SAMSUNG BIOEPIS

Clinical Study Protocol

A Phase III Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in Subjects with Paroxysmal Nocturnal Haemoglobinuria

Product	SB12 (proposed eculizumab biosimilar)	
EudraCT Number	2018-002857-31	
US pre-IND Number	PIND 135254	
Protocol Number	SB12-3003	
Study Phase	Phase III	
Version and Effective Date	Version 6.0	Nov 27, 2020
	Version 5.0	Aug 21, 2020
	Version 4.0	Nov 29, 2019
	Version 3.0	Dec 12, 2018
	Version 2.0	Oct 08, 2018
	Version 1.0	Jul 31, 2018
Sponsor	Samsung Bioepis Co., Ltd.	
	107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea	

SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.	
Name of Finished Product:	SB12 (proposed eculizumab biosimilar)	
Name of Active Ingredient:	Eculizumab	
Title of Study: A Phase III Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in Subjects with Paroxysmal Nocturnal Haemoglobinuria		
Protocol No:	SB12-3003	**Phase:** III
Planned Study Period: After Screening, the duration of study participation will be 58 weeks per subject including 50 weeks of treatment and 8 weeks of post-treatment follow-up. After completion of study treatment, subjects may be entered into an extended supply of up to 2 years.		

Objectives:

Primary objective

The primary objective of this study is to demonstrate comparable clinical efficacy of SB12 and Soliris®, by evaluating the lactate dehydrogenase (LDH) in subjects with paroxysmal nocturnal haemoglobinuria (PNH).

Secondary objectives

The secondary objectives are:

- To evaluate the efficacy of SB12 compared to Soliris® by
  - LDH profile over time
  - Number of units of packed red blood cells (pRBCs) transfused
- To evaluate the safety and tolerability of SB12 compared to Soliris®
- To evaluate the pharmacokinetic (PK) of SB12 compared to Soliris®
- To evaluate the immunogenicity of SB12 compared to Soliris®
- To evaluate the pharmacodynamic (PD) of SB12 compared to Soliris®

Study Design:

This is a randomised, Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH.

Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26.

In special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner.

After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.

Number of Subjects:

A total of approximately 50 subjects (25 subjects per treatment sequence) will be randomised in this study.

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB12 (proposed eculizumab biosimilar)
Name of Active Ingredient:	Eculizumab

Treatment Sequence	Period 1	Period 2
I (n = 25)	SB12	Soliris®
II (n = 25)	Soliris®	SB12

Target Population:

Eculizumab-naïve patients with PNH

Eligibility Criteria:

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Male or female aged 18 or older at the time of signing the informed consent form (ICF), if local regulations are different in this regard, follow the local regulations.
2. Documented diagnosis of PNH.
3. Presence of the PNH white blood cell (WBC) clone, with a granulocyte or monocyte clone size of ≥ 10% by high-sensitivity flow cytometry at Screening.
4. Documented LDH level ≥ 1.5 × upper limit of normal (ULN) at Screening.
5. History of transfusion for anaemia within 12 months prior to Screening or having PNH-related symptoms (e.g., fatigue, haemoglobinuria, abdominal pain, chest pain, shortness of breath [dyspnoea], dysphagia, erectile dysfunction) at Screening.
6. All subjects must be vaccinated against *Neisseria meningitidis* within 3 years prior to or on Day 1 in accordance with current local guidelines or Soliris® Summary of Product Characteristics (SmPC) to reduce the risk of meningococcal infection.
7. Female subjects who are not pregnant or nursing at Screening and on initiation of study drug (Day 1) and who are not planning to become pregnant from Screening until 5 months after the last dose of study drug.
8. Subjects and their partners of childbearing potential (female or male) who agree to use of a highly effective contraceptive method (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, male sterilisation, or true abstinence [see Section 8.4.1]) from Screening until 5 months after the last dose of study drug.
9. Subjects must be able to understand the implications of taking part in the study and be willing to follow the study instructions and requirements fully.
10. Subjects must be able to provide informed consent, which must be obtained prior to any study related procedures.

Exclusion criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Previous treatment with a complement pathway inhibitor (including eculizumab).

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB12 (proposed eculizumab biosimilar)
Name of Active Ingredient:	Eculizumab

2. Known hypersensitivity to the investigational product (IP) or any of the ingredients or excipients of the IP.
3. Known contraindication/hypersensitivity for meningococcal vaccine or the antibiotic to be used in the study.
4. Abnormal haematological parameters at Screening defined as the following:
    a. Absolute neutrophil count (ANC) $\leq 0.5 \times 10^3/\mu L$
    b. Platelet count $< 70 \times 10^3/\mu L$
5. History of meningococcal disease.
6. History of haematopoietic stem cell transplantation.
7. History of serious thrombotic event (e.g., stroke, myocardial infarction, pulmonary embolism, etc.).
8. Known or suspected active bacterial, virus, fungal infection within 30 days prior to initiation of study drug (Day 1).
9. Known history of human immunodeficiency virus (HIV) infection or have positive results at Screening.
10. Concomitant use of any of the following medications is prohibited if the following conditions apply.
    a. Erythropoietin, systemic corticosteroids, low-molecular-weight heparins, iron supplements, and androgen therapy that have not been on a stable dose for at least 4 weeks prior to initiation of study drug (Day 1).
    b. Warfarin with an unstable international normalised ratio (INR) for at least 4 weeks prior to initiation of study drug (Day 1) at the discretion of the Investigator.
    c. Cyclosporine that has not been on a stable dose for at least 8 weeks prior to initiation of study drug (Day 1).
11. Subjects who have received or participated in another investigational drug, device, or procedures within 30 days or within 5 half-lives of that IP prior to Screening, whichever is greater.
12. History of malignancy within 5 years prior to Screening, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin, or squamous cell carcinoma of the skin.
13. Any other cardiac, hepatic, immunologic, pulmonary, rheumatoid disease, other conditions causing rise in LDH (e.g., tumours, muscular dystrophies, liver and bile disease, etc.), or the disorder which, at the discretion of the Investigator, will put the subjects at risk if they are enrolled.
14. Other unspecified reasons that, at the discretion of the Investigator or Sponsor, make the subjects unsuitable for enrolment.

Investigational Products:

- Name: SB12 (proposed eculizumab biosimilar) or Soliris®
- Formulation: A vial of 30 mL contains 300 mg of eculizumab (10 mg/mL)
- Route of administration: Intravenous (IV) infusion 35 ± 10 minutes

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB12 (proposed eculizumab biosimilar)
Name of Active Ingredient:	Eculizumab

- Dose regimen: 600 mg every 7 days for the first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 14 ± 2 days until Week 50 (maintenance phase).

Main Criteria for Evaluation

Primary endpoints

- LDH level (U/L) at Week 26
- Time-adjusted area under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52

Secondary endpoints

Efficacy endpoints

- LDH profile over time
- Number of units of pRBCs transfused throughout the study period

Safety endpoints

- Incidence of adverse events (AEs)
- Incidence of serious AEs (SAEs)
- Incidence of infection-related AEs
  - Meningococcal infection
  - Other systemic infections
- Incidence of infusion-related reactions (IRRs)

Safety of subjects will be monitored by 12-lead electrocardiogram (ECG), vital sign assessment, and physical examination. Haematological, biochemical, and urinalysis laboratory parameters will be also measured.

PK endpoint

- Concentration prior to infusion (trough serum concentration [C_{trough}]) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52

Immunogenicity endpoints

- Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and early termination (ET) visit
- Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET visit

PD endpoint

- Terminal complement activity at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52

Statistical Methods

Analysis sets for efficacy analyses

Modified Full Analysis Set (M-FAS) consists of all randomised subjects who do not have positive result of pharmacogenetic analysis (C5 gene polymorphism). However, subjects who do not have any efficacy assessment result after randomisation and do not receive IP during the study period will be excluded from this analysis set. Following the intent-to-treat principle, subjects will be analysed according to the treatment sequence they are assigned to at randomisation.

Per-Protocol Set for AUEC of LDH (PPS-AUEC) consists of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major protocol deviations (PDs) that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. In addition, subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.

Per-Protocol Set for LDH at a single time point (PPS-single) consists of all M-FAS subjects who have LDH assessment at Week 26 without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. In addition, subjects who received different treatment in Period 1 from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.

Efficacy analyses

[redacted] for those who are in favour of the time-adjusted AUEC of LDH, the primary efficacy analysis will be performed for the PPS-AUEC using a linear mixed model with treatment, sequence, period, and gender as fixed effects, and subject nested within sequence as a random effect. The analysis will be performed with $\log_e$-transformed time-adjusted AUEC of LDH estimating the difference in least squares means and its 90% confidence interval (CI), and back transformation of those values will provide the ratio of geometric means and 90% CI. The equivalence will be declared if the two-sided 90% CI of the ratio of geometric means in time-adjusted AUEC of LDH between SB12 and Soliris® lies within the pre-defined equivalence margin of [0.77, 1.29].

[redacted] for those who are in favour of the LDH level at a single time point, the primary efficacy analysis will be performed for the PPS-single using a linear mixed model with treatment, and gender as a fixed effect. The analysis will be performed with $\log_e$-transformed LDH at Week 26 estimating the difference in least squares means and its 95% CI, and the delta method will be used to provide the mean difference and 95% CI in original scale. The equivalence will be declared if the two-sided 95% CI of the mean difference in LDH level at Week 26 between SB12 and Soliris® lies within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study. If normal range of LDH is gender specific, the smaller/smallest ULN will be used for the equivalence margin; otherwise ULN is not gender specific, unified ULN will be used for the equivalence margin.

For sensitivity analysis, the primary efficacy analysis will be repeated for the M-FAS. Missing data will be imputed using multiple imputation method for subjects who drop out for the study prior to the primary analysis time point. Complete case analysis will also be performed.

As a secondary efficacy endpoint, the number of units of pRBCs transfused will be summarised descriptively by treatment sequence and treatment sequence within period and will be analysed using Wilcoxon rank-sum test. And mean LDH profile will be presented over time.

Safety analyses

Safety analyses will be performed in the Safety Set (SAF).

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB12 (proposed eculizumab biosimilar)
Name of Active Ingredient:	Eculizumab

All reported terms for AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be collected and classified according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

All AE data will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term. TEAEs leading to IP discontinuation and treatment-emergent AEs (TEAEs) by causality and severity will be summarised similarly. Infection-related AEs including meningococcal infection and other systemic infection, and IRRs will also be summarised.

Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence and visit. Other safety variables will be summarised unless otherwise specified.

Additional analyses will be performed for the subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator if needed. For example, AEs and concomitant medications will be analysed based on the actual switched treatment.

PK analyses

PK analysis will be performed for the PK Analysis Set (PKS). C_{trough} will be summarised descriptively by treatment sequence and visit.

Immunogenicity analyses

The immunogenicity analyses will be performed for the SAF. ADA and NAb results will be summarised with count and percentage by treatment sequence and visit. The incidence of overall ADA will be summarised by treatment sequence and period.

PD analyses

PD analysis will be performed for the PD Analysis Set (PDS). The absolute value and change from baseline in terminal complement activities will be summarised by treatment sequence and visit.

Sample size

The equivalence margin for the mean difference of LDH at Week 26 is derived from two historical studies with Soliris®. In TRIUMPH study, the mean (standard deviation [SD]) of LDH at Week 26 is 327.3 (432.9) U/L and 2,418.9 (930.6) U/L for eculizumab and non-eculizumab arms, respectively. PNH registry study reported the mean of LDH at 6 months is 352.1 (224.0) U/L and 1,201.0 (815.6) U/L for eculizumab and non-eculizumab arms, respectively.

A meta-analysis with fixed-effect model estimates −1,152.5 U/L of LDH mean at Week 26 with a 95% CI [−1,303.4, −1,001.7]. The [redacted] of upper limit of 95% CI was approximately [redacted] U/L, which implies that at least [redacted] treatment effect is obtained to preserve the treatment effect over placebo if the [redacted] U/L was statistically chosen as the equivalence limit.

In the clinical study, LDH detection level or normal range of LDH would depend on the specification of laboratory parameters chosen for the study. Therefore, it is not likely to be clinically meaningful to propose any specific LDH level as the equivalence margin without the consideration of normal range of LDH level.

