography and reason for screen failure.

6.1.2 Treatment period (up to 16 weeks)

[redacted]

At Week 12, if a clinical and/or TMA response according to the protocol definition is not reached, the investigator may decide to continue treatment, according to his/her judgment, for a total of 16 weeks of treatment. If at Week 12 the patient has reached a partial clinical response (defined as improvement in signs/symptoms in 1 or more affected organs without meeting the protocol definition of 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), 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.

6.1.2.1 Clinical worsening

Clinical worsening will be defined as active laboratory TA-TMA as per Inclusion Criterion #3 (see Section 6.3.1) **and** 3 of the 5 organ injuries listed below:

a. Kidney: requirement of renal replacement therapy after initial TA-TMA control, sustained (> 7 days) and attributable to TA-TMA.
b. Lungs: requirement of sustained (> 7 days) positive pressure ventilation, and attributable to TA-TMA.
c. Cardiovascular: uncontrolled severe hypertension with > 2 medications (excluding diuretics), and attributable to TA-TMA.
d. CNS: uncontrolled seizures under medication attributable to posterior reversible encephalopathy syndrome or to hypertension resulting from TA-TMA.
e. GI tract: clinically significant GI bleeding requiring ≥ 20 mL/kg/day of PRBC transfusion daily for at least 7 days.

6.1.3 Follow-up period (up to 12 weeks)

After completion of the treatment period, all patients will enter in the follow-up period until Week 24. This includes an End of treatment visit 4 weeks after the last IMP dose and 1 or 2 more follow-up visits every 4 weeks for patients who have completed 16 or 12 weeks of treatment, respectively. The main analysis will be performed after all patients have completed their Week 24 visit.

6.1.4 Unscheduled visits

Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.

6.1.5 Stopping criteria

In the context of this study, the term toxicity means clinically significant drug related adverse reaction(s). In case of serious toxicity defined as a Grade 4 to 5 SAE, an ad hoc SRC meeting will be held within 24 hours after Sobi awareness of the AE. The SRC will decide on the impact on an individual or entire study level, continue study unchanged, continue study with modifications, or to put the study on hold.

Standard toxicity grading according to the NCI-CTCAE are used to grade AEs and to decide on suspension level:

- The study will be halted if a patient develops a Grade 5 SAE suspected to be IMP related.
- The treatment will be halted if 2 patients experience a similar drug-related Grade 4 SAE.
- Study treatment will be discontinued on an individual level if assessment by an ad hoc SRC or the investigator conclude significant risk to the patient's safety.

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

6.2 Discussion of study design

This study will be the initial exploration of pegcetacoplan in patients with TA-TMA. The assessments of the PK, PD, safety and efficacy following administration of [redacted] induction doses followed by s.c. maintenance doses [redacted] will guide decisions to further develop the drug.

The proposed inclusion criteria of the study will ensure that only patients who have not responded to first-line management of TA-TMA including withdrawal or minimization of medication insult to endothelium such as immunosuppressants and treatment of co-existing conditions such as infections and GVHD are enrolled.

Measures will be taken to minimize risk to participants in this study, including recommendation for vaccination against encapsulated pathogens, mandatory administration of prophylactic antibiotics and measurement of antibodies, apart from standard safety assessments.

6.3 Selection of study population

6.3.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Male and female patients aged ≥ 18 years at the time of ICF signature.
2. Received allogeneic HSCT from a related or unrelated, human leukocyte antigen-matched or mismatched donor. Patients having received any of the following stem cell sources are eligible: granulocyte colony stimulating factor mobilized peripheral blood stem cells, bone marrow, umbilical cord blood.
3. Diagnosis of TA-TMA established as per the laboratory markers below, indicating TMA:
   a. De novo or progressing thrombocytopenia (platelet count < 50 x 10^9/L or > 50 % decrease in platelet count from the highest value achieved after transplantation). AND
   b. Elevated LDH (> 1.5 x ULN).

   AND at least 2 additional laboratory/clinical criteria among the following:

   c. Presence of schistocytes on the peripheral blood smear (≥ 2 per hpf) or histologic evidence of microangiopathy in any biopsied organ. OR
   d. De novo anemia (hemoglobin < LLN or anemia requiring PRBC transfusion support as per local institutional standard). OR
   e. Proteinuria (random urinalysis protein concentration ≥ 30 mg). OR

f. Elevated plasma concentration of sC5b-9 above ULN. OR

g. Arterial hypertension, defined by systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg.

4. Have a diagnosis of TA-TMA that persists despite initial management of any triggering condition.
5. Have a rUPCR ≥ 1 mg/mg.
6. Women of childbearing potential, defined as any women who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative serum pregnancy test at screening and agree to use protocol-defined methods of contraception for the duration of the study and 8 weeks after their last dose of IMP.

   Note: Postmenopausal is defined as having had 12 consecutive months with no menses without an alternative medical cause.
7. Men must agree to the following for the duration of the study and 8 weeks after their last dose of IMP:
   a. Avoid fathering a child.
   b. Use protocol-defined methods of contraception.
   c. Refrain from donating sperm.
8. Patient and/or legally authorized representative must be capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF.

6.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Positive direct Coombs test.
2. Known familial or acquired ADAMTS13 deficiency.
3. Known Shiga toxin-related hemolytic uremic syndrome.
4. Known bone marrow or graft failure.
5. Diagnosis of disseminated intravascular coagulation.
6. Diagnosis of VOD.
7. Active GI bleeding (hematemesis or hematochezia) at baseline.
8. Body weight < 30 kg and > 100 kg.
9. Uncontrolled systemic bacterial or fungal infection, presence or suspicion of sepsis.
10. Previously or currently treated with a complement inhibitor (approved or investigational).

11. Pregnancy or breastfeeding.
12. Positive human immunodeficiency virus antibody at screening or documented in pre-HSCT medical record.
13. Hepatitis C virus detectable by polymerase chain reaction at screening or documented in pre-HSCT medical record.
14. Chronic inactive hepatitis B virus with viral loads > 1000 IU/mL (> 5000 copies/mL) at screening or documented in pre-HSCT medical record. Eligible patients who are chronic active carriers (≤ 1000 IU/mL) must receive prophylactic antiviral treatment (e.g., entecavir, tenofovir, lamivudine) according to local country guidelines.
15. Known or suspected hereditary fructose intolerance.
16. Hypersensitivity to pegcetacoplan or any of its excipients.
17. Inability to cooperate with study procedures or any condition that, in the opinion of the investigator, could increase the patient's risk by participating in the study or confound the outcome of the study.

6.3.3 Withdrawal of patients from treatment or study

6.3.3.1 Discontinuation from treatment

A patient should be discontinued from the study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. See treatment stopping criteria in Section 6.1.5.

Study treatment must be discontinued if a female patient becomes pregnant.

When a patient is discontinued from treatment, the study site must immediately notify the medical monitor, the date of last IMP dose, and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the eCRF. If a patient is removed from treatment because of an AE, the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's decision.

When patients are discontinued from treatment, every effort should be made to continue their participation in the study without taking study treatment. Discontinued patients will be followed for survival until the end of the study. Patients who stop study treatment prior to the exit visit should undergo all follow-up visits and procedures through study completion, unless consent has been withdrawn (see Table 1).

6.3.3.2 Withdrawal from study

A patient may withdraw from the study at any time at his/her own request or at the request of their legally authorized representative, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Whenever possible and irrespective of the reason for withdrawal, the patient should be examined as soon as possible. Relevant samples should be obtained, and all relevant

assessments should be completed. The eCRF should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the eCRF.

Once a patient leaves the study, he/she may not reenter the study.

6.3.3.3 Lost to follow-up

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

Should the patient continue to be unreachable, they will be considered to have withdrawn from the study.

6.3.4 Replacement of withdrawn patients

Withdrawn patients will not be replaced.

6.3.5 Specific restrictions/requirements

6.3.5.1 Acceptable methods of contraception

Acceptable methods of contraception include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral, intravaginal or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral, injectable or implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the women of childbearing potential trial participant and the vasectomized partner has received medical assessment of the surgical success).
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).
- Male condom, with or without spermicide (for male study patients with female partners of childbearing potential only).

Not all methods of contraception may be available in all of the countries in which the study is being conducted.

Note: Sexual abstinence is accepted only when it is the preferred and usual lifestyle of the patient.

Patients must agree to use an acceptable method of contraception during the study and for 8 weeks after their last dose of IMP.

Male patients will be counseled to avoid donating semen during the time between the first screening and the final exit visit and for the 8 weeks after their last dose of IMP.

6.4 Treatments

6.4.1 Treatments administered

6.4.1.1 Investigational medicinal products

All patients will receive open-label pegcetacoplan.

Table 2 Investigational medicinal product

[redacted]				
[redacted]				
[redacted]				

[redacted]

6.4.2 Identity of investigational medicinal products

The IMP is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan at [redacted] provided in single-use stoppered glass vials. Additional information is provided in the pegcetacoplan IB.

Possible deficiencies related to the handling and quality of the IMP(s) should be reported to the study monitor and also directly to complaints@sobi.com.

6.4.2.1 IMP packaging and labeling

The IMP is supplied in 20-cc glass vials. Please refer to the pharmacy manual for details.

All IMP will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

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

6.4.2.2 IMP storage and handling

The IMP should be stored refrigerated at 2 °C to 8 °C, both at home and in the clinic. Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the IMP is maintained within an established temperature range.

The investigator or appropriately qualified site staff will be responsible for the following activities:

- Ensuring that the IMP is stored in a secure, limited-access location at the site.
- Ensuring that the temperature is monitored throughout the duration of the study and that records are maintained.

Limited responsibility may be delegated to the pharmacy or to another member of the study team, but this delegation must be documented.

A pharmacist or appropriately qualified designated person will be responsible for the following:

- Storing the IMP appropriately.
- Dispensing the IMP vials to the patient and entering the unique subject identifier as appropriate.