[redacted]

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB12 (proposed eculizumab biosimilar)
Name of Active Ingredient:	Eculizumab

[redacted]

Therefore, the equivalence margin will be [−1.2 × ULN, 1.2 × ULN] for the comparison with the 95% CI of the mean difference in LDH at Week 26 where ULN of LDH to be specified in the central laboratory specification for this study. For sample size calculation, [−268 U/L, 268 U/L] is chosen to be 23 subjects per treatment sequence with the assumptions of no mean difference and common SD of 270 U/L at the overall 5% significance level. Assuming a 5% loss from randomised subjects after 26 weeks, a sample size of 25 subjects per treatment sequence (overall sample size of 50) will give 23 completers per treatment sequence after 26 weeks, which is estimated to give 80% power to detect the equivalence within the margin of 268 U/L.

For calculation of the equivalence margin for time-adjusted AUEC of LDH, mean and coefficient of variation (%CV) were referred from TRIUMPH study. The mean (%CV) of AUEC of LDH at Week 26 is 81,140.0 U/L × day (142.45%) and 429,874.1 U/L × day (33.49%) for eculizumab and non-eculizumab arms, respectively.

From the results in the reference study, mean ratio of AUEC of LDH is estimated to be 0.19 with a 90% CI [0.1308, 0.2724]. The upper limit of the equivalence margin is calculated as [redacted] where it preserves at least [redacted] of eculizumab treatment effect over the placebo, but [redacted] the equivalence margin will be [0.77, 1.29] for the comparison with the 90% CI of mean ratio of time-adjusted AUEC of LDH.

With the given equivalence margin of [0.77, 1.29], 22 subjects per treatment sequence was calculated with the assumptions of the mean ratio of 1, common %CV of 42% at the overall 10% significance level. Assuming a 10% loss from randomised subjects after 52 weeks, a sample size of 25 subjects per treatment sequence (overall sample size of 50) will give 22 completers per treatment sequence after 52 weeks, which is estimated to give 80% power to detect the equivalence within the margin of [0.77, 1.29].

Therefore, the sample size of 50 allows enough power to detect the equivalence in both situations.

GRAPHICAL STUDY DESIGN AND SCHEDULE OF ACTIVITIES

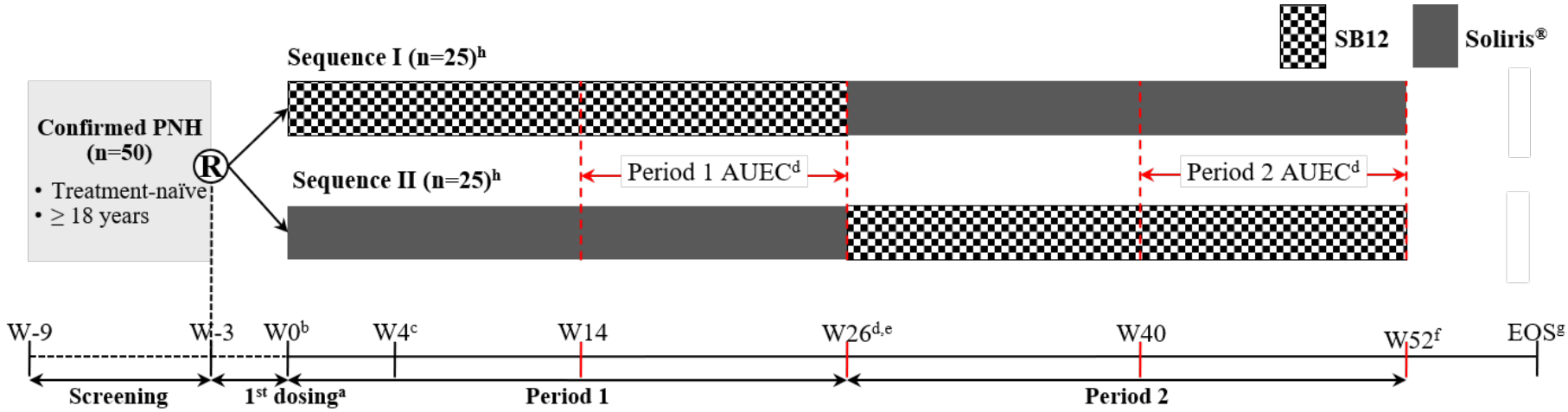


Figure 1. Graphical Study Design

® = Randomisation; AUEC = Area under the Effect Curve; EOS = End of Study; n = No. of Subjects; PNH = Paroxysmal Nocturnal Haemoglobinuria; W = Week

a. Randomisation will trigger the shipping of study drugs to investigational site. The initiation of study drug should be done within 21 days of randomisation.
b. Week 0 (Day 1) is defined as the day of the initiation of study drug. During Week 0 (Day 1) to Week 3, 600 mg of SB12 or Soliris® every 7 ± 2 days
c. From Week 4, 900 mg of SB12 or Soliris® every 14 ± 2 days up to Week 50.
d. Primary endpoints: 1) LDH level (U/L) at Week 26 and 2) AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52
e. Cross-over from SB12 to Soliris® and Soliris® to SB12 at Week 26
f. After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.
g. EOS is defined as either completion of safety follow-up at Week 58 or completion of ET visit (8 weeks after the last dose of SB12 or Soliris®), which may be up to Week 56.
h. During the treatment period, in special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner.

Table 1. Schedule of Activities (Period 1, before Cross-over)

Assessments	Study Period																
Study Visit	**Scree-ning**	**Randomi-sation**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Week			**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Day (± Visit Window)	**−63 to −22**	**−21 to −1**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**43 (±2)**	**57 (±2)**	**71 (±2)**	**85 (±2)**	**99 (±2)**	**113 (±2)**	**127 (±2)**	**141 (±2)**	**155 (±2)**	**169 (±2)**
Obtain informed consent[1]	✓																
Demographic information	✓																
Medical, transfusion, and thrombosis history	✓																
Vaccination for *Neisseria meningitidis*[2]	✓	✓	✓														
Serology (HIV-1 and HIV-2)	✓																
FSH[3]	✓																
Randomisation[4]		✓															
Pharmacogenetic sampling[5]			✓														
12-lead ECG[6]	✓											✓					
Pregnancy test[7]	✓		✓				✓		✓		✓		✓		✓		✓
PNH clone size[8]	✓		✓									✓					
Coagulation profile[9]	✓		✓									✓					
Ferritin, vitamin B_{12}, folate	✓		✓									✓					
LDH[10]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Haematology and chemistry tests[11]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reticulocyte count, haptoglobin, free haemoglobin	✓		✓		✓		✓	✓		✓		✓		✓		✓	
Urinalysis	✓		✓		✓		✓	✓		✓		✓		✓		✓	
Blood sampling for PK analysis[12]			✓		✓		✓	✓		✓		✓		✓		✓	
Blood sampling for PD analysis[13]			✓		✓		✓	✓		✓		✓					
Blood sampling for immunogenicity assay[14]			✓		✓		✓	✓		✓		✓		✓		✓	
PNH symptomatology[15]	✓		✓				✓					✓					
Physical examination[16]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital sign[17]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IP administration[18]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events[19]	Continuously																
Previous and concomitant medications[20]	Continuously																
Thrombosis record (MAVEs)	Continuously																
Transfusion record (date and number of pRBCs)[21]	Continuously																

HIV = Human Immunodeficiency Virus; FSH = Follicle Stimulating Hormone; ECG = Electrocardiogram; PNH = Paroxysmal Nocturnal Haemoglobinuria; LDH = Lactate Dehydrogenase; PK = Pharmacokinetic; PD = Pharmacodynamic; IP = Investigational Product; MAVEs = Major Adverse Vascular Events; pRBCs = Packed Red Blood Cells

1. Informed consent should be obtained prior to any study related procedures.
2. *Neisseria meningitidis* vaccination should be conducted prior to or on Day 1 according to current local guidelines or Soliris® SmPC. In case subjects were vaccinated against meningococcal infection within 3 years prior to Day 1, which is properly documented, vaccination could be omitted. Subject who initiates study drug administration less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., ciprofloxacin) until 14 days after vaccination.
3. FSH levels will be measured at Screening and Week 26 in order to confirm postmenopausal status only for women who present natural (spontaneous) amenorrhea for at least 12 months prior to Screening regardless of the subjects' age.
4. All screening procedures must be completed and reviewed within 42 days prior to randomisation. All eligibility criteria not dependent on Day 1 must be reviewed and confirmed prior to randomisation. The initiation of study drug (Day 1) should be done within 21 days of randomisation. Eligibility criteria that are dependent on Day 1 should be checked at Day 1 and if found in violation then should be withdrawn according to discontinuation criteria.
5. Blood sample for pharmacogenetic analysis (C5 gene polymorphism) will be taken at Day 1. If missing, it would be taken at the next scheduled blood sampling time.
6. Twelve-lead ECG will be collected at Screening and pre-dose on Week 14, Week 26, Week 40, and Week 52.
7. Females of childbearing potential only. Serum pregnancy test at Screening and 8 weeks after the last dose of study drug in case of early termination (ET); urine pregnancy test at other applicable visits before study drug administration.
8. Both white blood cell (WBC) and red blood cell (RBC) clone size will be measured by flow cytometry at Screening and prior to dosing at Day 1 and Week 52. At other visits (Week 14, Week 26, and Week 40), only RBC clone size will be measured prior to dosing.
9. Parameters included in coagulation profile are prothrombin time, partial thromboplastin time, and international normalised ratio (INR).
10. LDH will be measured at pre-dose on each visit and will also be measured if the suspected sign or symptom of breakthrough haemolysis occurs.
11. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, nucleated RBC, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean platelet volume (MPV), and red cell distribution width (RDW). Parameters included in chemistry tests are sodium, potassium, creatinine, blood urea nitrogen (BUN), glucose, calcium, phosphorus, total bilirubin, direct/indirect bilirubin, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase. All these parameters will be measured at pre-dose on each visit.
12. Blood sample for PK analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PK samples will also be collected if the suspected sign or symptom of breakthrough haemolysis occurs.
13. Blood sample for PD (terminal complement activity) analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PD analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PD samples will also be collected if the suspected sign or symptom of breakthrough haemolysis occurs.
14. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET visit. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis.
15. Investigator and/or designee will assess the PNH-related symptoms including fatigue, haemoglobinuria (discolouration of urine), chest pain, abdominal pain, dyspnoea, dysphagia, and erectile dysfunction.
16. Physical examination including height and weight at Screening; physical examination including weight at subsequent visits. Physical examination will be conducted before study drug administration.
17. Measured in a sitting position after remaining in a sitting or supine position for at least 5 minutes, including blood pressure, heart rate, and body temperature. On dosing days, vital signs will be taken before study drug administration.
18. Intravenous (IV) infusion will be performed for 35 ± 10 minutes.

19. Adverse events (AEs) will be collected from the time of signing the informed consent until end of study (EOS).
20. Previous medications (within 4 weeks prior to Screening except immunosuppressant, 8 weeks prior to Screening for immunosuppressant) will be recorded and concomitant medications will be recorded until EOS.
21. Transfusion record will be collected from the time of signing the informed consent until EOS.