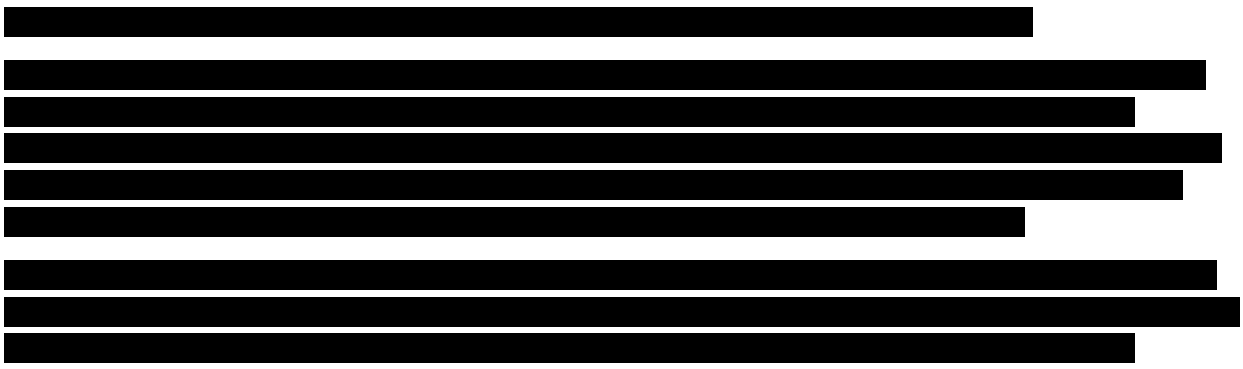
When the patient receives the IMP from the site, it should be transported in a sponsor-approved bag or box containing previously temperature-conditioned cold plates to ensure that the storage temperature (2 °C to 8 °C) is maintained. Temperature monitoring will not be required during transport or at the patient's residence, but a log will be kept for every infusion to ensure that all IMP was kept refrigerated.

6.4.3 Method of assigning patients to treatment groups

This is a single-arm, open-label study.

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, and will receive a unique subject identifier through an IRT system.

6.4.4 Selection of doses



[redacted]

Figure 2 [redacted]

TA-TMA is an acute life-threatening condition, characterized by an overwhelming complement cascade activation, where the treatment approach is tailored to achieve a disease control in the shortest possible time through the complement system blockade, in order to prevent the multiorgan dysfunction syndrome progression, which, in many cases, may become irreversible. Differently from PNH, treatment for TA-TMA is not chronic, but limited to the achievement of a clinical response corresponding to the resolution of sign and symptoms of end-organ damage. Given the premises on the disease severity, the more intense maintenance dosing is, therefore, administered for TA-TMA.

6.4.5 Selection and timing of doses for each patient

[redacted]

Pegcetacoplan [redacted] will also be administered by the investigator's site staff as long as the patient is hospitalized. If deemed by the investigator that a patient can be discharged from hospital upon clinical improvement, pegcetacoplan administration will occur at home. Patients will self-administer s.c. IMP, after receiving appropriate training by research personnel.

When the patient's pegcetacoplan dosing schedule aligns with study visit days, pegcetacoplan should be administered at the study site and the study procedures should be completed as outlined in this protocol (Table 1). In some instances, however, a patient may not be able to align the date of a study visit with his/her pegcetacoplan administration schedule (e.g., if the patient has to utilize the visit window in order to be able to attend a study visit). In such instances it is important that pegcetacoplan dosing occurs according to the dosing schedule and not the visit schedule.

Patients will be instructed to self-administer pegcetacoplan only as prescribed and to contact the investigator immediately for guidance in the event of any missed doses.

Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. Patients should not deviate from the every-3-days dosing schedule.

The preferred site of s.c. infusion will be the abdomen. If administration into the abdomen is not feasible, alternative appropriate sites are acceptable (see the Pump Instructions for Use document for more details).

Pegcetacoplan will be administered using a syringe pump. Details of infusion volume and time will be detailed in the pharmacy manual.

During initial qualification, a research nurse or other appropriately qualified research personnel will administer the s.c. infusions (as needed) and will qualify and supervise the self-administration or caregiver administration. These qualified research personnel will be made available for a minimum of 6 days on treatment (2 doses) to ensure the patient has been qualified to conduct self-administration; the duration can be shortened if qualification happens sooner. During qualification, the patient or caregiver must demonstrate to the research personnel their ability to safely and effectively administer the IMP using the infusion pump. Following self-administration or caregiver administration qualification, patients or caregivers may self-administer the s.c. infusions without supervision. Once qualified, the patient or caregiver will continue to administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the patient on all other days. Self-administration or caregiver administration conducted at the clinic will be supervised to ensure that the patient or caregiver continues to remain compliant with the administration guidelines.

Missed doses will be handled on a case-by-case basis between the investigator and medical monitor, with the general approach being to administer a missed dose as soon as noticed, unless the next dose has already been administered.

NOTE: If the patient or caregiver requires further training, the self-administration qualification period may be extended beyond 6 days on treatment (2 doses). Caregiver administration may be conducted by a member of the patient's household, a family member, etc, who will undergo the same qualification criteria (qualification is not intended to be restricted to the patient).

6.4.6 Dose modification

No dose modification is foreseen in this study. Treatment interruption or discontinuation necessary to manage toxicities will be decided upon investigator's judgment and should be discussed with the study medical monitor.

6.4.7 Infusion supplies

The sponsor will supply syringes, vial adapters, infusion sets, ambulatory syringe infusion pumps, and any other supplies needed for the safe home IMP administration as required. Refer to the pharmacy manual for further details.

6.4.8 Blinding and unblinding

Not applicable.

6.4.9 Prior and concomitant therapy

Other therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. All such therapy must be recorded in the eCRF.

All medications administered and procedures performed within 12 weeks of the first IMP dose through the end of study visit will be recorded. Those that stop before first IMP dose will be regarded as prior medications and procedures. Medications administered and procedures performed that are ongoing at the time of first IMP dose or start after first IMP dose are regarded as concomitant and will be documented as such. Prior and concomitant medication information must be recorded on the appropriate eCRF page.

With the exception of prohibited medications, any concomitant medications deemed necessary for the patient's standard of care or wellbeing during the study or for the treatment of any AE may be given at the discretion of the investigator. It is the responsibility of the investigator to ensure that the details regarding all medications are recorded in full in the patient's eCRF.

6.4.9.1 Permitted concomitant therapy

All medications already taken at study entry for other indications will be allowed (e.g., rituximab).

All patients must continue to be administered coverage with prophylactic antibiotics and antifungals according to institutional posttransplant infection prophylaxis guidance, including coverage against *N. meningitidis* the entire treatment period and for 8 weeks following the final dose of pegcetacoplan.

6.4.9.2 Prohibited medications

Other than pegcetacoplan, any therapy for TA-TMA is prohibited during patient's participation in the study, including:

- Defibrotide.
- Any other complement inhibitor (e.g., eculizumab, ravulizumab, or narsoplimab).
- Plasma-exchange.

6.4.10 Treatment compliance

Dosing diaries will be utilized for pegcetacoplan and are to be completed for each dose administered at the study site or outside regular clinic visits. Patients should not deviate from their dosing schedule.

When patients are dosed at the site, they will receive pegcetacoplan directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in eCRF. The dose of pegcetacoplan and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When patients self-administer pegcetacoplan at home, compliance will be assessed at each visit. Patients must be instructed to bring their empty/partially used/unused IMP packaging to every visit in case of home administration. Compliance will be assessed during the site visits and documented in the source documents and eCRF. The pharmacist/designee will record details on the drug accountability form. Refer to the pharmacy manual for further details.

6.4.11 IMP accountability

Accountability and maintenance of the IMP at the study center is the responsibility of the investigator. The investigator will ensure that the IMP is used only in accordance with this study protocol. Where allowed, the investigator may choose to delegate drug accountability responsibilities to a pharmacist or other appropriate individual.

Investigators will be provided with the IMP to carry out this protocol for the agreed number of patients. The investigator/designee will acknowledge receipt of the IMP, and documenting shipment contents and conditions. Accurate records of all IMP dispensed, used/unused, returned,

and/or destroyed must be maintained. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and participant numbers. The sponsor/designee will review IMP accountability at the study center on an ongoing basis during monitoring visits. The IMP must not be used for any purpose other than the present study. IMP that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

The investigator is responsible for ensuring the retrieval of all returnable study supplies from patients.

6.4.12 IMP disposal

All unused and used IMP vials should be retained at the center until accountability and reconciliation has been performed by the study monitor. At the end of the treatment period, any unused IMP will either be destroyed at the investigator site or be returned to the sponsor/designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

6.5 Baseline, efficacy, safety, pharmacokinetic, pharmacodynamic and pharmacogenetics assessments

6.5.1 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 enrollment in the study. Additional preexisting conditions that started before and are ongoing at the date of enrollment are to be regarded as current medical conditions. Medical history will include alcohol consumption and smoking history, if applicable.

Information about HSCT and related complications will be also collected, including underlying disease diagnosis; donor type; HLA mismatch; stem cell source; type and start date of conditioning regimen; conditioning medications; date of transplant; transplant manipulation; donor chimerism; date of confirmed engraftment; GVHD date of onset; GVHD grade according to the International Bone Marrow Transplant Registry severity Index [22]; presence of infections; presence of donor specific antibodies; posttransplant treatments and date (e.g., donor lymphocyte infusion, stem cell boost, growth factors; infusion of antiviral T cells); GVHD prophylaxis.

Information about TA-TMA will be collected including date of diagnosis (defined as the earliest date when all required laboratory criteria outlined in Inclusion Criterion #3 are met); diagnostic laboratory markers; initial management; and presence of signs and symptoms of end organ injury.