Table 2. Schedule of Activities (Period 2 and Safety Follow-up/ET, after Cross-over)

Assessments	Study Period															
Study Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**Safety Follow-up[21]**	**ET[22]**
Week	**26[1]**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52[20]**	**58**	**8 (±1) weeks after the last dose of study drug**
Day (± Visit Window)	**183 (±2)**	**197 (±2)**	**211 (±2)**	**225 (±2)**	**239 (±2)**	**253 (±2)**	**267 (±2)**	**281 (±2)**	**295 (±2)**	**309 (±2)**	**323 (±2)**	**337 (±2)**	**351 (±2)**	**365 (±2)**	**407 (±7)**	
FSH[2]	✓															
12-lead ECG[3]	✓							✓						✓		
Pregnancy test[4]	✓	✓		✓		✓		✓		✓		✓		✓		✓
PNH clone size[5]	✓							✓						✓		
Coagulation profile[6]	✓							✓						✓		
Ferritin, vitamin B_{12}, folate	✓							✓						✓		
LDH[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Haematology and chemistry tests[8]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Reticulocyte count, haptoglobin, free haemoglobin	✓	✓		✓		✓		✓		✓		✓		✓		✓
Urinalysis	✓	✓		✓		✓		✓		✓		✓		✓		✓
Blood sampling for PK analysis[9]	✓	✓	✓	✓		✓		✓		✓		✓		✓		
Blood sampling for PD analysis[10]	✓	✓	✓	✓		✓		✓						✓		
Blood sampling for immunogenicity assay[11]	✓	✓	✓	✓		✓		✓		✓		✓		✓		✓
PNH symptomatology[12]	✓		✓					✓						✓		
Physical examination[13]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Vital sign[14]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
IP administration[15]	✓[16]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Adverse events[17]	Continuously															
Previous and concomitant medications[18]	Continuously															
Thrombosis record (MAVEs)	Continuously															
Transfusion record (date and number of pRBCs)[19]	Continuously															

ET = Early Termination; FSH = Follicle Stimulating Hormone; ECG = Electrocardiogram; PNH = Paroxysmal Nocturnal Haemoglobinuria; LDH = Lactate Dehydrogenase; PK = Pharmacokinetic; PD = Pharmacodynamic; IP = Investigational Product; MAVEs = Major Adverse Vascular Events; pRBCs = Packed Red Blood Cells

1. All subjects who roll over into Period 2 will be switched to receive the other IP (SB12 or Soliris®) on Week 26 after all assessments have been performed.
2. FSH levels will be measured at Screening and Week 26 in order to confirm postmenopausal status only for women who present natural (spontaneous) amenorrhea for at least 12 months prior to Screening regardless of the subjects' age.
3. Twelve-lead ECG will be collected at Screening and pre-dose on Week 14, Week 26, Week 40, and Week 52.

4. Females of childbearing potential only. Serum pregnancy test at Screening and 8 weeks after the last dose of study drug in case of ET; urine pregnancy test at other applicable visits before study drug administration.
5. Both WBC and RBC clone size will be measured by flow cytometry at Screening and prior to dosing at Day 1 and Week 52. At other visits (Week 14, Week 26, and Week 40), only RBC clone size will be measured prior to dosing.
6. Parameters included in coagulation profile are prothrombin time, partial thromboplastin time, and INR.
7. LDH will be measured at pre-dose on each visit and will also be measured if the suspected sign or symptom of breakthrough haemolysis occurs.
8. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, nucleated RBC, MCH, MCHC, MCV, MPV and RDW. Parameters included in chemistry tests are sodium, potassium, creatinine, BUN, glucose, calcium, phosphorus, total bilirubin, direct/indirect bilirubin, albumin, total protein, ALT, AST, ALP, and gamma-glutamyl transpeptidase. All these parameters will be measured at pre-dose on each visit.
9. Blood sample for PK analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PK samples will also be collected if the suspected sign or symptom of breakthrough haemolysis occurs.
10. Blood sample for PD (terminal complement activity) analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PD analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PD samples will also be collected if the suspected sign or symptom of breakthrough haemolysis occurs.
11. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET visit. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis.
12. Investigator and/or designee will assess the PNH-related symptoms including fatigue, haemoglobinuria (discolouration of urine), chest pain, abdominal pain, dyspnoea, dysphagia, and erectile dysfunction.
13. Physical examination including height and weight at Screening; physical examination including weight at subsequent visits. Physical examination will be conducted before study drug administration.
14. Measured in a sitting position after remaining in a sitting or supine position for at least 5 minutes, including blood pressure, heart rate, and body temperature. On dosing days, vital signs will be taken before study drug administration.
15. IV infusion will be performed for 35 ± 10 minutes.
16. The switched IP will be received on Week 26 and dosing on Week 26 is the start of Period 2.
17. AEs will be collected from the time of signing the informed consent until EOS.
18. Concomitant medications will be recorded until EOS.
19. Transfusion record will be collected from the time of signing the informed consent until EOS.
20. After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis. The Week 52 activities must be completed prior to initiation of extended supply. Subjects who are eligible to participate should provide separate informed consent prior to enter an extended supply of SB12.
21. Safety follow-up will be done at Week 58 for subjects who complete the study treatments until Week 50, regardless whether subject receives extended supply of SB12 or not. These activities will be conducted either by visit or by phone call on subjects' preference.
22. ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®, which may be up to Week 56. Subjects who discontinue from the study at any time post-Day 1 (after the initiation of study drug) before completion of last study treatment at Week 50 will be required to have an ET visit.

LIST OF ABBREVIATIONS

ADAs	Anti-drug antibodies
ADL	Activities of daily living
AEs	Adverse events
aHUS	Atypical haemolytic uremic syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUEC	Area under the effect curve
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRO	Contract research organisation
CSR	Clinical study report
C_{trough}	Trough serum concentration
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
ESF	Eligibility screening form
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

GCP	Good Clinical Practice
gMG	Generalised myasthenia gravis
GMP	Good Manufacturing Practice
GPI	Glycosylphosphatidylinositol
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International normalised ratio
IP	Investigational product
IRB	Institutional Review Board
IRRs	Infusion-related reactions
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MAC	Membrane attack complex
MAVE	Major adverse vascular event
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA®	Medical Dictionary for Regulatory Activities
M-FAS	Modified Full Analysis Set
MFDS	Ministry of Food and Drug Safety
MPV	Mean platelet volume
NAbs	Neutralising antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NMOSD	Neuromyelitis optica spectrum disorder
NO	Nitric oxide

PC	Product Complaints
PD	Pharmacodynamic
PDs	Protocol deviations
PDS	PD Analysis Set
PIG-A	Phosphatidylinositol glycan class-A
PK	Pharmacokinetic
PKS	PK Analysis Set
PNH	Paroxysmal nocturnal haemoglobinuria
PPS-AUEC	Per-Protocol Set for AUEC of LDH
PPS-single	Per-Protocol Set for LDH at a single time point
pRBCs	Packed red blood cells
PSUR	Periodic Safety Update Report
RAN	Randomised Set
RBC	Red blood cell
RDW	Red cell distribution width
RSI	Reference safety information
SAEs	Serious adverse events
SAF	Safety Set
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
TEAEs	Treatment-emergent adverse events
TOST	Two one-sided test
ULN	Upper limit of normal
US	United States of America
WBC	White blood cell
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

TABLE OF CONTENTS

SYNOPSIS **2**
GRAPHICAL STUDY DESIGN AND SCHEDULE OF ACTIVITIES **9**
LIST OF ABBREVIATIONS **15**
TABLE OF CONTENTS **18**
LIST OF TABLES **23**
LIST OF FIGURES **23**
LIST OF STUDY STAFF **24**
1. INTRODUCTION **25**
1.1. Paroxysmal Nocturnal Haemoglobinuria 25
1.2. Overview of SB12 25
1.2.1. Non-clinical Studies of SB12 26
1.2.2. Clinical Pharmacology of SB12 26
1.3. Comparator Investigational Product: Soliris® 26
1.3.1. Non-clinical Data of Soliris® 26
1.3.2. Clinical Data of Soliris® 27
1.4. Study Rationale 28
1.5. Risk and Benefit Assessment 28
1.5.1. Known Potential Risks 28
1.5.2. Known Potential Benefits 29
1.5.3. Assessment of Potential Risks and Benefits 29
2. STUDY OBJECTIVES AND ENDPOINTS **29**
2.1. Study Objectives 29
2.1.1. Primary Objective 29
2.1.2. Secondary Objectives 29
2.2. Endpoints 30
2.2.1. Primary Endpoints 30
2.2.2. Secondary Endpoints 30
3. STUDY DESIGN **31**
3.1. Overview of Study Design 31
3.2. Rationale for Study Design 31
3.2.1. Scientific Rationale for Study Design 31

3.2.2. Rationale for Dose Selection 32
3.2.3. Rationale for Pharmacokinetic Assessments 32
3.2.4. Rationale for Immunogenicity Assessments 32
3.3. Duration of Study Participation 32
3.4. Number of Subjects 33
3.5. End of Study Definition 33
4. STUDY POPULATION 33
4.1. Overview 33
4.2. Inclusion Criteria 33
4.3. Exclusion Criteria 34
4.4. Screen Failures and Re-screening 35
5. TREATMENT AND INVESTIGATIONAL PRODUCT 35
5.1. Treatment of the Subjects 35
5.1.1. Dosing and Treatment Schedule 35
5.1.2. Assignment of Subjects to Treatment Sequence 36
5.1.3. Blinding 36
5.2. Investigational Product 36
5.2.1. Identity of Investigational Product 36
5.2.2. Formulation, Packaging, and Labelling 37
5.2.3. Product Storage and Stability 37
5.2.4. Preparation and Administration of Investigational Products 37
5.2.5. Treatment Compliance and Investigational Product Accountability 38
5.3. Concomitant Medication or Treatment 39
5.3.1. Permitted Concomitant Medications or Treatment 39
5.3.2. Prohibited Concomitant Medications or Treatment 39
6. STUDY ASSESSMENT 39
6.1. Efficacy Assessment 39
6.1.1. Disease-related Laboratory Parameters 39
6.1.2. Breakthrough Haemolysis 40
6.1.3. Transfusions 40
6.1.4. Major Adverse Vascular Events 40
6.1.5. Paroxysmal Nocturnal Haemoglobinuria-related Symptoms 40

6.2. Safety Assessment 41
6.2.1. Adverse Events 41
6.2.2. Clinical Laboratory Evaluations 41
6.2.3. Physical Examinations 43
6.2.4. Twelve-lead Electrocardiograms 43
6.2.5. Vital Signs 43
6.3. Other Assessments 43
6.3.1. Pharmacokinetic Assessments 43
6.3.2. Immunogenicity Assessments 43
6.3.3. Pharmacodynamic Assessments 44
6.3.4. Pharmacogenetic Assessments 44
7. STUDY PROCEDURES 45
7.1. Study Flow and Visit Schedule 45
7.1.1. Screening Period 45
7.1.2. Randomisation 47
7.1.3. Treatment Period 47
7.1.4. Unscheduled Visits 50
7.2. Discontinuation 50
7.2.1. Subject Discontinuation from Study Treatment 50
7.2.2. Investigational Site Discontinuation 52
7.3. Early Termination of the Study 52
8. SAFETY MONITORING AND REPORTING 52
8.1. Adverse Events 52
8.1.1. Definition of Adverse Event 52
8.1.2. Period of Observation for Adverse Events 53
8.1.3. Reporting Adverse Events 53
8.1.4. Severity Assessment 53
8.1.5. Causality Assessment 54
8.1.6. Expectedness Assessment 54
8.1.7. Withdrawal due to Adverse Events 54
8.2. Serious Adverse Events 54
8.2.1. Definition of Serious Adverse Event 54

8.2.2. Reporting Serious Adverse Events 56
8.3. Adverse Events of Special Interest 56
8.3.1. Meningococcal Infection 56
8.3.2. Other Systemic Infections 57
8.3.3. Infusion-related Reactions 57
8.4. Pregnancy 58
8.4.1. Pregnancy Prevention 58
8.5. Emergency Unblinding of Assigned Treatment 59
8.6. Independent Data and Safety Monitoring Board 59
9. STATISTICAL METHODS AND DATA ANALYSIS 59
9.1. Statistical Hypotheses 59
9.2. Analysis Sets 60
9.3. Subject Demographic and Baseline Characteristics 60
9.4. Analysis of the Primary Objectives 61
9.5. Analysis of the Secondary Objectives 61
9.5.1. Efficacy Variable Analyses 61
9.5.2. Safety Analyses 62
9.5.3. Pharmacokinetic Analyses 62
9.5.4. Immunogenicity Analyses 62
9.5.5. Pharmacodynamic Analyses 62
9.6. Sample Size Calculations 62
10. DATA COLLECTION AND MANAGEMENT 64
10.1. Data Confidentiality 64
10.2. Monitoring 64
10.3. Data Handling and Record Keeping 65
10.4. Future Use of Stored Specimens and Data 65
10.5. Database Management and Coding 65
10.6. Quality Control and Quality Assurance 66
10.7. Protocol Deviation 66
11. ETHICS CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES 66
11.1. Institutional Review Boards and Independent Ethics Committees 66
11.2. Ethical Conduct of the Study 67

11.3. Written Informed Consent 67
11.4. Investigator Information 67
11.4.1. Investigator Obligations 67
11.4.2. Training of Investigational Site Personnel 67
11.4.3. Protocol Signatures 67
11.4.4. Financing and Insurance 68
12. PUBLICATION POLICY 68
13. EXTENDED SUPPLY 69
14. REFERENCES 70
APPENDIX A. PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA SYMPTOMS SUBJECT QUESTIONNAIRE 72
PROTOCOL SIGNATURE PAGES 73
CHANGE HISTORY OF PROTOCOL AMENDMENT 76
Amendment 1: Version 2.0, Oct 08, 2018 76
Amendment 2: Version 3.0, Dec 12, 2018 82
Amendment 3: Version 4.0, Nov 29, 2019 91
Amendment 4: Version 5.0, Aug 21, 2020 138
Amendment 5: Version 6.0, Nov 27, 2020 166

LIST OF TABLEs

Table 1. Schedule of Activities (Period 1, before Cross-over) 10
Table 2. Schedule of Activities (Period 2 and Safety Follow-up/ET, after Cross-over) 13
Table 3. Investigational Products Description 36
Table 4. Parameters for Clinical Laboratory Tests 42
Table 5. Severity Grade of NCI-CTCAE v5.0 53
Table 6. LDH Level from Reference Studies 63

LIST OF FIGUREs

Figure 1. Graphical Study Design 9

LIST OF STUDY STAFF

Sponsor:	**Samsung Bioepis Co., Ltd.** 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea Tel: +82 (32) 455 6114
Clinical Project Manager	[redacted]
Clinical Development Lead	[redacted]
Clinical Research Physician	[redacted]
Clinical Research Scientist	[redacted]
Statistician	[redacted]
Safety Physician	[redacted]
Project Safety Lead	[redacted]

1. Introduction

1.1. Paroxysmal Nocturnal Haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired haematopoietic disorder characterised by intravascular haemolysis and manifested by haemoglobinuria, anaemia, and venous thrombosis, which in turn produces severe and even potentially fatal clinical consequences. PNH is a very rare disease with a prevalence of about 16 per million people, and it can present at any range but mainly occurs in young adults, with the usual age at diagnosis being early 30s [1; 2; 3].

PNH results from a somatic mutation in the phosphatidylinositol glycan class-A (PIG-A) gene which is necessary for the synthesis of glycosylphosphatidylinositol (GPI)-anchors. The mutation leads to a deficiency of the GPI-anchored terminal complement inhibitors (e.g., CD55, CD59) on the surface of clonal populations of haematopoietic stem cells. Normally CD59 forms a defensive shield for red blood cells (RBCs) against complement-mediated lysis and inhibits the assembly of the membrane attack complex (MAC). The CD55 prevents formation and augments instability of the C3 convertases, attenuating the complement cascade. Without these complement inhibitors on the surface of cells, the cells are subjected to complement-mediated haemolysis, which in turn produces the clinical manifestations of the disease. The clinical features of the PNH arise as a result of complement-mediated haemolysis in unprotected RBCs, leukocytes, and platelets as well as the release of free haemoglobin that occurs with RBCs destruction [4].

Haemolysis contributes significantly to the anaemia and treatment is indicated for the following reasons: (1) Patients with chronic haemolysis complain of lethargy, malaise, myalgia, and loss of sense of well-being that diminishes significantly quality of life; (2) there is evidence that chronic haemolysis has an untoward effect on renal function; (3) the dysphagia and male impotence of PNH appear related to haemolysis; (4) a correlation between thrombosis and haemolysis may exist [5].

Conventional treatment options such as corticosteroids were limited, and the outcome of treatment was often unsatisfactory. Bone marrow transplantation is a curative treatment for PNH, but the procedure has risks of transplant-related morbidity and mortality and most PNH patients lack a suitable donor [6].

Soliris® (eculizumab, Alexion Pharmaceuticals, Inc.) is a humanised monoclonal antibody that blocks terminal complement by binding to C5 and is the approved therapy for PNH. The drug is highly effective in stopping intravascular haemolysis, eliminating or decreasing the need for RBC transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH [7; 8; 9].

1.2. Overview of SB12

SB12 has been developed as a similar biological medicinal product to Soliris® (eculizumab, Alexion Pharmaceuticals, Inc.). Soliris® is currently indicated for the treatment of patients with PNH, atypical haemolytic uremic syndrome (aHUS), refractory generalised myasthenia gravis (gMG), and neuromyelitis optica spectrum disorder (NMOSD) [10; 21]. SB12 and Soliris® have identical primary structure and the active substance for both products is eculizumab, a humanised monoclonal antibody (immunoglobulin G[IgG]2/4 kappa) that binds to the human C5 complement protein with high affinity. Binding to this protein blocks its cleavage into C5a and C5b, thereby inhibiting terminal complement-mediated intravascular haemolysis.

SB12 is produced by recombinant deoxyribonucleic acid (DNA) technology in a chinese hamster ovary (CHO) mammalian cell expression system and purified by various affinity and ion exchange chromatography steps that include specific viral inactivation and removal procedures.

According to the guideline International Council for Harmonisation (ICH) Q6B, characterisation of a biological therapeutic must involve its physicochemical properties, biological activities, purity, impurities, and quantity. The characterisation study will employ the 'state-of-the-art' analytical methods in order to investigate the primary, secondary, higher-order structures, and the post-translational modifications associated the structural heterogeneity, the charge variants, the purity, and the biological activities. It was demonstrated that SB12 has similar structural, physicochemical, and biological characteristics with Soliris®.

1.2.1. Non-clinical Studies of SB12

As outlined in the "Guideline on similar biological medicinal products containing monoclonal antibodies" [11], a risk-based approach was taken to the non-clinical evaluation of SB12. A series of *in vitro* biologic activity studies was performed in order to demonstrate similarity between SB12 and Soliris®. In addition, *in vivo* non-clinical study may not be necessary to provide non-clinical evidence of similarity between the two products, as eculizumab does not inhibit C5 in animal species. Therefore, no pharmacology or toxicology studies were conducted with eculizumab in normal rodents or non-human primates. Also, non-clinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies were not performed, as they are not required for non-clinical testing of biosimilars as outlined in the "Guideline on similar biological medicinal products containing monoclonal antibodies" [11]. There were no significantly different results observed in the *in vitro* studies between SB12 and Soliris®.

1.2.2. Clinical Pharmacology of SB12

Based on biosimilarity between SB12 and Soliris®, which was demonstrated through extensive quality and non-clinical similarity exercise, a Phase I study was conducted in healthy subjects to compare the pharmacokinetic (PK), safety, tolerability, immunogenicity, and pharmacodynamic (PD) profiles and a Phase III study will be conducted in subjects with PNH to compare the efficacy, safety, pharmacokinetics, and immunogenicity of SB12 to Soliris®. Information on the safety of SB12 based on the product information of Soliris®, non-clinical, and clinical exercise is presented in the Investigator's Brochure (IB).

1.3. Comparator Investigational Product: Soliris®

1.3.1. Non-clinical Data of Soliris®

The tissue cross-reactivity of eculizumab was evaluated by assessing binding to a panel of 38 human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression, as C5 has been reported in smooth muscle, striated muscle, and renal proximal tubular epithelium. No unexpected tissue cross-reactivity was observed.

Animal reproduction studies have not been conducted with eculizumab due to lack of pharmacologic activity in non-human species and no animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of eculizumab.

In a 26-week toxicity study performed in mice with a surrogate antibody directed against murine C5, treatment did not affect any of the toxicity parameters examined. Haemolytic activity during the course of the study was effectively blocked in both female and male mice.

No clear treatment-related effects or adverse effects were observed in reproductive toxicology studies in mice with a surrogate terminal complement inhibitory antibody, which was utilised to assess the reproductive safety of C5 inhibitor. These studies included assessment of fertility and early embryonic development, developmental toxicity, and pre and post-natal development.

When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human Soliris® dose, based on a body weight comparison); however, the exposure did not increase foetal loss or neonatal death.

Regarding *in vivo* non-clinical study, the publicly available information of Soliris® performed a species cross-reactivity of eculizumab to the functional complement C5 inhibition activity of eculizumab in human serum samples compared to primate and non-primate serum samples including eight-different species. The result concluded that there is no cross-reactivity of the eculizumab with non-primate species and primate species and that the result suggests that eculizumab effectively inhibits C5 only in human serum. In this context, the *in vivo* study in irrelevant non-primate animal species is unlikely to provide any additional meaningful non-clinical evidence.

1.3.2. Clinical Data of Soliris®

In 40 patients with PNH, a 1-compartmental model was used to estimate PK parameters after multiple doses. Mean clearance was 0.31 ± 0.12 mL/h/kg, mean volume of distribution was 110.3 ± 17.9 mL/kg, and mean elimination half-life was 11.3 ± 3.4 days. The steady state is achieved by 4 weeks using the PNH adult dosing regimen.

In PNH patients, PD activity correlates directly with eculizumab serum concentrations and maintenance of trough levels above ≥ 35 µg/mL results in essentially complete blockade of haemolytic activity in the majority of PNH patients.

The safety and efficacy of Soliris® in PNH patients were assessed in a randomised, double-blind, placebo-controlled 26-week study (C04-001). PNH patients were also treated with Soliris® in a single arm 52-week study (C04-002) and in a long term extension study (E05-001). Patients received meningococcal vaccination prior to receipt of Soliris®. In all studies, the dose of eculizumab was 600 mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris® was administered as an intravenous (IV) infusion over 25-45 minutes. An observational non-interventional registry in patients with PNH (M07-001) was also initiated to characterise the natural history of PNH in untreated patients and the clinical outcomes during Soliris® treatment.

In study C04-001 (TRIUMPH), PNH patients with at least 4 transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells, and platelet counts of at least 100,000/µL were randomised to either Soliris® (n = 43) or placebo (n = 44). Prior to randomisation, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the haemoglobin concentration (the 'set-point') which would define each patient's haemoglobin stabilisation and transfusion outcomes. The haemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Primary efficacy endpoints were haemoglobin stabilisation (patients who maintained a haemoglobin concentration above the haemoglobin set-point and avoid any RBC transfusion for the entire 26-week period) and blood transfusion requirement. Fatigue and health-related quality of life were relevant secondary endpoints. Haemolysis was monitored mainly by the measurement of serum lactate dehydrogenase (LDH) levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Major baseline characteristics were balanced. Study patients treated with Soliris® had significantly reduced ($p < 0.001$) haemolysis resulting in improvements in anaemia as indicated by increased haemoglobin stabilisation and reduced need for RBC transfusions compared to placebo treated patients. These effects were seen among patients within each of the three pre-study RBC transfusion strata (4-14 units; 15-25 units; > 25 units). After 3 weeks of Soliris® treatment, patients reported less fatigue and improved health-related quality of life.

Because of the study sample size and duration, the effects of Soliris® on thrombotic events could not be determined.

In the non-controlled study C04-002 (SHEPHERD), PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/μL received Soliris® over 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroid in 40% of the patients. Ninety-six of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular haemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in increased transfusion avoidance, a reduced need for RBC transfusion and less fatigue.

1.4. Study Rationale

Patients with PNH suffer from severe impaired quality of life arising from haemolysis leading to anaemia, thrombosis, renal impairment, and fatigue, which are the most common morbidities for this disease, with a significant increase in free haemoglobin levels. Cell-free haemoglobin consumes the serum nitric oxide (NO) and reduction in serum NO causes smooth muscle dystonia including vasoconstriction and gastrointestinal contractions and these consequences induce abdominal pain, dysphagia, pulmonary hypertension, dyspnoea, or erectile dysfunction [12; 13; 14; 15; 16]. Low serum NO also results in platelet activation/aggregation and thrombosis which may lead arterial myocardial infarction or cerebral vascular accident [12].

Thrombosis and renal failure are the leading cause of death in PNH and PNH patients with haemolysis whose LDH level is equal to or greater than 1.5 × upper limit of normal (ULN) showed a 4.8-fold increase in mortality rate compared with the general population [16].

Currently there are no approved treatments for PNH except for Soliris® but several types of supportive care have no any impact on progression or risk of severe morbidities and mortality. Unfortunately eculizumab does not alter the underlying defect of the disease, thus, treatment needs to continue life-long or until spontaneous remission, however Soliris® is barely affordable for the most of PNH patients as it costs 700,000 USD a year [1; 17].

Considering all the treatment options available, it is highly expected there are still patient needs for the right treatment with reasonable price. SB12 would meet this patient needs in extending the treatment opportunity by providing the medicine with lower price than the originator.