Baseline end organ injury will be evaluated as follows, with associated medications:

a. Kidney: doubling of serum creatinine compared with pre-HSCT level or patient receiving renal replacement therapy or proteinuria ≥ 30 mg/dL OR rUPCR ≥ 1 mg/mg.
b. Lungs: hypoxemia or any need for noninvasive or invasive positive pressure ventilation.
c. Cardiovascular: pulmonary hypertension diagnosed by a cardiologist using cardiac catheterization, or pulmonary hypertension criteria on echocardiography or arterial hypertension, defined by systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg at baseline or hypertension requiring > 2 medications (excluding diuretics).
d. Serositis: clinically significant pleural effusion or pericardial effusion requiring surgical therapy (e.g., pericardiocentesis/ thoracocentesis).
e. CNS: seizures attributable to posterior reversible encephalopathy syndrome.
f. GI tract: presence of biopsy-proven GI TA-TMA. Patients with GI bleeding (hematemesis or hematochezia) will be excluded.

Illnesses first occurring or detected during the study and worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 6.5.5.1.2.

6.5.1.1 Vaccines medical history

Patients should be vaccinated against *N. meningitidis* (Types A, C, W, Y, and B) either within 2 years prior to Day 1 or, if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. Patients should be re-vaccinated against *H. influenzae* Type B and *S. pneumoniae,* if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. Received vaccines with dates will be recorded in the eCRF.

6.5.2 Demography

Demographic data, including age, sex, race and ethnicity, will be collected for all patients, as allowed, per applicable regulations and recorded in the eCRF.

6.5.3 Biopsy samples of affected organs

Diagnosis of TA-TMA may be established by histologic evidence of microangiopathy in any biopsied organ. Biopsy of affected organs is optional. In the case that any biopsy sample results are available prior to screening (up to 1 month before), these results can be used to confirm diagnosis.

6.5.4 Pharmacokinetic assessments

Blood sampling and processing blood samples for the PK assessment of pegcetacoplan will be collected via direct venipuncture at the time points outlined in the schedule of assessments (Table 1). Should the patient have a central catheter already in place, in order to minimize patient

discomfort, the central line can be used to collect PK samples, except for the 15 and 30 minutes postdose samples.

On dosing Days 1, 3 and 5, PK samples will be taken up to 30 minutes predose and at 15 minutes (± 5 min), 30 minutes (± 5 min), 1 hour (± 10 min), 4 hours (± 10 min), 8 hours (± 30 min), and 24 hours (± 30 min) postdose. From Day 8 and onwards, PK samples will be taken predose at all other visits.

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

Serum sample analysis will be performed using validated liquid chromatography tandem mass spectrometry methods. The methods used and the results obtained will be included in the CSR as an appendix.

6.5.4.1 Pharmacokinetic parameters

PK parameters for pegcetacoplan will be computed from the individual serum concentration-time data, using actual sample times using a non-compartmental approach. Appropriate validated PK software (e.g., Phoenix WinNonlin®) will be used.

The following PK parameters will be calculated:

[redacted] induction phase:

- $AUC_{0\text{-}tau}$: area under the concentration-time curve over the dosing interval.
- C_{max}: maximum observed serum concentration.
- T_{max}: time of the maximum measured 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.

s.c. maintenance phase:

- C_{trough}: observed serum concentration predose.

6.5.5 Safety assessments

6.5.5.1 Adverse events

6.5.5.1.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a patient or study patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

AEs include the following:

- Abnormal test findings, as specified below.
- Changes in physical examination findings.

- Progression/worsening of underlying disease.
- Signs and symptoms resulting from overdose, withdrawal of treatment, drug-drug interactions, abuse and misuse.
- Increase in frequency or intensity of a preexisting episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.

For pregnancies and breastfeeding, see Section 6.5.5.1.5.

Abnormal test findings

An abnormal test finding, e.g. abnormal laboratory analysis results, vital signs or ECG, should be recorded as an AE in any of the following situations:

- The investigator considers the abnormal test finding to be clinically significant.
- The abnormal test finding leads to a medical/surgical intervention including withdrawal of IMP(s) or discontinuation from the study. Repeat/confirmatory testing is not considered a medical intervention.

Preexisting conditions

A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

AEs diagnosis versus signs/symptoms

For any AE, a diagnosis should be recorded rather than individual signs and symptoms or abnormal laboratory findings. However, if at the time of AE reporting a diagnosis is not available, each individual sign/symptom should be recorded. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be removed and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the start date of the first symptom of the eventual diagnosis.

Procedures

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy entered in the comments section of the eCRF.

Treatment-emergent adverse event

A treatment-emergent AE is any AE temporally associated with the use of study treatment, i.e., from study treatment initiation until 8 weeks after study treatment discontinuation.

Serious adverse event

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death.
- Is life-threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient).
- Is a medically important AE.

Medically important AEs are events that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission of an infectious agent via IMP shall also be considered serious.

Hospitalization

In general, hospitalization means that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures/ambulatory care.
- Emergency department visits.

Hospitalization in the absence of an AE occurring during the study should not be considered an SAE. This includes:

- Pre-planned hospitalization due to a preexisting condition not associated with a worsening of the preexisting condition.
- Protocol specified admission.

- Elective admission, e.g. due to cosmetic surgery.

Complications that occur during hospitalization should not be considered SAEs unless the complication prolongs hospitalization.

Suspected unexpected serious adverse reaction

A SUSAR is an untoward and unintended response to a study drug that is not listed in the reference safety information of the IB, meets at least 1 of the seriousness criteria, and is assessed as causally related to the IMP.

6.5.5.1.2 Adverse event reporting period

The AE/SAE reporting period will be as follows:

Screening period: Any SAEs occurring between signing of the ICF and the first IMP dose should be reported to Sobi.

Treatment period: All AEs (including SAEs) occurring upon receiving the first IMP dose up to 8 weeks after last IMP administration must be recorded in the AE pages of the eCRF. In addition, SAEs should be reported to Sobi.

Follow-up period: New SAEs occurring at any time after the 8-week AE follow-up period up to EOS should be reported to Sobi only if considered causally related to previous exposure to the IMP by the investigator. These SAEs are only entered in the drug safety database and, hence, will not affect study closure.

6.5.5.1.3 Obtaining and recording adverse event information

The investigator obtains AE information that is directly observed or solicited from the patient or patient relative during the course of the study. All AEs must be recorded in the eCRF using concise medical terminology.

The investigator is responsible for obtaining sufficient information to determine seriousness, causality and outcome of each AE.

Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum severity of the AE. For the purpose of consistency, these severity grades are defined as follows:

MILD	Does not interfere with patient's usual function
MODERATE	Interferes to some extent with patient's usual function
SEVERE	Interferes significantly with patient's usual function

Note the distinction between the gravity (seriousness) and the severity of an AE. **Severe** is a measure of intensity; thus, a **severe** event is not necessarily a **serious** event. For example, a

headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

Causality assessment

For each AE, the investigator must make a causality assessment to determine whether there is a reasonable possibility that the IMP(s) caused the AE. The AE is assessed as **related** or **not related** to the IMP(s).

6.5.5.1.4 Serious adverse event reporting

Both serious and nonserious AEs are to be reported on the AE page of the eCRF as specified in the eCRF instructions.

In addition, all SAEs must be reported by the investigator to the Sobi Global Pharmacovigilance & Patient Safety within 24 hours of the investigator's first knowledge of the event.

If an SAE occurs, it is to be reported by e-mail (e-mail address is indicated on the SAE form) using the designated Serious Adverse Event form.

The SAE collection form is not always the same as the AE eCRF form. The forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

All new information obtained, relevant to an SAE report, should be forwarded to Sobi Global Pharmacovigilance & Patient Safety within the same timeframe as the initial information.

If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

New SAEs occurring after the 8-week AE follow-up period must be reported to Sobi Global Pharmacovigilance & Patient Safety within 24 hours of the investigator's knowledge of the event, only if considered causally related to previous exposure to the study treatment by the investigator.

The investigator shall provide Sobi Global Pharmacovigilance & Patient Safety with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi Global Pharmacovigilance & Patient Safety with additional information related to any SAE as requested.

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the IB.

6.5.5.1.5 Exposure during pregnancy and breastfeeding

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Any pregnancy occurring after study initiation (i.e., signing of ICF) up to 8 weeks following study treatment discontinuation must be reported within 24 hours of the investigator's

knowledge of the event. This includes all situations where a woman is or has been found to be pregnant after being exposed to IMP – directly, indirectly or via her partner (paternal exposure).

All events of exposure to the IMP during pregnancy (female patient or male patient's partner) or breastfeeding, whether the exposure is associated with an AE or not, shall be reported to Sobi Global Pharmacovigilance & Patient Safety by e-mail using the pregnancy notification form by e-mail (e-mail address is indicated on the pregnancy notification form).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy report form that shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi Global Pharmacovigilance & Patient Safety of relevant information and any information requested related to the outcome of the pregnancy.

Any AEs and SAEs observed during and in relation to pregnancy, delivery or breastfeeding should be recorded in the eCRF and, as applicable, be reported to Sobi Global Pharmacovigilance & Patient Safety as described previously in this section.

6.5.5.1.6 Follow-up of unresolved adverse events

All AEs should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends, i.e., until the last scheduled visit. How to report changes in an ongoing AE during a patient's participation in the study is described in the eCRF instructions.

In addition, all serious and nonserious AEs assessed by the investigator as related to the IMP should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable," even after the patient's participation in the study is over, but without further recordings into the eCRF.

6.5.5.2 Laboratory safety assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the schedule of assessments (Table 1). Blood collection for safety laboratory tests at Day 1 can be omitted if screening samples were collected on Day -1.

On dosing days, all blood samples will be collected predose.