1.5. Risk and Benefit Assessment

1.5.1. Known Potential Risks

According to Soliris® Summary of Product Characteristics (SmPC) [10], supportive safety data were collected from 31 completed clinical studies that included 1,503 patients exposed to eculizumab in complement-mediated disease populations, including PNH, aHUS, refractory gMG and NMOSD. The most common adverse reaction was headache (occurred mostly in the initial phase) and the most frequently reported serious adverse reaction was meningococcal sepsis.

Considering the mechanism of action of eculizumab, C5 inhibition is known to increase the susceptibility to infection caused by encapsulated bacteria, especially by *Neisseria meningitidis.* In order to minimise the risk of meningococcal infection, all subjects participating in this study will receive meningococcal vaccines according to current local guidelines or Soliris® SmPC before investigational product (IP) administration. However, vaccination may not be sufficient to prevent meningococcal infection. Consideration will be given to current local guidelines and/or the discretion of the Investigator on the appropriate use of antibacterial agents. All subjects will be monitored for early signs of

meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary.

According to the study design, the switch of IP (cross-over) occurs during the study. The potential negative impact from this IP switch is considered to be minimal given similarity and comparability of SB12 to Soliris® and low antibody responses in Soliris® (3.4%) similar to that of placebo (4.8%) in placebo controlled studies in subjects with PNH [10].

In order to ensure the safety of subjects who participate in the study, the followings will be performed during the study. This study will take place at multicentre with accessible medical facilities which will allow immediate treatment of medical emergencies. All study related procedures will be conducted by medical staff with appropriate level of training and expertise and an understanding of the IPs, its target and mechanism of action. Subjects will have a safety follow-up until 8 weeks after the last dose of study drug. An independent Data and Safety Monitoring Board (DSMB) will convene at pre-specified intervals to conduct interim monitoring of accumulating safety data. Following each data review, the DSMB will make recommendations regarding the conduct of the study, including continuation of the study without modifications, modification of the protocol, pausing of subject enrolment until the resolution of issues, or termination of the study for safety reasons.

1.5.2. Known Potential Benefits

Soliris® is the approved therapy for PNH and is indicated for the treatment patients with aHUS, gMG, and NMOSD [10; 21]. The drug is highly effective in stopping intravascular haemolysis, eliminating or decreasing the need for RBC transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH [7; 8; 9].

Although clinical data is currently unavailable, SB12 is expected to have similar clinical outcome to Soliris® based on the physicochemical and biological similarity.

1.5.3. Assessment of Potential Risks and Benefits

The available data demonstrate a high degree of physicochemical and biological similarity of SB12 with the reference medicinal product (Soliris®). The suitability of the methodology employed to evaluate the similarity of SB12 and Soliris® in a pharmaceutical setting and these data were confirmed by the European Medicines Agency (EMA) and the United States of America (US) Food and Drug Administration (FDA). The known and potential risks of receiving SB12 are expected to be similar to those seen with Soliris®. In conclusion, sufficient evidence exists for the justification of the administration of SB12, as a similar biological medicinal product of Soliris®, to subjects with PNH.

The study protocol provides adequate instructions for the detection and treatment of adverse events (AEs) arising following the administration of the IP.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to demonstrate comparable clinical efficacy of SB12 and Soliris®, by evaluating the LDH in subjects with PNH.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of SB12 compared to Soliris® by
  - LDH profile over time
  - Number of units of packed red blood cells (pRBCs) transfused
- To evaluate the safety and tolerability of SB12 compared to Soliris®
- To evaluate the PK of SB12 compared to Soliris®
- To evaluate the immunogenicity of SB12 compared to Soliris®
- To evaluate the PD of SB12 compared to Soliris®

2.2. Endpoints

2.2.1. Primary Endpoints

- LDH level (U/L) at Week 26
- Time-adjusted area under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52

2.2.2. Secondary Endpoints

Efficacy endpoints

- LDH profile over time
- Number of units of pRBCs transfused throughout the study period

Safety endpoints

- Incidence of AEs
- Incidence of serious AEs (SAEs)
- Incidence of infection-related AEs
  - Meningococcal infection
  - Other systemic infection
- Incidence of infusion-related reactions (IRRs)

Safety of subjects will be monitored by 12-lead electrocardiogram (ECG), vital sign assessment, and physical examination. Haematological, biochemical, and urinalysis laboratory parameters will be also measured.

PK endpoint

- Concentration prior to infusion (trough serum concentration [C_{trough}]) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52

Immunogenicity endpoints

- Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and early termination (ET) visit
- Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28,

30, 32, 36, 40, 44, 48, 52, and ET visit

PD endpoint

- Terminal complement activity at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52

3. Study Design

3.1. Overview of Study Design

This is a randomised, Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH.

Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects randomly assigned to treatment with SB12 or Soliris® will receive 600 mg of eculizumab IV every week for first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter. Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. SB12 or Soliris® will be given until Week 50. However, in special circumtances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner.

Details of assessment that will be conducted and treatment that will be administered are presented in, Table 1 and Table 2. The last assessment will be performed at Week 58 or 8 weeks after the last dose of SB12 or Soliris® in case of ET.

After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.

3.2. Rationale for Study Design

3.2.1. Scientific Rationale for Study Design

It is acknowledged that PNH is a rare disease with an estimated incidence of 0.1-0.2/100,000 persons/year [18] and executing an adequately powered comparative trial is therefore challenging. The guiding principle of a biosimilar development is, however to demonstrate similar clinical efficacy and safety compared to the reference medicinal product, not patient benefit per se, which has already been shown for the reference medicinal product [11]. In view of this, the two arms design with randomisation between SB12 and Soliris® is endorsed. And in view of the very limited sample size (approximately 50 subjects), the study will be conducted in treatment-naïve patients to allow proper evaluation of safety and immunogenicity of the compound, as it reduces heterogeneity of the population.

LDH has been considered an authentic and useful clinical marker and direct measure of intravascular haemolysis in patients with PNH, published data support. And also, LDH is useful in evaluating response to treatment, as its level decreases along with the reduction of the haemolytic rate, which has been described in PNH following treatment [19; 20]. Results from the eculizumab clinical study showed that serum LDH levels continued markedly elevated and unchanged in untreated patients, while eculizumab treated patients had an immediate reduction in serum LDH to normal or near normal level [10; 21]. The reduction of serum LDH level reflected a rapid, sustained reduction in haemolysis and improvement in fatigue as well [9].

This study has two different primary endpoints, depending on regulatory agency's requirements for

assessing equivalence in efficacy between SB12 and Soliris®.

[redacted] for analysis of haemolysis reduction as measured by time-adjusted AUEC of LDH between two different time points in each period, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of time-adjusted AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52.

[redacted], for analysis of haemolysis reduction as measured by the LDH level at single time point, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of the LDH level (U/L) at Week 26.

3.2.2. Rationale for Dose Selection

The dosing regimen for adult patients (≥ 18 years of age) of Soliris® is approved for the treatment of PNH as 4-week initial phase followed by a maintenance phase as below:

- Initial phase: 600 mg of Soliris® administered via a 25-45 minutes IV infusion every 7 days for the first 4 weeks
- Maintenance phase: 900 mg of Soliris® administered via a 25-45 minutes IV infusion for the fifth week, followed by 900 mg of Soliris® administered via a 25-45 minutes IV infusion every 14 ± 2 days

As SB12 is a proposed biosimilar of Soliris®, an identical dose is selected for both treatments.

3.2.3. Rationale for Pharmacokinetic Assessments

A randomised, three-arm, parallel, single-dose Phase I PK study was conducted in healthy subjects to demonstrate similarity in PK profiles of SB12, European Union (EU) sourced Soliris®, and US sourced Soliris®. However, since target-mediated clearance of eculizumab can be more accurately investigated in patients, additional PK assessments will be performed in this Phase III study to provide supportive evidence to PK similarity.

3.2.4. Rationale for Immunogenicity Assessments

Biological/biotechnology-derived proteins can induce an unwanted immune response that is triggered by more than a single factor and the consequence of immunogenicity may vary considerably, ranging from irrelevant to therapy to serious and life-threatening. Immune responses may affect both safety and effectiveness such as altering PK, inducing anaphylaxis, or promoting development of NAbs that neutralise the product as well as its endogenous protein counterpart.

In all clinical studies of Soliris®, the frequency of ADAs has been reported as 0.0% to 4.8%. In PNH placebo controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%). There has been no observed correlation of antibody development to clinical response or AEs.

For subject safety and for demonstrating biosimilarity, immunogenicity will be assessed in this study according to the recommended guideline.

3.3. Duration of Study Participation

After Screening, the duration of study participation will be 58 weeks per subject including 50 weeks of treatment and 8 weeks of post-treatment follow-up . After completion of study treatment, subjects may be entered into an extended supply of up to 2 years.

3.4. Number of Subjects

Approximately 50 subjects (25 subjects per treatment sequence) are planned to be randomised in this study over a planned recruitment period.

3.5. End of Study Definition

A subject is considered to have completed the study if he or she has completed all study treatment and the last visit or the last scheduled procedure shown in Table 2. The end of study (EOS) is defined as completion of safety follow-up at Week 58 or completion of ET visit (8 weeks after the last dose of SB12 or Soliris®). The end of this clinical study is defined as completion of the last subject's EOS.

4. Study Population

4.1. Overview

The study population for this study is subjects with PNH.

4.2. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Male or female aged 18 or older at the time of signing the informed consent form (ICF), if local regulations are different in this regard, follow the local regulations.

2. Documented diagnosis of PNH.

3. Presence of the PNH white blood cell (WBC) clone, with a granulocyte or monocyte clone size of ≥ 10% by high-sensitivity flow cytometry at Screening.

4. Documented LDH level ≥ 1.5 × ULN at Screening.

5. History of transfusion for anaemia within 12 months prior to Screening or having PNH-related symptoms (e.g., fatigue, haemoglobinuria, abdominal pain, chest pain, shortness of breath [dyspnoea], dysphagia, erectile dysfunction) at Screening.

6. All subjects must be vaccinated against *Neisseria meningitidis* within 3 years prior to or on Day 1 in accordance with current local guidelines or Soliris® SmPC to reduce the risk of meningococcal infection.

7. Female subjects who are not pregnant or nursing at Screening and on initiation of study drug (Day 1) and who are not planning to become pregnant from Screening until 5 months after the last dose of study drug.

8. Subjects and their partners of childbearing potential (female or male) who agree to use of a highly effective contraceptive method (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, male sterilisation, or true abstinence [see Section 8.4.1]) from Screening until 5 months after the last dose of study drug.

9. Subjects must be able to understand the implications of taking part in the study and be willing to follow the study instructions and requirements fully.

10. Subjects must be able to provide informed consent, which must be obtained prior to any study related procedures.

4.3. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Previous treatment with a complement pathway inhibitor (including eculizumab).
2. Known hypersensitivity to the IP or any of the ingredients or excipients of the IP.
3. Known contraindication/hypersensitivity for meningococcal vaccine or the antibiotic to be used in the study.
4. Abnormal haematological parameters at Screening defined as the following:
    a. Absolute neutrophil count (ANC) $\leq 0.5 \times 10^3/\mu L$
    b. Platelet count $< 70 \times 10^3/\mu L$
5. History of meningococcal disease.
6. History of haematopoietic stem cell transplantation.
7. History of serious thrombotic event (e.g., stroke, myocardial infarction, pulmonary embolism, etc.).
8. Known or suspected active bacterial, virus, fungal infection within 30 days prior to initiation of study drug (Day 1).
9. Known history of human immunodeficiency virus (HIV) infection or have positive results at Screening.
10. Concomitant use of any of the following medications is prohibited if the following conditions apply.
    a. Erythropoietin, systemic corticosteroids, low-molecular-weight heparins, iron supplements, and androgen therapy that have not been on a stable dose for at least 4 weeks prior to initiation of study drug (Day 1).
    b. Warfarin with an unstable international normalised ratio (INR) for at least 4 weeks prior to initiation of study drug (Day 1) at the discretion of the Investigator.
    c. Cyclosporine that has not been on a stable dose for at least 8 weeks prior to initiation of study drug (Day 1).
11. Subjects who have received or participated in another investigational drug, device, or procedures within 30 days or within 5 half-lives of that IP prior to Screening, whichever is greater.