Table 3 Laboratory assessments

Hematology	ARC Hemoglobin Hematocrit	Platelet count Red blood cell count WBC count with differential
Serum chemistry	Albumin ALT ALP AST Bilirubin (total, direct, and indirect) BUN Calcium Chloride Creatinine Creatine kinase Haptoglobin Estimated Glomerular Filtration Rate (using CKD-EPI formula)	GGT Glucose Iron Ferritin TIBC LDH Magnesium Phosphorus Potassium CRP Sodium Uric acid
Urinalysis	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite	pH Pregnancy, when applicable Proteinuria rUPCR Specific gravity Urobilinogen
Coagulation [a]	aPTT D-dimer Fibrinogen	International normalized ratio Prothrombin
Additional	HBV-DNA HCV-RNA HIV ADAMTS13 activity test [redacted] Biomarkers of complement activation: including but not limited to sC5b-9; C3a; C3; Bb; C4a; functional assays for classical and alternative complement pathways	Antibodies to PEG and pegcetacoplan [redacted] [redacted] Peripheral blood smear for schistocytes evaluation Direct Coomb's test Serum pregnancy test (β-hCG) FSH (postmenopausal women)

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; ARC, Absolute reticulocyte counts; AST, Aspartate aminotransferase; β-hCG, Human chorionic gonadotropin-beta; Bb, Activated factor B; BUN, Blood urea nitrogen; C3, Complement component 3; C3a, Complement component 3a; C4a, Complement component 4a; CKD-EPI, Chronic Kidney Disease – Epidemiology Collaboration; CRP, C-reactive protein; [redacted] FSH, Follicle stimulating hormone; GGT, Gamma-glutamyltransferase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; [redacted] LDH, Lactate dehydrogenase; PEG, Polyethylene glycols; rUPCR, Random urine protein:creatine ratio; sC5b-9, Terminal complement complex; TIBC, Total iron binding capacity; [redacted] WBC, White blood cells.

[a] The use of silica reagents in coagulation panels should be avoided in all patients.

Blood and urine samples will be analyzed at a central laboratory unless a local laboratory facility is necessary, as defined in the laboratory manual. Urine samples will be analyzed by dipstick and microscopic analysis. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit.

In the event that a patient's medical condition warrants rapid treatment initiation and the results of tests from the central laboratory cannot be awaited, results of tests performed at the site can be considered for screening purposes (inclusion/exclusion criteria checks), with the sponsor's agreement. In such cases, the local test results will be entered in the eCRF to confirm the eligibility.

Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention), see Section 6.5.5.1.1 for details. Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

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

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

6.5.5.3 Vital signs

Vital signs (body temperature, respiration rate, heart rate and systolic and diastolic BP measurements) will be evaluated per institutional practices at the visits indicated in the schedule of assessments (Table 1).

When the IMP is administered at the study site, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 minutes) postdose.

Vital signs measurements will be repeated if clinically significant or if machine/equipment errors occur. Out-of-range BP, respiratory rate, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital signs measurements must be reported as AEs (see Section 6.5.5.1.1 for details).

6.5.5.4 Body weight and height

Body weight and height (both assessed without shoes on) will be recorded at screening. Body weight will also be recorded at each physical examination.

6.5.5.5 Physical examination

Full physical examinations will be performed by the investigator/designee at the time points outlined in the schedule of assessments (Table 1) and will include assessments of the following items: general; head, ears, eyes, nose, and throat; dentition; thyroid (endocrine); heart; chest; lungs; abdomen; skin; extremities; back/neck; musculoskeletal system and lymph nodes.

If any abnormalities are reported at screening, they should be recorded as medical history. New or worsening of abnormalities after first IMP dose should be reported as AEs (see Section 6.5.5.1.1 for details).

6.5.5.6 Electrocardiograms

Single 12-lead ECGs will be recorded prior to dosing at the time points outlined in the schedule of assessments (Table 1). The ECG will be taken after the patient has been resting in the supine position for 5 minutes in a quiet environment and prior to any blood sampling procedures, unless specified at time points after timed blood sampling procedures.

The ECGs will be classified as normal, having a not clinically significant abnormality or having a clinically significant abnormality. For patients with an abnormal ECG, it is recommended that the ECG recording is reviewed by a cardiologist in addition to the treating investigator.

Any significant ECG finding present prior to the start of IMP administration is to be documented in the medical history section of the eCRF. Any significant ECG finding with an onset time after IMP initiation and that was not present at screening, or worsened during the study, is to be reported as an AE.

Clinically significant abnormal ECG findings should be reported as AEs (see Section 6.5.5.1.1 for details).

6.5.5.7 Infusion-site reactions/pump-safety assessments

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

Patients will be instructed to notify the investigator or other study personnel in the event that an infusion-site reaction occurs after self-administration of pegcetacoplan. All clinically relevant AEs, as determined by the investigator, from infusion site or related to pump use will be recorded as AEs (see Section 6.5.5.1.1 for details).

6.5.5.8 Appropriateness of safety measurements

The methods and measurements used for safety during the study are standard and are appropriate for the clinical evaluation of the patients with TA-TMA treated with pegcetacoplan.

6.5.5.9 Safety review committee

An SRC will be established for this study. The SRC will review PK and safety data after the first patient has completed 4 weeks of treatment, then after the first 3 patients have completed 12 weeks of treatment, and then every 6 months afterwards until all patients have completed the treatment period. Additional SRC meetings may be scheduled ad hoc as per investigator or Sobi SRC member requests (see stopping criteria in Section 6.1.5).

The SRC will consist of internal Sobi staff and will include as a minimum the Safety Physician, Study Physician and Clinical Pharmacologist. An SRC charter will specify the operating procedures including SRC membership, voting members, responsibilities, data review meeting details and lines of communication with the study teams at Sobi and investigational sites.

6.5.6 Pharmacodynamic assessments

Blood samples for PD assessment of hemolytic complement activation will be collected on study days designated in the schedule of assessments (Table 1). On dosing days, all blood samples will be collected predose.

Biomarkers of complement activation will include but are not limited to sC5b-9, C3a, C3, Bb, C4a and functional assays for classical and alternative complement pathways.

Since recently published data have also suggested a key relationship between increased interferon signaling, complement activation, and TA-TMA [23], [redacted]

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

6.5.6.1 Immunogenicity

Blood samples for antibodies will be collected on study days designated in the schedule of assessments throughout treatment and follow-up periods (Table 1). On dosing days, all blood samples will be collected predose.

The presence of antibodies to PEG and pegcetacoplan will be analyzed after study completion. Samples that are confirmed positive for anti-pegcetacoplan peptide or anti-PEG antibodies will be characterized with an antibody titer for that specific antibody. Any samples that are confirmed positive for anti-pegcetacoplan peptide antibody will be further characterized with a neutralizing antibody assay.

6.5.7 Efficacy assessments

6.5.7.1 Clinical response

Clinical response is defined as an improvement in laboratory markers and, in patients with signs or symptoms of organ dysfunction at baseline, also as an improvement in clinical status (see Section 5.2.1).

To assess laboratory improvement, LDH and platelets count will be collected at baseline and at each time point of clinical response evaluation.

To assess the clinical status, the following clinical and laboratory parameters will be collected at baseline and at each time point of clinical response evaluation:

- Creatinine; presence of renal replacement therapy (including start date, end date and reason).
- Presence of noninvasive or invasive positive pressure ventilation or oxygen, including start date, stop date and reason.
- Presence of nausea, vomiting or anorexia including attributed reason.
- Stool output/day (reported either as number of episodes or mL).
- Neurological status (e.g. presence of seizures, mental alteration, stability of irreversible neurological conditions) including attributed reason.
- Presence of pulmonary hypertension and related medications.
- Systolic and diastolic BP and anti-hypertensive medications excluding diuretics.
- Presence of pericardial or pleural effusion requiring pericardiocentesis or thoracocentesis including attributed reason.

6.5.7.2 TMA response

TMA response is defined as an improvement in TA-TMA specific markers (see Section 5.2.1). To assess TMA response, LDH, platelets counts and rUPCR will be collected at the time points outlined in the schedule of assessments (Table 1).

6.5.7.3 Overall survival, time to response, duration of response, TA-TMA relapse

Overall survival will be assessed at Day 100 from the day of TA-TMA diagnosis and at Week 24 from treatment start. The day of TA-TMA diagnosis will be defined as the earliest date when all required laboratory criteria outlined in Inclusion Criterion #3 are met. Date of death and reason for death will be collected (whether related to TA-TMA or not).

Time to clinical/TMA response will be measured from the time of first IMP dose to the first documentation of attainment of a clinical or of a TMA response as defined in Section 5.2.1. Duration of clinical and of TMA response will be measured from the first documentation of attainment of a response until TA-TMA relapse.

TA-TMA relapse will be defined as reappearance of all laboratory markers as outlined in Inclusion Criterion #3 in a patient who has reached a clinical response.

6.5.7.4 Transfusions

All the platelet and PRBC transfusions performed during the study period from screening until end of the study will be recorded, including date, number of units and whether the transfusion is attributed or not to TA-TMA.

6.5.7.5 [redacted]

[redacted]

6.5.7.6 Appropriateness of efficacy measurements

The methods and measurements used for efficacy during the study (overall survival, TA-TMA relapse, clinical response, TMA response, time to and duration of clinical and TMA response, laboratory parameters, number of platelet and PRBC transfusions and health-related quality of life tools) will be used to determine responses to IMP and are appropriate measures to assess the efficacy objectives.

6.5.8 Other study assessments

6.5.8.1 [redacted]

[redacted]

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study-specific procedures, Sobi standard operating procedures, contract research organization standard operating procedures, the ICH Guideline for GCP [1], and applicable regulatory requirements, including EU CT Regulation 536/2014.

The sponsor will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data that would affect patient safety and reliability of study data.

The sponsor will establish a systematic, prioritized, risk-based approach to monitoring and has chosen a combination of on-site and centralized monitoring.

The sponsor will notify the authorities as applicable (in line with country/region requirements) about a serious breach of the regulations or of the version of the protocol applicable at the time of the breach. A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

In case of new waves of restricted access to trial sites due to the unforeseeable evolution of the COVID-19 pandemic, to ensure ongoing patients’ rights, safety and wellbeing, and control risks to study critical processes, the sponsor might decide to apply alternative mechanisms of oversight and monitoring. Among these mechanisms, remote source data verification would be implemented only if allowed by country regulations and within the limits established.

Monitoring visits to the study site will be performed periodically during the study, to help ensure compliance with the protocol, study-specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in eCRFs. All patient

ICFs will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

8 Statistical plan

A formal first version of the SAP will be developed and finalized before the first patient is screened. The full details of data presentations and analyses will be provided in the SAP. Any potential update of the SAP will include description of changes/additions. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the CSR.

8.1 Determination of sample size

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 rates is 70 %).

8.2 Definition of study populations

8.2.1 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.

8.2.2 Safety set

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

8.2.3 Intent-to-treat set

The ITT set will include all patients enrolled. This analysis set will be used for efficacy endpoints.

8.2.4 Pharmacokinetic set

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

8.2.5 Pharmacodynamic set

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

8.3 Overall statistical and analytical plan

All details of the statistical analyses for primary and secondary endpoints will be described in the SAP.

8.3.1 General statistical issues

All endpoints will be evaluated with descriptive statistics. PK and PD may also be presented graphically.

Baseline will be defined as the Baseline visit. If no assessment is available at the Baseline visit, then the last assessment during the screening period will be used. If multiple values assessments are available, then the last assessment prior to first dose will be used.

No statistical tests will be performed.

8.3.2 Demographics and baseline characteristics

Demographics, baseline characteristics, concomitant medications/treatments, medical history, and IMP exposure will be summarized.

The WHO-DD and MedDRA coding dictionaries will be used for the coding of concomitant medications/treatments and medical histories, respectively.

8.3.3 Analysis related to primary objective

8.3.3.1 Analysis of pharmacokinetics

A primary objective is to evaluate the pegcetacoplan PK in patients with TA-TMA. The primary endpoints are the PK parameters computed from the individual serum concentration-time data, using actual sample times and a non-compartmental approach, i.e., $AUC_{0\text{-}tau}$, C_{max}, T_{max} and C_{trough}. For further details, see Section 6.5.4.

PK parameters will be summarized using descriptive statistics (arithmetic means, standard deviation, coefficients of variation, N, minimum, maximum, median, first quartile [Q1] and third quartile [Q3]). In addition, geometric means with 95% CI will be calculated for AUC

parameters, and for C_{max}. Figures will be created to display median and individual pegcetacoplan concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

The analysis of the PK endpoints will be performed on the PK set.

A separate pegcetacoplan population PK Analysis Plan will be developed, and results will be reported separately.

8.3.3.2 Analysis of safety and tolerability data

Pretreatment AEs are those occurring between ICF signature and the first IMP administration. TEAEs are defined as those AEs that develop or worsen after the first dose of IMP and up to 8 weeks after the last IMP dose.

All AEs will be coded using the MedDRA. Pretreatment AEs will be summarized in individual listings. TEAEs will be summarized by SOC and preferred term in frequency tables with the number of patients and proportion reporting the event. A similar summary will be produced for SAEs, AEs leading to premature discontinuation of IMP and AEs related to the IMP. The intensity of AEs and the relationship to the IMP will be summarized for each SOC and preferred term.

The AE summaries will be presented across all patients. All AEs will be listed by patient, along with information regarding onset, duration, relationship to IMP, severity, action taken with IMP, treatment of event and outcome.

Changes from baseline in clinical laboratory test results will be summarized, using descriptive statistics, by visit and nominal time postdose. Out-of-range values will be flagged in data listings.

Changes from baseline in vital signs will be summarized, using descriptive statistics, visit and nominal time postdose.

Changes in physical examinations will be described in a data listing.

8.3.4 Analysis related to secondary objectives

8.3.4.1 Analysis of pharmacodynamics

A secondary objective is to evaluate the pegcetacoplan PD in patients with TM-TMA.

The related secondary PD endpoints are the following:

- Absolute levels, change from baseline, and % change from baseline to Week 24 in biomarkers of complement activation, which include but are not limited to sC5b-9, C3a, C3, Bb, C4a, functional assays for classical and alternative complement pathways).

PD parameters will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum values).

The analysis of the PD endpoints will be performed on the PD set.

8.3.4.2 Analysis of secondary efficacy endpoints

The secondary efficacy endpoints are described in Section 5.2.1.

A secondary endpoint is clinical response at 24 weeks. A composite estimand is used where patients meeting intercurrent events are considered as failures. The intercurrent events of interests are use of prohibited medication or study withdrawal before Week 24. Patients meeting these intercurrent events will be considered as failures/nonresponders.

A 2-sided 95 % confidence interval for the proportion will be calculated using the Clopper-Pearson method.

Clinical response at Week 12 as well as TMA response at Week 12 and Week 24 will be evaluated the same way as clinical response at Week 24.

Another secondary endpoint is overall survival at Day 100 from diagnosis of TA-TMA. Pegcetacoplan withdrawn patients for which survival at Day 100 is unknown will be censored at the date of last contact. Kaplan-Meier curve estimates of survival at Day 100 and survival curves will be estimated.

Overall survival at Week 24 from study Day 1 will be evaluated the same way as overall survival at Day 100 from diagnosis of TA-TMA.

Time to clinical response will be defined as the time from study Day 1 to first occurrence of clinical response and will be evaluated for:

- Patients achieving clinical response (without a preceding ICE) at any time during the study.
- Patients achieving clinical response at Week 24 without meeting an ICE.

Time to clinical response will be analyzed using Kaplan-Meier methodology. Kaplan-Meier curves and estimates will be presented.

Time to TMA response will be evaluated in the same way as time to clinical response.

Duration of clinical response 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. Duration of clinical response will be analyzed using Kaplan-Meier methodology. Kaplan-Meier curves will also be presented.

Duration of TMA response will be evaluated the same way as duration of clinical response.

TA-TMA relapse at Week 24 will be defined for patients reaching clinical response at some point of the study. Counts and proportions of patients with and without relapse at Week 24 will be summarized.

The analysis of the secondary endpoints will be performed on the ITT set.

8.3.5 Analysis related to exploratory objective

The exploratory endpoints are described in Section 5.3.1. Exploratory endpoints will be evaluated with descriptive statistics.

8.3.6 Interim analysis

No interim analysis will be conducted.

8.3.7 Multiple comparison/multiplicity

No formal statistical tests are performed in this study.

8.3.8 Exploratory subgroup analyses

Subgroup analyses will be conducted on subgroups based on BATAP score [29] (categories will be defined based on distribution of BATAP scores). The following endpoints will be considered for subgroup analyses: PK parameters, clinical response and TMA response, and overall survival. In each defined subgroup, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. For subgroups without an adequate number of patients, the analyses will not be performed. Details will be provided in the SAP.

8.3.9 Handling of missing data

Imputation of missing data (e.g., partial or missing dates) will be described in the SAP.

9 Data collection, handling and record keeping

9.1 Data standards

Collection of data should be performed in the Clinical Data Acquisition Standards Harmonization format, according to the Clinical Data Interchange Standards Consortium. The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the Clinical Data Interchange Standards Consortium standard is to collect all core variables specified as ‘Required’ in the Study Data Tabulation Model format.

9.2 Case report form

An eCRF is required and should be completed for each included patient. In this study, an eCRF will be used, and the designated investigator site staff will only be given access to the electronic

data capture system upon completion of the user training. The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

It is the responsibility of the investigator to ensure completion and to review and approve all eCRFs. eCRFs must be signed electronically by the investigator. These signatures serve to attest that the information contained on these eCRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs.

9.3 Source data

Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In those cases, the information collected in the eCRFs must match those charts. In some cases, a portion of the source documents for a given patient may be the eCRF.

A separate source document location agreement will be completed and signed by the principle investigator and the monitor before study start.

Source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available (ALCOA+). Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trial).

The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

9.4 Protocol deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes to, the protocol, unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

When a deviation from the protocol is identified, the investigator or designee must ensure the medical monitor is notified. The medical monitor will follow up with the investigator, as

applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the patient to determine patient continuation in the study.

The investigator and contract research organization must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human patient protection or the reliability of study results.

The investigator will also assure that deviations are reported and documented in accordance with IEC/IRB and applicable regulatory requirements.

9.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked and before generation of any results. The database lock will be approved by relevant study personnel, and all edit accesses will be removed. The study database can only be unlocked in cases where critical errors, affecting the main conclusions of the study, are discovered.

9.6 Record retention

The investigator should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline [1] including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g., source documents, eCRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline [1].

The records should be retained by the investigator as specified in the Clinical Trial Agreement and in accordance with local regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to Sobi.

10 End of study

The end of study is defined as when all enrolled patients have completed the follow-up period and performed the End of study visit (the date of the last visit of the last patient) at Week 24, or the Early Termination visit in case of early discontinuation.

11 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients within 30 days. All study materials must be collected, and all the eCRFs must be completed to the greatest extent possible.

12 Dissemination and publication of results

A CSR will be prepared once all patients have completed their Week 24 visit and the database has been cleaned for all visits up to and including Week 24.

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on www.clinicaltrials.gov and EudraCT/Clinical Trial Information System portal. The results of this study will be published within 12 months of the end of study, including a summary written in a manner that is understandable to laypersons.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship [30].

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

13 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB/IEC personnel, the sponsor and its authorized representatives are allowed full access to the records.

The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of personal data breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

All study patients must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for their data to be used as described in the ICF. The patients must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Identification of patients and CRFs shall be by unique subject identification numbers only. All personal identifiers according to applicable regulations (e.g., name, phone number) must be redacted permanently by the site personnel and replaced with the subject's unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and sponsor's or designated staff. The investigator and the contract research organization must contact Sobi immediately if a potential serious breach is discovered that significantly affects the safety and rights of a subject, the physical and mental integrity of a subject, or has the potential to significantly affect human subject protection and the reliability of study results. The investigator will also assure that deviations are reported and documented in accordance with applicable regulatory and legal requirements.