12. History of malignancy within 5 years prior to Screening, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin, or squamous cell carcinoma of the skin.

13. Any other cardiac, hepatic, immunologic, pulmonary, rheumatoid disease, other conditions causing rise in LDH (e.g., tumours, muscular dystrophies, liver and bile disease, etc.), or the disorder which, at the discretion of the Investigator, will put the subjects at risk if they are enrolled.

14. Other unspecified reasons that, at the discretion of the Investigator or Sponsor, make the subjects unsuitable for enrolment.

4.4. Screen Failures and Re-screening

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet one or more criteria required for participation in the trial during the screening procedures. A minimal set of screen failure information is required.

Subjects who are screen failure due to technical issue, not medical issue, might be re-screened once based on discussion and agreement between the Investigator and the medical monitor.

During Coronavirus Disease 2019 (COVID-19) pandemic circumstances, eligibility may not be confirmed at Screening due to unexpected COVID-19 related restrictions. These cases may fall into screen failures due to out of 42 days screening window or consent withdrawal related with COVID-19 concern, etc. These will be considered as technical issue so that re-screening is applicable after COVID-19 related restrictions are relieved.

5. Treatment and Investigational Product

5.1. Treatment of the Subjects

5.1.1. Dosing and Treatment Schedule

SB12 or Soliris® will be administered up to Week 50 (a total of 28 administrations of IP) unless they are early discontinued from study treatment. Dosing and treatment schedule should be kept as follows:

- 600 mg every 7 ± 2 days for the first 4 weeks, followed by
- 900 mg for the fifth dose (Week 4) 7 ± 2 days later, then
- 900 mg every 14 ± 2 days thereafter

The treatment schedule is dependent on the previous treatment date rather than the absolute (i.e., fixed) number of days from Day 1. In other words, the next 7 ± 2 days or 14 ± 2 days treatment schedule described above is re-scheduled every time based on the date when the previous treatment is given.

The subject receiving SB12 or Soliris® therapy may require dosing interval adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. If a 12 or 13 day dosing interval conflicts with administrative schedules (e.g., holidays or weekends) but a shortened dosing interval is considered necessary for safety of subject, consultation with medical monitor (or Sponsor) is recommended. For subjects whose dosing interval is adjusted to 12 days in Period 1, it is recommended that the dosing interval be switched back to 14 days after switching IP at Week 26. Once the above event has occurred, the Investigator should inform the

medical monitor and/or Sponsor immediately.

In special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner. Rules for allocation of remaining comparators during the comparator shortage situation will be prespecified prior to execution of the potential change of IP assignment from Soliris® to SB12 in a blinded manner. This is to avoid the risk of unblinding and potential bias.

5.1.2. Assignment of Subjects to Treatment Sequence

Subjects who meet all criteria for enrolment will be randomly assigned to treatment sequence I (SB12 to Soliris®) or II (Soliris® to SB12). The randomisation numbers will be generated by the interactive web response system (IWRS) to ensure that treatment sequence assignment is unbiased and concealed from subjects, Investigators, and other study personnel. These randomisation numbers are linked to the each treatment sequence, which in turn are linked to IP kit numbers.

Subjects will not be stratified and the assigned randomisation numbers will not be re-used.

5.1.3. Blinding

This study is double-blinded. Subjects, Investigators, and other study personnel will remain blinded to the treatment sequence assignment throughout the study period after randomisation.

To ensure the blinding for the treatment sequence assignment, one carton will contain only one IP vial (SB12 or Soliris®). The carton and IP vial will be packed and labelled in identical appearance.

Emergency unblinding is referred to Section 8.5.

5.2. Investigational Product

5.2.1. Identity of Investigational Product

The IPs will be supplied to investigational site in one carton containing a single vial. These IP vials will be packed and labelled in a double-blinded manner for clinical use.

The Investigator shall take responsibility for all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of IPs in accordance with the protocol and any applicable laws and regulations.

A detailed guidance for IP preparation, administration, storage, and destruction will be provided in the pharmacy manual.

Details of the IPs are provided in Table 3.

Table 3. Investigational Products Description

Active Pharmaceutical Ingredient: Eculizumab	
SB12	
Formulation	Solutions for IV infusion
Contents	One vial of 30 mL contains 300 mg of eculizumab (10 mg/mL)
Storage conditions	Stored in a refrigerator (2-8°C), do not freeze Stored in the original package in order to protect from light
Soliris®	

Formulation	Solutions for IV infusion
Contents	One vial of 30 mL contains 300 mg of eculizumab (10 mg/mL)
Storage conditions	Stored in a refrigerator (2-8°C), do not freeze Stored in the original package in order to protect from light

5.2.2. Formulation, Packaging, and Labelling

Eculizumab (SB12 or Soliris®) will be supplied for use as a concentrate for solution for infusion (300 mg per vial for SB12, Soliris®).

Packaging and labelling of SB12 or Soliris® will follow standard operating procedure (SOP) of the manufacturing site and regulatory requirements in each country, as well as will be in accordance with ICH-Good Clinical Practice (GCP). SB12 or Soliris® will be pre-packaged and labelled in a double-blinded form. The labels will contain the following information: The pharmaceutical dosage form, route of administration, identification number, the protocol number, use by date, storage details, and all other details required by local regulations and Good Manufacturing Practice (GMP).

5.2.3. Product Storage and Stability

SB12 and Soliris® should be stored at 2-8°C (36-46°F) in the original carton in order to protect from light. The temperature will be monitored properly during the study period. If continuous monitoring is not available then manual temperature logs should be generated and recorded to ensure proper storage conditions. If a temperature deviation occurred, responsible person should contact the Sponsor to determine if the drug is still appropriate for use. The IPs should be stored in a secure area, clearly labelled, and stored away from other IPs or medication to prevent confusion (for example, in a clearly marked box on a separate shelf of the refrigerator).

Do not freeze and do not shake SB12 or Soliris® vials. The IPs must not be used beyond the expiration date.

5.2.4. Preparation and Administration of Investigational Products

When IPs arrive at investigational sites, responsible site staff should check the IPs for damage, quantity, integrity, and temperature conditions during shipment, and report any deviations or product complaints (PC) to the Sponsor according to written procedure.

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis. Withdraw the total amount of SB12 or Soliris® from the vials using a sterile syringe. Transfer the recommended dose to an infusion bag. Dilute SB12 or Soliris® to a final concentration of 5 mg/mL by addition to the infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection, sodium chloride 4.5 mg/mL (0.45%) solution for injection, or 5% dextrose in water, as the diluent.

The final admixed SB12 or Soliris® 5 mg/mL infusion volume is 120 mL for 600 mg doses and 180 mL for 900 mg doses. The solution should be clear and colourless. Gently agitate the infusion bag containing the diluted solution to ensure thorough mixing of the product and diluent. Although the chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 2-8°C (36-46°F), the medicinal product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions. The diluted solution should be allowed to warm to room temperature (18-25°C, 64-77°F) prior to administration by exposure to ambient air and must not be heated in a microwave or with any

heat source.

The pharmacist and/or designee are responsible for preparing infusion setting for IP administration. Prior to administration, the IPs should be visually inspected for particulate matter and discolouration and checked to ensure match between subject number and assigned treatment.

IP injection will be performed by the Investigator and/or designee according to delegation of study personnel for this study. Do not administer IPs as an IV push or bolus injection. The diluted solution of IPs should be administered by IV infusion over 25-45 minutes via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of IPs from light during administration to the subject.

Subjects should be monitored and documented for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction. If an adverse reaction occurs during the administration of IPs, the infusion may be slowed or stopped at the discretion of the Investigator. If the infusion is slowed, the total infusion time may not exceed 2 hours.

5.2.5. Treatment Compliance and Investigational Product Accountability

Compliance will be assessed by the subject's source documents and electronic case report form (eCRF). All dosing information including exact date and time of IV infusion should be recorded in the subject's source documents and eCRF.

Also any reason for non-compliance should be documented. For example, insufficient compliance is defined when a subject missing more than one IP for reasons other than toxicity, missed scheduled study activities.

IP accountability and dispensing records must be kept current and contain the following information:

- The identification of the subjects to whom the drug was dispensed
- The dates and quantity of the drug dispensed to the subject
- The dispensing and inventory logs must be available for inspection by the study monitor

The Investigator and/or designee is responsible for accounting all unused IP and all used IP containers. The Investigator uses this information to maintain an accurate and complete dispensing and inventory record provided by the Sponsor.

IP supplies are shipped to the investigational site as needed. The monitor will review drug accounting during routine monitoring visits with the documents containing relevant information provided by the Sponsor. At the completion or termination of the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their resolution must be documented.

To avoid accidental unblinding, used drug kits (empty vials, vials with residual materials, and cartons) should be promptly discarded after the infusion bag is prepared and in accordance with the local destruction SOP/policies for clinical study drugs. All unused IPs should be returned to the Sponsor or designated vendor unless local destruction site is approved by the Sponsor. If destruction is authorised at the investigational site, the Investigator must ensure that the materials are destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IPs must be adequately documented.

5.3. Concomitant Medication or Treatment

All medication including both prescription and non-prescription drugs, and any procedures undertaken between 4 weeks prior to Screening (except for immunosuppressant) and EOS should be recorded in the subject's source documents and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for PNH. Details to be recorded include: Name (generic name preferred), dose number and unit, frequency of administration, route of administration, start and stop dates, reason for administration, and the AE it relates to (if applicable).

Medication ended prior to the first IP administration will be reported as a prior medication and medication ended on or after IP administration will be reported as a concomitant medication. It is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the subject's source documents and eCRF.

5.3.1. Permitted Concomitant Medications or Treatment

The following concomitant medications are allowed if given on a stable dose (only for chronic administration) during the study period. However, for the subject's welfare, medications can be adjusted under discussion between the Investigator and medical monitor and/or Sponsor.

- Erythropoietin, systemic corticosteroids, low-molecular-weight heparins, iron supplements, and androgen therapy with a stable dose from at least 4 weeks prior to initiation of study drug (Day 1).
- Warfarin with a stable INR from at least 4 weeks prior to initiation of study drug (Day 1).
- Cyclosporine with a stable dose from at least 8 weeks prior to initiation of study drug (Day 1).

5.3.2. Prohibited Concomitant Medications or Treatment

Immunosuppressant except for cyclosporine is prohibited during the study period from randomisation including but not limited to:

- Anti-thymocyte globulin (ATG), cyclophosphamide, etc.

Investigator should discuss with the medical monitor and/or Sponsor before using any other immunosuppressant.

6. Study Assessment

6.1. Efficacy Assessment

6.1.1. Disease-related Laboratory Parameters

Blood samples will be collected before IP administration at the visits specified in Table 1 and Table 2. Blood samples for the parameters will be analysed in central laboratory. Laboratory reports will be available to the Investigator in a timely manner. The parameters include PNH clone size of RBC and WBC evaluated by high-sensitivity flow cytometry, LDH, reticulocyte count, haptoglobin, and free haemoglobin.

If the LDH level is not changed after the initiation of study drug (lack of efficacy), the Investigator and medical monitor and/or Sponsor should discuss to determine how to manage this case including whether or not to perform pharmacogenetic analysis (C5 gene polymorphism).

Detail instructions of collection, processing, labelling, storage, and shipment for blood samples will be

provided in the laboratory manual.

6.1.2. Breakthrough Haemolysis

The Investigator and/or designee will record the breakthrough haemolysis in the source documents and eCRF during the study period.

The breakthrough haemolysis is defined as ≥ 1 new or worsening sign or symptom of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, chest pain, shortness of breath, dysphagia, erectile dysfunction, anaemia [haemoglobin < 10 g/dL], or major adverse vascular event [MAVE] including thrombosis) in the presence of elevated LDH ≥ 2 × ULN after prior LDH reduction to < 1.5 × ULN on treatment.

If a suspected sign or symptom of breakthrough haemolysis occurs, blood collection is required for evaluation of LDH, PK, and PD parameters by central laboratory. If necessary, an unscheduled visit should occur for evaluation of the subject and collection of the required LDH, PK, and PD parameters. For purposes of confirming breakthrough haemolysis, assessment of LDH must be based on a central laboratory value.