14 Reference list

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Appendix 1 Additional protocol signatures

Sponsor's Clinical Study Manager

[redacted]
Clinical Study Manager
[redacted]

[redacted]

01-Oct-2024 | 3:44 PM CEST

Date

Sponsor's Statistician

[redacted]
Statistical Science Director
[redacted]

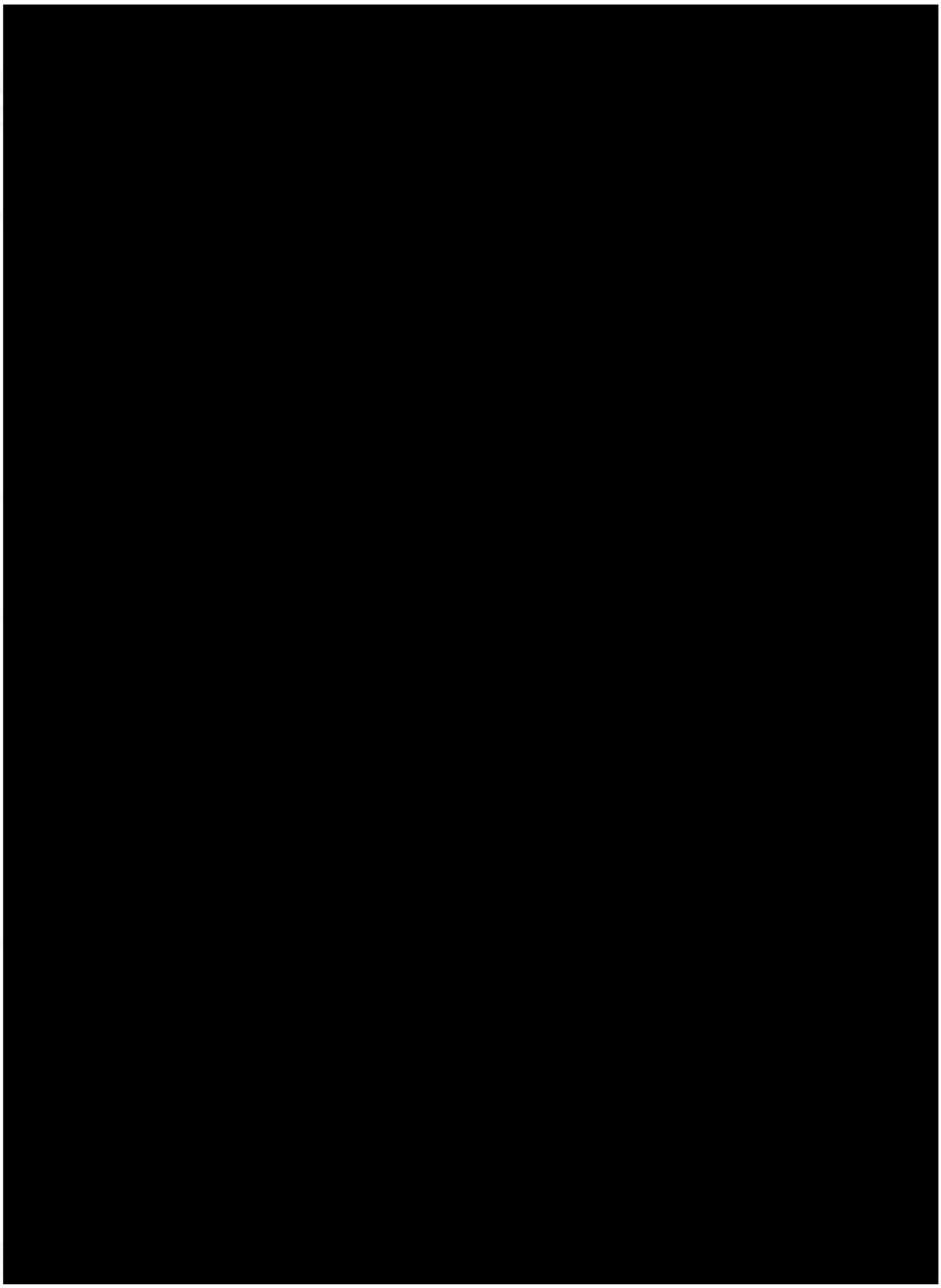
[redacted]

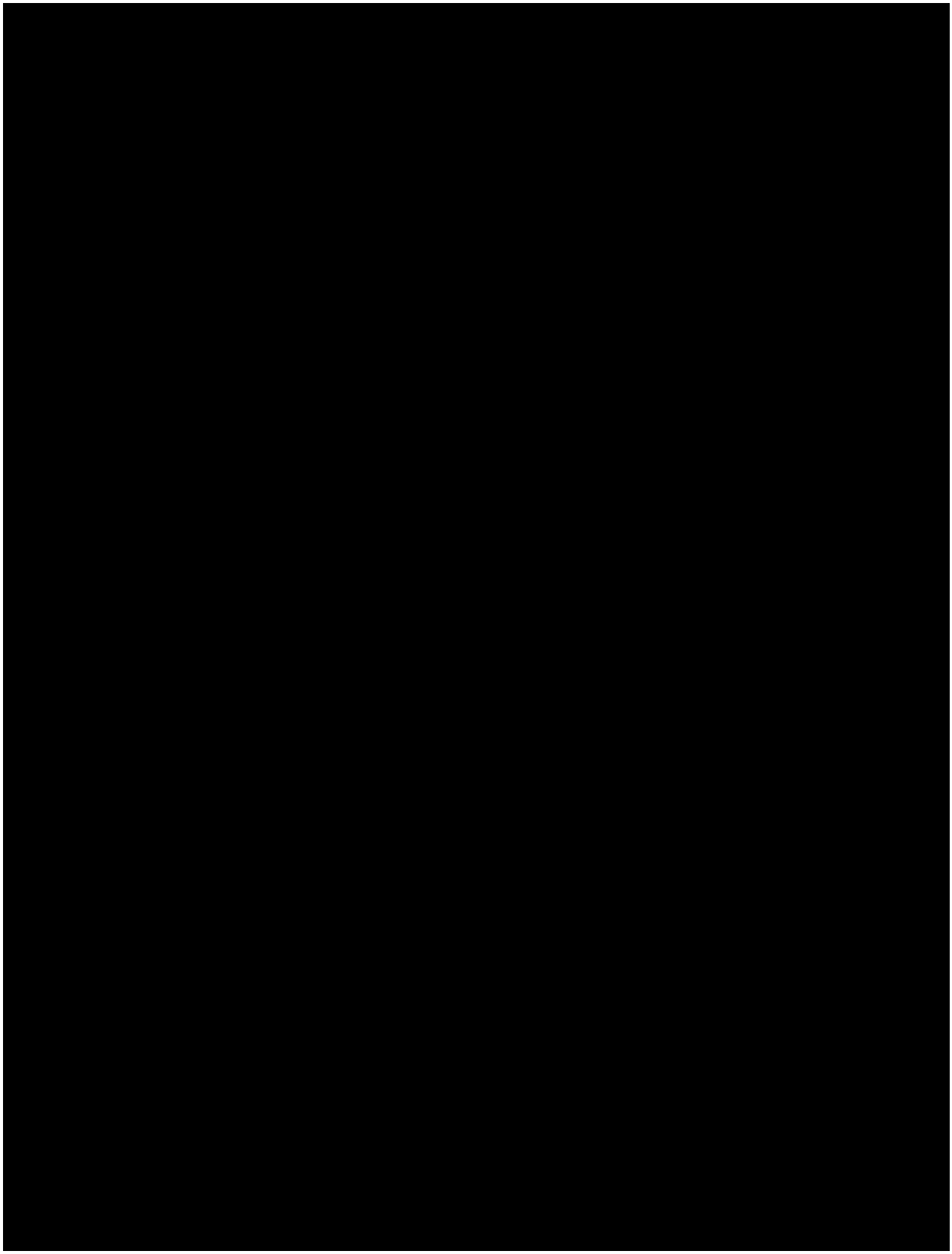
01-Oct-2024 | 4:05 PM CEST

Date

Appendix 2

[redacted]