6.1.3. Transfusions

The subjects will receive pRBC transfusion in case the Investigator discovers a subject's haemoglobin warrants a transfusion;

- Haemoglobin value ≤ 9 g/dL with signs or symptoms, or
- Haemoglobin value ≤ 7 g/dL regardless of signs or symptoms

It is recommended that the transfusion would be performed within 48 hours of the haemoglobin assessment. The decision to give a transfusion may be based on either local or central laboratory haemoglobin values.

Transfusion record will be collected from the signing of the informed consent until EOS. Anaemia-related signs or symptoms, haemoglobin value, number of units of pRBCs will be documented on the source documents and eCRF.

6.1.4. Major Adverse Vascular Events

The description of MAVEs, anatomical site, method of diagnosis, date of diagnosis, and outcome will be recorded in the source documents and eCRF as AEs during the study period.

The MAVE is defined as following;

- Thrombophlebitis/deep vein thrombosis, pulmonary embolus, cerebral arterial/venous occlusion, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis (Budd-Chiari syndrome), acute mesenteric ischaemia, etc.

6.1.5. Paroxysmal Nocturnal Haemoglobinuria-related Symptoms

The PNH-related symptom questionnaire will be completed by subjects. The questionnaire should be completed by subjects before IP administration at the visits specified in Table 1 and Table 2; at Screening, Weeks 0 (Day 1), 4, 14, 26, 30, 40, and 52.

The symptoms in the past 7 days will be rated by severity. The questionnaire is provided in APPENDIX A. Investigator and/or designee will record the presence or absence of the following signs and symptoms

of PNH;

- Fatigue, haemoglobinuria (discolouration of urine), chest pain, abdominal pain, dyspnoea (shortness of breath), dysphagia, and erectile dysfunction

6.2. Safety Assessment

6.2.1. Adverse Events

All AEs will be recorded according to Section 8.

6.2.2. Clinical Laboratory Evaluations

Blood and urine sampling for clinical laboratory tests will be collected before IP administration at the visits specified in Table 1 and Table 2.

Blood and urine samples will be analysed in central laboratory except urine pregnancy test which will be performed at investigational site using centrally supplied pregnancy kit. A detailed process for clinical laboratory sampling, handling, storage, and shipping will be provided in the laboratory manual for safety lab testing. Laboratory reports will be available to the Investigator in a timely manner.

If laboratory tests are performed as per local practice and found to be abnormal, it is recommended that the Investigator uses their best clinical judgement to determine if the abnormal values would affect subjects' safety while participating in the study. It is highly recommended to test the abnormal parameter by central laboratory as well, if available.

During COVID-19 pandemic circumstances, it may be unable to get central laboratory values in time due to COVID-19 related restrictions. For those cases, local laboratory will be allowed in addition to central laboratory for scheduled visit after randomisation until COVID-19 restrictions are relieved under discussion with Sponsor.

The parameters for clinical laboratory tests are listed in the Table 4.

Table 4. Parameters for Clinical Laboratory Tests

Haematology	• WBC count • RBC count • Haemoglobin • Haematocrit • Platelet count • Differential WBC count • Nucleated RBC	• Mean corpuscular haemoglobin (MCH) • Mean corpuscular haemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Mean platelet volume (MPV) • Red cell distribution width (RDW)
Chemistry	• Sodium • Potassium • Creatinine • Blood urea nitrogen (BUN) • Glucose • Calcium • Phosphorus	• Total bilirubin • Direct/indirect bilirubin • Albumin • Total protein • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Alkaline phosphatase (ALP) • Gamma-glutamyl transpeptidase
Coagulation Profile	• Prothrombin time • Partial thromboplastin time • INR	
Urinalysis	• Protein • Blood • Leukocyte esterase • Nitrate • Ketone • Glucose	• pH • Specific gravity • Bilirubin • Urobilinogen • Appearance • Colour
Others	• Ferritin • Vitamin B_{12} • Folate	• Serology (HIV-1 and HIV-2) • Pregnancy test (serum or urine)[1] • Serum follicle stimulating hormone (FSH)[2]

[1] Pregnancy test will be performed for women of childbearing potential (serum or urine). Serum pregnancy test will be performed at Screening and 8 weeks after the last dose of study drug in case of ET and urine pregnancy test will be performed at other applicable visits before study drug administration.
[2] Serum FSH levels will be measured at Screening and Week 26 in order to confirm postmenopausal status only for women who present natural (spontaneous) amenorrhea for at least 12 months prior to Screening regardless of the subjects' age.

The Investigator will check any laboratory values which have potential significance in subject's safety during the study period. The Investigator will also evaluate any change in laboratory values. Each out

of range result should be assessed as not clinically significant or clinically significant by the Investigator. All laboratory abnormalities that require intervention (i.e., IP temporary discontinuation, IP discontinuation, concomitant medication, etc.) should be assessed as clinically significant and the clinically significant abnormalities should be recorded as AEs (see Section 8.1).

6.2.3. Physical Examinations

Physical examination including height and weight will be performed at Screening and physical examination including weight before IP administration at the visits specified in Table 1 and Table 2.

Abnormal findings will be documented on the source documents and eCRF, and any clinically significant abnormality or worsening of a previously noted abnormality should be recorded as an AE (see Section 8.1).

6.2.4. Twelve-lead Electrocardiograms

Twelve-lead ECG measurements will be performed before IP administration at the visits specified in Table 1 and Table 2.

6.2.5. Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed at the visits specified in Table 1 and Table 2. When vital signs are scheduled to be assessed at the same time point with blood sampling, it is recommended that the vital signs should be measured prior to the blood collection being performed.

The Investigator should assess all vital signs before IP administration on dosing days and any clinically significant abnormalities should be recorded as AEs (see Section 8.1).

6.3. Other Assessments

6.3.1. Pharmacokinetic Assessments

Blood sampling for PK analysis will be performed in all randomised subjects before IP administration at the visits specified in Table 1 and Table 2. Blood samples should be collected at the same day of study drug administration. Subjects' samples may be used for PK analysis method development and/or method validation.

If the IP administration is delayed for any reasons after blood sample for PK is collected, blood sample for PK analysis should be repeated on actual dosing day and be used for analysis.

In all cases, the exact date and time of the PK sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for PK samples are described in the laboratory manual.

The Sponsor or its designated representative will store PK samples after the end of the clinical study for maximum 15 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).

6.3.2. Immunogenicity Assessments

The purpose of immunogenicity assay is to determine whether ADAs and NAbs against SB12 or Soliris® occur in similar rate and influence the safety or efficacy. Blood sampling for immunogenicity assay will be done before IP administration at the visits specified in Table 1 and Table 2. Blood samples should be collected at the same day of study drug administration. Subjects' samples may be used for immunogenicity testing assay method development and/or method validation.

If the IP administration is delayed for any reasons after blood sample for immunogenicity is collected, blood sample for immunogenicity assay should be repeated on actual dosing day and be used for analysis.

In all cases, the exact date and time of the ADAs and NAbs sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for immunogenicity samples are described in the laboratory manual.

The Sponsor or its designated representative will store immunogenicity samples after the end of the clinical study for maximum 15 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).

6.3.3. Pharmacodynamic Assessments

Blood samples for PD analysis will be collected at prior to infusion before IP administration at the visits specified in Table 1 and Table 2. Blood samples should be collected at the same day of study drug administration. Subjects' samples may be used for PD analysis method development and/or method validation.

Complement activity will be measured within the secured sample stability period by the validated method by the Sponsor or its designated representative.

If the IP administration is delayed for any reasons after blood sample for PD is collected, blood sample for PD analysis should be repeated on actual dosing day and be used for analysis.

In all cases, the exact date and time of the PD sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for PD samples are described in the laboratory manual.

The Sponsor or its designated representative will store PD samples after the end of the clinical study for maximum 15 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).

6.3.4. Pharmacogenetic Assessments

Blood sample will be collected for pharmacogenetic analysis, ideally on Day 1 before initiation of study drug, or at the next scheduled blood sampling.

Genetic variants in C5 is associated with poor response to eculizumab since C5 mutation causes the structural change in binding site of eculizumab, resulting in less suppression of complement-mediated haemolysis. These blood samples can be used for extraction and analysis of DNA in order to investigate the mutational status of the subjects including, but not limited to C5. The analysis will be performed during or after the study for subjects who present poor response to study drug, or only if scientifically appropriate and data required.

The exact date and time of blood sampling for pharmacogenetic analysis must be recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for pharmacogenetic samples are described in the laboratory manual.

The Sponsor or its designated representative will store pharmacogenetic samples after the end of the clinical study for maximum 15 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).

7. Study Procedures

7.1. Study Flow and Visit Schedule

During this study, efficacy, safety, PK, immunogenicity, and PD assessments will be performed. The complete schedule of activities is outlined in Table 1 and Table 2.

7.1.1. Screening Period

7.1.1.1. Screening Visit (D−63 to D−22)

Screening should be performed within 42 days before randomisation. All subjects must provide written informed consent prior to any study related procedures being performed.

An eligibility screening form (ESF) documenting the subject's fulfilment of the entry criteria is to be completed by the Investigator or designee for all individuals considered for the study and subsequently included or excluded from the study. ESF should be reviewed by study monitor and submitted to medical monitor to determine the eligibility. Subjects who are confirmed to meet all criteria for enrolment will be randomly assigned in a 1:1 ratio to receive SB12 or Soliris®. Subjects who are considered for study entry but fail to meet the eligibility requirements should also have an ESF completed with the reason for lack of eligibility included, since this provides information on the selected study population. All ESFs should be kept in the study files at the investigational sites.

The following procedures and assessments should be performed within 42 days before randomisation. Retesting or re-evaluation is allowed within the screening period, but the latest result will be used to determine the eligibility.

- Written informed consent
- Demographic data
- Review of medical history including clinically significant diseases especially related to eligibility criteria (see Section 4.3), surgical procedures, and thrombosis history
- Review of transfusion history (anaemia-related signs or symptoms which precipitated transfusion, haemoglobin level before transfusion, number of units of pRBCs, date of transfusion, if available) within 12 months prior to Screening
- Physical examination (including height and body weight)
- Vital signs (blood pressure, heart rate, and body temperature)
- Twelve-lead ECG
- FSH test (serum) for women with at least 12 months natural (spontaneous) amenorrhea prior to Screening.
- Pregnancy test (serum) for women of childbearing potential. Female subjects of non-childbearing potential are defined as:

  a. At least 12 months natural amenorrhea and FSH > 40 U/L confirmed by serum blood test

     OR

  b. Those with history of hysterectomy, ligation of both fallopian tubes, surgical removal of both ovaries, or appropriate sterilisation operation. Documentation of surgical procedure

performed at least 90 days prior to Screening or appropriate medical documentation is required for confirmation of surgical sterilisation.

- Review of laboratory results
  - Disease-related laboratory parameters: PNH clone size of RBC and WBC evaluated by high-sensitivity flow cytometry, LDH, reticulocyte count, haptoglobin, and free haemoglobin
  - Haematology: Haemoglobin, haematocrit, RBC count, total WBC count including differential count, platelet count, nucleated RBC, MCH, MCHC, MCV, MPV and RDW
    - ✓ **Note**: If concurrent bone marrow failure is suspected, bone marrow examination is highly recommended to rule out the combined disease (e.g., myelodysplastic syndrome, severe aplastic anaemia, etc.).
  - Chemistry: Sodium, potassium, serum creatinine, BUN, glucose, calcium, phosphorus, total bilirubin, direct/indirect bilirubin, albumin, total protein, ALT, AST, ALP, and gamma-glutamyl transpeptidase
  - Coagulation profile: Prothrombin time, partial thromboplastin time, and INR
  - Urinalysis: Protein, blood, leukocyte esterase, nitrite, ketone, glucose, pH, specific gravity, bilirubin, urobilinogen, appearance, and colour (if urinalysis result is abnormal, urine microscopic examination will be performed)
  - Serology: HIV-1 and HIV-2
  - Others: Ferritin, vitamin B_{12}, and folate
- PNH symptomatology will be assessed.
- AEs assessment
- Review of previous medication (within 4 weeks prior to Screening except immunosuppressant, which will be assessed for 8 weeks prior to Screening)
- Review of MAVEs
- Evaluate subject compliance with all eligibility criteria

7.1.1.2. Vaccination for *Neisseria meningitidis*

Due to its mechanism of action, the use of SB12 or Soliris® increases the subject's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur.