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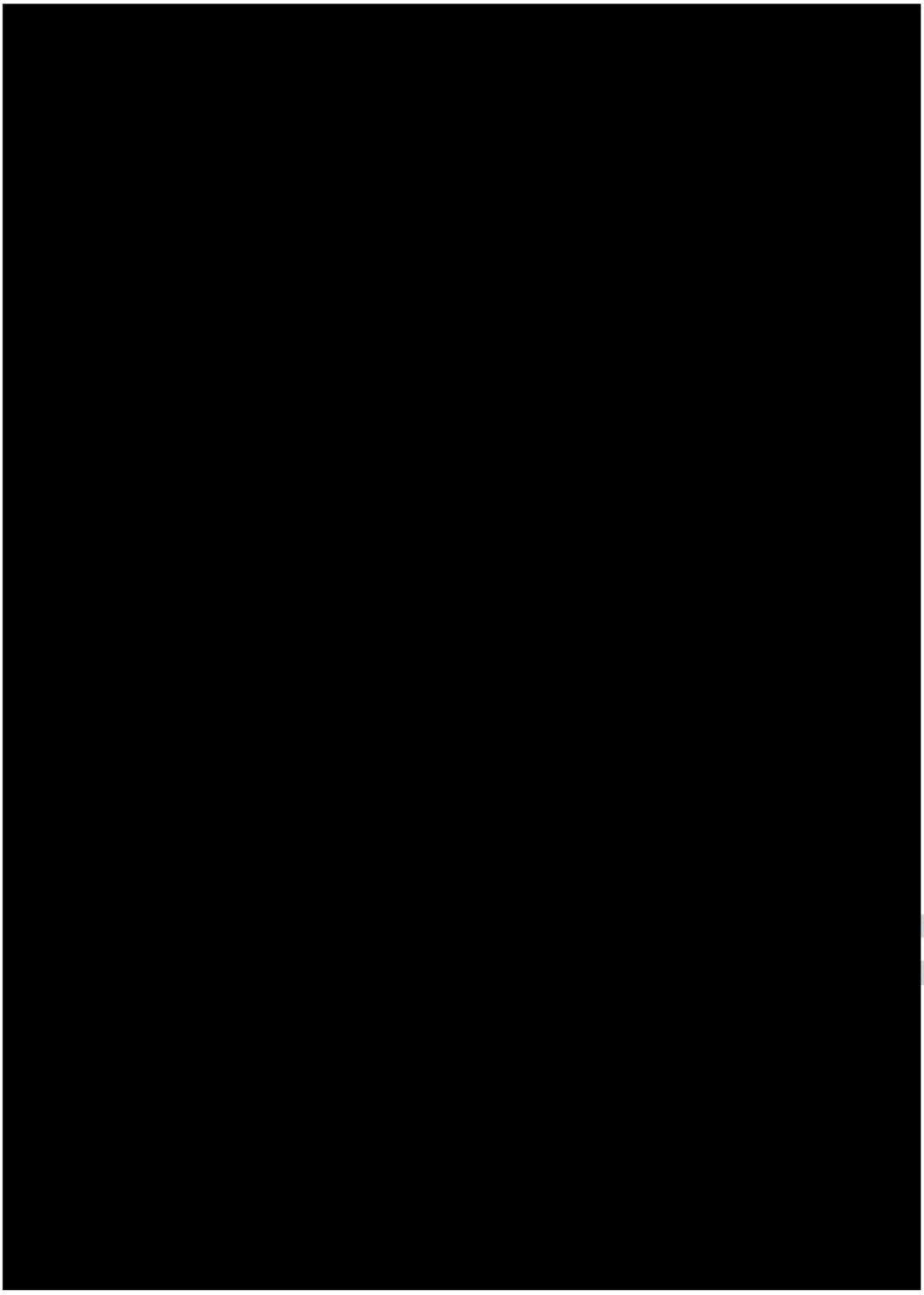


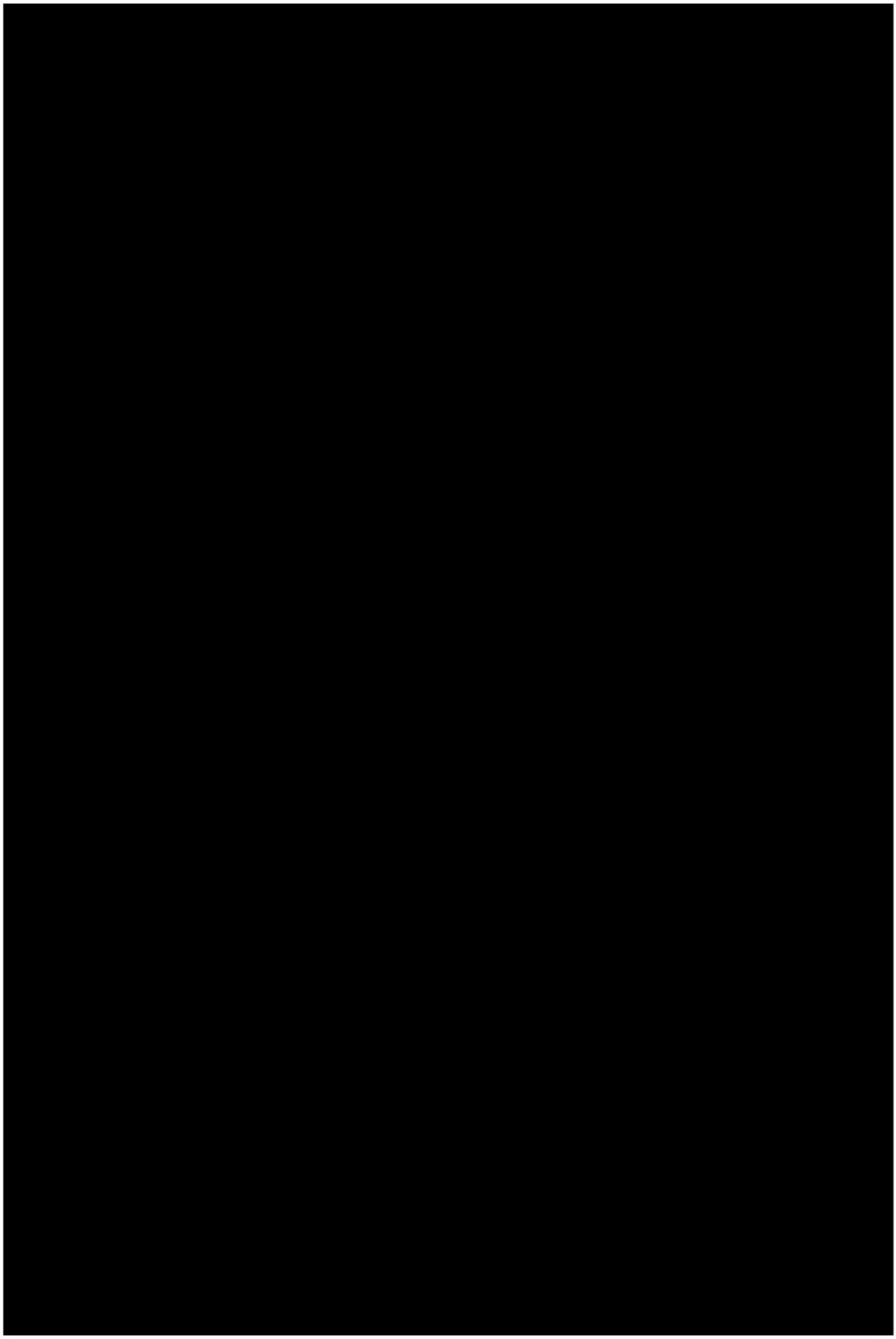
Appendix 4

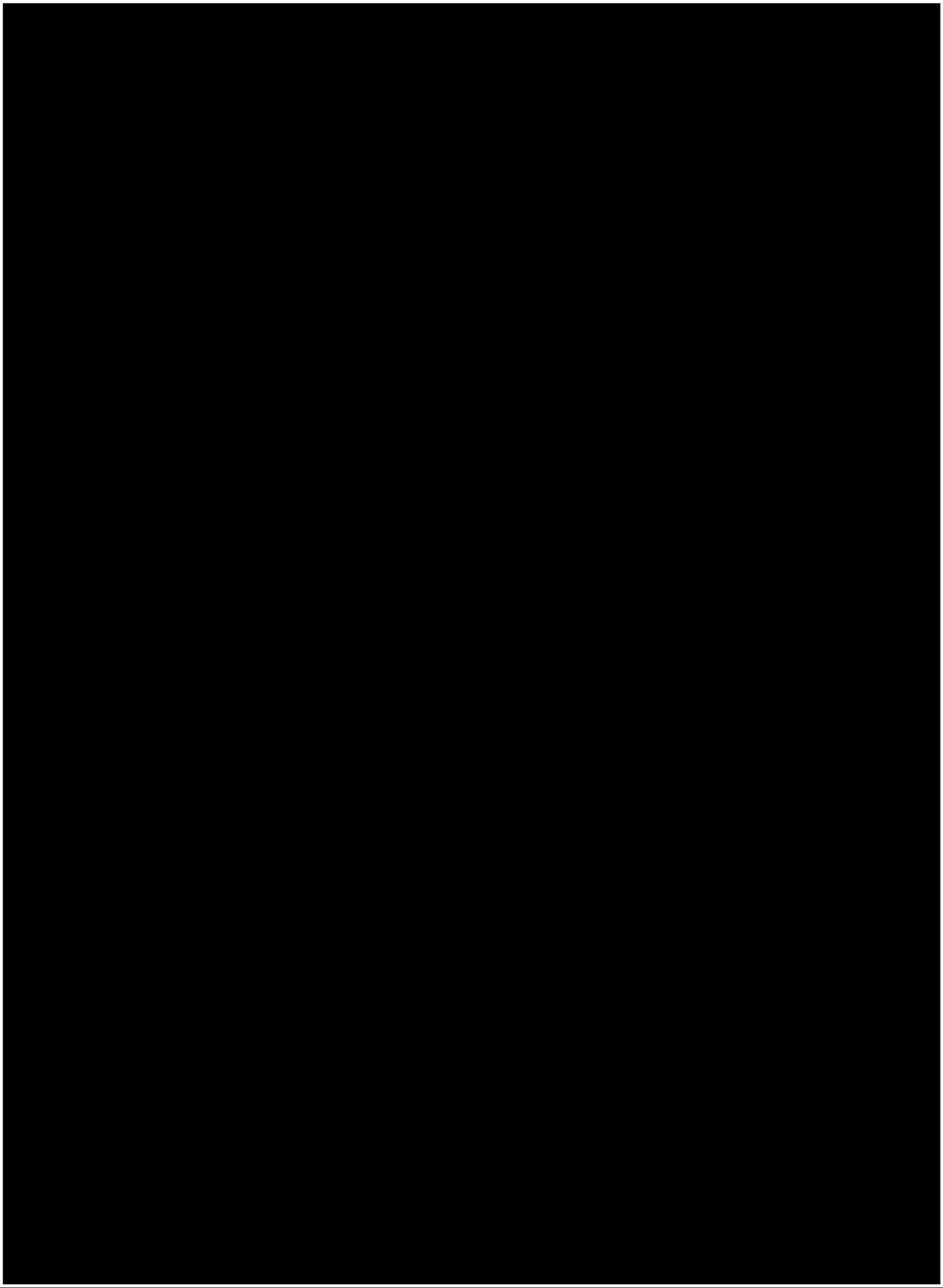
[redacted]

[redacted]

[redacted]

[redacted]





[redacted]

[redacted]

[redacted]

Appendix 6 Protocol changes to be followed during COVID-19 restrictions

OVERVIEW

It is expected that all patients will be vaccinated against coronavirus SARS-CoV-2 prior to the HSCT and routinely tested for COVID-19 as per standard of care.

In response to the COVID-19 crisis, to ensure the safety of study patients and investigative sites as well as proper conduct of the study, TEMPORARY changes to the protocol may be implemented. These changes should be followed only during COVID-19 restrictions. These changes will be reported as COVID-19-related protocol deviations.

In case of new waves of restricted access to trial sites due to the unforeseeable evolution of the COVID-19 pandemic, to ensure ongoing patients' rights, safety and wellbeing, and control risks to study critical processes, the sponsor might decide to apply alternative mechanisms of oversight and monitoring. Among these mechanisms, remote source data verification would be implemented only if allowed by country regulations and within the limits established.

MINIMUM SCHEDULE OF ACTIVITIES

Where feasible, sites could continue to follow the full schedule of activities The minimum assessment tables, only to be followed during this COVID-19 effort and if determined necessary to use on the basis of the investigator's clinical judgment, are provided below to reduce the time required for each study visit. Assessments not performed (even those that have been removed in the minimum assessment table) should be documented and captured in the eCRFs.

Patients who have been discharged and are not able to come into the clinic for a study visit because of COVID-19-related restrictions, should be contacted via the phone for the collection of AEs (including SAEs) and concomitant medications. **All SAEs are still required to be reported within 24 hours of site awareness, even if reported via phone call**. All communications via phone call should also be documented in the source documentation and in the respective eCRF page. In addition, these patients should be instructed to self-monitor their symptoms at home and report any changes in symptoms or their overall health via phone call. The site must inform the sponsor of any patients lost to follow-up.

It is critical that local, country, and regional governance regarding COVID-19 is followed along with your best clinical judgment when managing this situation.

MINIMUM STUDY REQUIREMENTS

The following are the minimum study requirements for Study Sobi.PEGCET-201 during the COVID-19 pandemic and should be used as guidance when the full protocol requirements cannot be conducted.

1. **Obtain** key safety laboratory assessments.

a. All laboratory assessments should be drawn at the frequency required by the minimized schedule of events (Table 4).
    i. Includes (at minimum): hematology with differential, chemistry including LDH and creatinine.
b. In the event that the clinical investigative site is closed or patients are unable/unwilling to travel, patients should be referred to a certified local laboratory that can perform the required safety testing (see schedule of events below). The investigator should collect the local laboratory reports, which must be redacted (e.g., name and other local requirements) and added to the study records.

2. Perform minimal medical safety assessments.

a. If the patient is unable to have an in-person assessment, the investigator (or delegated site staff) should have a telephone contact at a frequency noted in the protocol (at minimum) to solicit AEs (including SAEs), concomitant medications and transfusions. The appropriate forms in the eCRF should be completed.

3. **Document** appropriate contact with the patient.

a. Earnest and reasonable attempts must be made to solicit AEs and concomitant medications. The CRA/medical monitor must be notified of any patients lost to follow-up.
b. All communication with the patient (including failed attempts at contact) must be documented in the study records.

The modified schedule of activities is shown in Table 4.

Table 4 Revised COVID-19 minimum schedule of assessments

Study period	Screening	Treatment period									*Optional treatment*		Follow-up period		
Study Week	-2	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	*14*	*16*	**EOT/ET [c] 16**	**20 [c]**	**EOS 24**
Study Day	-14	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	*99*	*113*	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
Informed consent	X														
Demographics	X														
Medical history	X														
Inclusion/ Exclusion criteria	X	X													
Vaccination [a]	X														
Mandatory anti-infective prophylaxis [b]			----------→												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height	X														

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
~~12-lead ECG (prior to venipuncture)~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Pegcetacoplan administration [c]		----------→													
Infusion-site assessment [d]		----------→													
Concomitant medications/ treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs measurements [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
~~PK sampling [f]~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Hematology, serum chemistry, ~~coagulation profile[g]~~	X	X [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
~~Urinalysis [g]~~	~~X~~	~~X~~ [p]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Biomarkers of complement activation~~		~~X~~ [r]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
[redacted]		~~X~~[*]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
[redacted]		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Antibodies to PEG and pegcetacoplan~~ [h]	~~X~~	~~X~~		~~X~~		~~X~~				~~X~~		~~X~~	~~X~~	~~X~~	~~X~~
HIV, HCV-RNA, HBV-DNA [i]	X														
Serum pregnancy (β-HCG and FSH) [k]	X														
Urine pregnancy [k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs [m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusions collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear for schistocytes evaluation	X														

Study period	**Screening**	**Treatment period**									***Optional treatment***		**Follow-up period**		
Study Week	**-2**	**Baseline 0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	***14***	***16***	**EOT/ET [o] 16**	**20 [o]**	**EOS 24**
Study Day	**-14**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	***99***	***113***	**113**	**141**	**169**
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Visit window (± days)			**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(± 3)**	**(± 3)**
Biopsy collection of any affected organ (if performed)	X														
Direct Coomb's test	X														
ADAMTS13 activity test	X														
[redacted]	X	*X*													
rUPCR	X	X [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical response evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X				X		X		X					X
[redacted]		X								X					X
[redacted]															X
Survival status and evidence of TA-TMA relapse													X	X	X

Abbreviations: AE, Adverse event; β-hCG, Human chorionic gonadotropin-beta; COVID-19, Coronavirus disease 19; [redacted] ECG, Electrocardiogram; eCRF, Electronic case report form; EOS, End of study; EOT, End of treatment; [redacted] ET, Early Termination; [redacted] FSH, Follicle stimulating hormone; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HSCT, Hematopoietic stem cell transplantation; ICF, Informed consent form; [redacted] PEG, Polyethylene glycols; [redacted] PK, Pharmacokinetic; PRBC, Packed red blood cells; rUPCR, Random urine protein:creatine ratio SAE, Serious adverse event; s.c., Subcutaneously; [redacted] TA-TMA, Transplant-associated thrombotic microangiopathy; [redacted].

[a] Patients should be vaccinated against *Neisseria meningitidis* (Types A, C, W, Y, and B) either within 2 years prior to Day 1 or if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. Patients should be re-vaccinated against *Haemophilus influenzae* Type B and *Streptococcus pneumoniae* if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT.

[b] All patients must continue to be administered coverage with prophylactic antibiotics and antifungals according to institutional posttransplant infection prophylaxis guidance, including coverage against *N. meningitidis*, for the entire treatment period and for 8 weeks following the final dose of pegcetacoplan.

[c] [redacted] If deemed by the investigator that a patient can be discharged from hospital upon the clinical improvement, pegcetacoplan administration will occur at home. Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. Patients will self-administer pegcetacoplan, after receiving appropriate training by research personnel. When the patient's pegcetacoplan dosing schedule aligns with study visit days, pegcetacoplan should be administered at the study site and complete the study procedures as outlined in this schedule of assessments. In some instances, however, a patient may not be able to align the date of a study visit with his/her pegcetacoplan administration schedule (e.g., if the patient has to utilize the visit window in order to be able to attend a study visit). In such instances it is important that pegcetacoplan dosing occurs according to the dosing schedule and not the visit schedule.

[d] On the days of clinic visits, if pegcetacoplan is administered at the visit site, an assessment of the pegcetacoplan infusion site will be made as a part of the AE assessment. If pegcetacoplan is administered at the visit, the site staff will observe the dosing and pump use safety will be assessed. The infusion site will be checked again within 30 minutes after each study drug administration. The infusion-site assessments will be performed by an appropriately trained staff, as delegated by the investigator. The infusion site and surrounding area will be inspected for redness, swelling, induration and bruising. The patient will be asked about the presence of pain and/or tenderness, and any issue related to pump use. Patients will be instructed to notify the investigator or other study personnel if an infusion-site reaction occurs after self-administration of pegcetacoplan.

[e] Vital signs (body temperature, respiration rate, heart rate, systolic and diastolic blood pressure measurements) will be evaluated per institutional practices. When pegcetacoplan is administered at the study site, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 min) postdose.

[f] On dosing Days 1, 3 and 5, PK samples will be taken up to 30 minutes predose and at 15 minutes (± 5 min), 30 minutes (± 5 min), 1 hour (± 10 min), 4 hours (± 10 min), 8 hours (± 30 min), and 24 hours (± 30 min) postdose. From Day 8 and onwards, PK samples will be taken predose at all other visits.

[g] Laboratory tests: refer to Table 3. Blood and urine samples will be analyzed at a central unless a local laboratory facility is necessary, as defined in the laboratory manual. Urine samples will be analyzed by dipstick and microscopic analysis. The use of silica agents should be avoided in patients treated with pegcetacoplan.

[h] Samples that are confirmed positive for anti-pegcetacoplan peptide or anti-PEG antibodies will be characterized with an antibody titer for that specific antibody. Any samples that are confirmed positive for anti-pegcetacoplan peptide antibody will be further characterized with a neutralizing antibody assay. If a clinic visit is on a dosing day, the sample should be taken predose but otherwise a sample is still required.

[i] Pre-HSCT evaluations will be accepted as screening tests.

[k] β-HCG for women of childbearing potential and FSH for postmenopausal women. For women of childbearing potential, a serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all subsequent site visits. Patients with positive results will be excluded or discontinued from the study.

[m] All AEs occurring upon receiving the first IMP dose up to 8 weeks after last IMP administration must be recorded in the eCRF. SAEs will be reported from signing of the ICF up to 8 weeks after last IMP administration. New SAEs occurring at any time after the 8-week AE follow-up period up to EOS should be reported only if considered causally related to previous exposure to the IMP by the investigator.

[redacted]

[o] An 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. The main analysis will be performed after all patients have completed their Week 24 visit.

[p] Blood collection for safety laboratory tests at Day 1 can be omitted if screening samples were collected on Day -1.

Note: On dosing days, all blood samples will be collected predose. The date and time of the sample and the date and time of the previous dose of pegcetacoplan must be recorded in the eCRF.

Note: Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.