To reduce the risk of meningococcal infection, all subjects must be vaccinated against *Neisseria meningitidis* prior to or on Day 1 in accordance with current local guidelines or Soliris® SmPC. Vaccines against serogroups A, C, Y, W135, and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. In case subjects were vaccinated against meningococcal infection within 3 years prior to Day 1, which is properly documented, vaccination for this study could be omitted. For the information including formulation, preparation, and storage of vaccine, refer to the prescribing information in SmPC of vaccine. Subjects must be revaccinated later during the study if local guidelines indicate to do so.

Subjects who initiate SB12 or Soliris® treatment less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 14 days after vaccination. Vaccination for *Neisseria meningitidis* and the prophylactic antibiotics should be recorded in the source documents and eCRF. As vaccination might not be sufficient to prevent meningococcal infection, appropriate use of antibiotics may be considered according to the current local guidelines and/or at the discretion of the Investigator.

As vaccination may further activate complement, subjects with PNH may experience increased signs and/or symptoms of their underlying disease, such as haemolysis. Therefore, subjects should be closely monitored for disease symptoms after vaccination.

To raise risk awareness of meningococcal infection and its signs and/or symptoms, subjects will be given the safety card to carry with them during the study period.

The safety card will contain following:

- Signs and symptoms of infection and sepsis
- Warning to seek immediate medical care if signs and/or symptoms of meningococcal infection are present
- Statement that the patient is receiving eculizumab
- Contact details where a health care practitioner can receive further information

7.1.2. Randomisation

Investigator should check the whole eligibility criteria of the subjects based on the laboratory report, medical history, and subjects' assessment. After a subject's eligibility is confirmed by the Investigator and medical monitor, subject should be randomised to either treatment sequence through an IWRS.

Once the subject is confirmed eligible for the study, the subject will be advised on study restrictions such as contraception, prohibited medications, and other study requirements if any.

During COVID-19 pandemic circumstances, Day 1 (1st dosing) may not be started within 21 days of randomisation due to unexpected COVID-19 related restrictions. In such cases, the subject will be monitored for safety per Investigator's discretion. Day 1 will be started after the COVID-19 related restrictions are relieved.

7.1.3. Treatment Period

The Investigator should check if the subject does not meet the discontinuation criteria before the initiation of study drug at Day 1.

All procedures and assessments will be performed at the visits specified in Table 1 and Table 2, and before IP administration on same day or up to 2 days prior, unless otherwise specified.

Laboratory assessments will be performed at central laboratory. Detail instructions of collecting, processing, storing, and shipping for blood samples are described in the laboratory manual. Laboratory reports will be available to the Investigator in a timely manner for clinical management of subjects during treatment period.

The Investigator will evaluate the assessment results and manage subjects based on the medicinal judgement and/or knowledge.

In special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner. Investigators and subjects will be informed prior to the execution of the potential change of IP assignment. Subjects willing to continue the study treatment after knowing that they may receive SB12 instead of Soliris® in a blinded manner during the study, should have their agreement both documented in the source document and an ICF. If the Investigators or subjects do not agree to the potential change of IP assignment, then subjects may withdraw from the study and be closely monitored for at least 8 weeks after last dose of study drug.

7.1.3.1. Treatment Period 1 (before Cross-over)

- Blood sampling for pharmacogenetic analysis (C5 gene polymorphism) will be performed at Week 0 (Day 1). If missing, it would be taken at the next scheduled blood sampling time.
- Physical examination (including body weight) will be performed at each scheduled visit.
- Vital signs (blood pressure, heart rate, and body temperature) will be checked at each scheduled visit.
- Twelve-lead ECG will be performed at Week 14.
- Pregnancy test (urine) will be performed at the visits specified in Table 1 for women of childbearing potential only.
- Clinical laboratory tests including haematology, chemistry (includes or does not include ferritin, vitamin B_{12}, and folate), coagulation profile, and urinalysis will be performed at the visits specified in Table 1.
- Blood sample collection for disease-related laboratory parameters will be performed at the visits specified in Table 1.
- Blood sample collection for PK analysis will be performed at pre-dose of Week 0 (Day 1), Week 2, Week 4, Week 6, Week 10, Week 14, Week 18, and Week 22.
- Blood sample collection for immunogenicity assay will be performed at pre-dose of Week 0 (Day 1), Week 2, Week 4, Week 6, Week 10, Week 14, Week 18, and Week 22.
- Blood sample collection for PD analysis will be performed at pre-dose of Week 0 (Day 1), Week 2, Week 4, Week 6, Week 10, and Week 14.
- PNH symptomatology will be assessed at the visits specified in Table 1.
- AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded.

IP administration

- IP administrations by IV infusion for 35 ± 10 minutes (600 mg every week for first 4 weeks and 900 mg for the fifth week, followed by 900 mg every 2 weeks, the visit window allowed for each visit is ± 2 days)

7.1.3.2. Visit 16 (Week 26/Day 183)

Each subject will cross-over from the treatment initially assigned to another treatment at Visit 16 (Week 26) and IPs will be given until Visit 28 (Week 50).

- Physical examination (including body weight)
- Vital signs (blood pressure, heart rate, and body temperature)

- Twelve-lead ECG
- FSH test (serum) for women with at least 12 months natural (spontaneous) amenorrhea prior to Screening.
- Pregnancy test (urine) for women of childbearing potential only.
- Clinical laboratory tests including haematology, chemistry (includes ferritin, vitamin B_{12}, and folate), coagulation profile, and urinalysis.
- Blood sample collection for disease-related laboratory parameters.
- Blood sample collection for PK analysis will be performed at pre-dose.
- Blood sample collection for immunogenicity assay will be performed at pre-dose.
- Blood sample collection for PD analysis will be performed at pre-dose.
- PNH symptomatology will be assessed.
- AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded.

IP administration

- IP administration by IV infusion for 35 ± 10 minutes (900 mg)

7.1.3.3. Treatment Period 2 (after Cross-over)

- Physical examination (including body weight) will be performed at each scheduled visit.
- Vital signs (blood pressure, heart rate, and body temperature) will be checked at each scheduled visit.
- Twelve-lead ECG will be performed at Week 40 and Week 52.
- Pregnancy test (urine) will be performed at the visits specified in Table 2 for women of childbearing potential only.
- Clinical laboratory tests including haematology, chemistry (includes or does not include ferritin, vitamin B_{12}, and folate), coagulation profile, and urinalysis will be performed at the visits specified in Table 2.
- Blood sample collection for disease-related laboratory parameters will be performed at the visits specified in Table 2.
- Blood sample collection for PK analysis will be performed at pre-dose of Week 28, Week 30, Week 32, Week 36, Week 40, Week 44, Week 48, and Week 52.
- Blood sample collection for immunogenicity assay will be performed at pre-dose of Week 28, Week 30, Week 32, Week 36, Week 40, Week 44, Week 48, and Week 52.
- Blood sample collection for PD analysis will be performed at pre-dose of Week 28, Week 30, Week 32, Week 36, Week 40, and Week 52.
- PNH symptomatology will be assessed at the visits specified in Table 2.
- AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded.

IP administration

- IP administrations by IV infusion for 35 ± 10 minutes (900 mg every 14 ± 2 days)

7.1.3.4. Safety Follow-up (Week 58/Day 407)

Safety follow-up will be done at Week 58 (± 7 days) which is 8 weeks after the last dose of SB12 or Soliris® for subjects who complete the study treatments until Week 50, regardless whether subject receives extended supply of SB12 or not to ensure subject's safety. These activities will be conducted either by visit or by phone call based on subjects' preference.

- AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded.

7.1.3.5. Early Termination Visit

ET visit is defined as 8 weeks (± 7 days) after the last dose of SB12 or Soliris® during the treatment period.

- Physical examination (including body weight)
- Vital signs (blood pressure, heart rate, and body temperature)
- Pregnancy test (serum) for women of childbearing potential only.
- Clinical laboratory tests including haematology, chemistry, and urinalysis
- Blood sample collection for disease-related laboratory parameters
- Blood sample collection for immunogenicity assay
- AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded.

7.1.4. Unscheduled Visits

If a sign or symptom of breakthrough haemolysis is suspected, an unscheduled visit should be occurred and samples should be collected for LDH, PK, and PD assessment for central laboratory at that time. Additionally, other unscheduled visits are permitted at the discretion of the Investigator. Any tests, procedures, or assessments performed at the unscheduled visits must be recorded in the source documents and eCRF.

7.2. Discontinuation

7.2.1. Subject Discontinuation from Study Treatment

The study treatment must be discontinued for a subject in the event of the following:

- Consent withdrawal by subject
  - Subjects may withdraw from the study or study specific procedures at any time for any reason during the entire duration of the study without prejudicing future treatment.
  - If subjects withdraw his/her consent, the Investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (e.g., documented lack of efficacy, AE, or pregnancy); however, the subject could refuse to provide such reason.
  - If the main reason for consent withdrawal is considered related to the study, the Investigator may select appropriate reason among the reasons listed below other than consent withdrawal.
- Pregnancy (study treatment should be immediately stopped when a pregnancy is made known

and the pregnant woman will be removed from the study)

- Unblinding the study treatment to the Investigator or subject (i.e., breaking the double-blind).
- Other complement inhibitor use

The Investigator should discuss with the medical monitor prior to discontinuing a subject's study treatment in case of the following criteria, but not limited to:

- Conditions or intercurrent illness that preclude compliance with the protocol in terms of their safety or well-being
- Lack of efficacy (e.g., C5 gene polymorphism)

  Note: If the LDH level is not changed after the initiation of study drug (lack of efficacy), the Investigator and medical monitor and/or Sponsor should discuss to determine how to manage this case including whether or not to perform pharmacogenetic analysis (C5 gene polymorphism).
- Unacceptable toxicity including meningococcal infection or anaphylaxis
- Serious protocol deviations (PDs) including lack of subject's compliance (e.g., repeated delay in study treatment and lost to follow-up) that preclude continuation of the study

  Note: Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject.
- Investigator discretion or other reasons

Discontinuation from study treatment does not mean immediate discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. Subjects who discontinue from the study at any time post-Day 1 (after the initiation of study drug) before completion of last study treatment at Week 50 will be required to have an ET visit. The data to be collected at the 8 weeks after the last dose of study drug are described in the Section 7.1.3.5. Every effort will be employed to keep subjects who discontinued from study treatment to undertake the scheduled ET visit procedures.

Subjects who discontinue study treatment after being exposed to study treatment will be monitored closely for signs of a potentially life-threatening haemolytic breakthrough event. Serious haemolysis is identified by serum LDH levels greater than the pre-treatment level, along with any of the following:

- Greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in 1 week or less
- A haemoglobin level of < 5 g/dL or a decrease of > 4 g/dL in 1 week or less
- Angina
- Change in mental status
- A 50% increase in serum creatinine level
- Thrombosis as defined by MAVEs

Any subject who discontinues SB12 or Soliris® should be monitored for at least 8 weeks after last dose of study drug to detect serious haemolysis and other reactions. If serious haemolysis occurs after SB12 or Soliris® discontinuation, consider the following procedures and/or treatments:

- Blood transfusion (pRBCs) or exchange transfusion if the PNH RBCs are > 50% of the total RBCs by flow cytometry
- Anticoagulation
- Corticosteroids
- Complement inhibitors

7.2.2. Investigational Site Discontinuation

Investigational site participation may be discontinued if the Sponsor, the Investigator, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the investigational site judge it necessary for any reason. Health authorities and IRB/IEC will be informed about the discontinuation of the study in accordance with applicable regulations.

7.3. Early Termination of the Study

The study can be terminated at any time for medical or ethical reasons by the Sponsor. If the study is terminated or discontinued prematurely, the Sponsor will promptly notify to the Investigator. Investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the subject's interests.

Health authorities and IRB/IEC will be informed about the discontinuation of the study in accordance with applicable regulations.

8. Safety Monitoring and Reporting

8.1. Adverse Events

8.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered the medicinal (investigational) product or other protocol-imposed intervention and which does not necessarily have to have a causal relationship with this treatment or intervention. An AE can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any dose of a medicinal (investigational) product or other protocol-imposed intervention regardless of attribution.

All AEs during the period of observation (as specified in Section 8.1.2) including the events that occurred prior to administration of an IP should be reported as an AE.

Pre-existing conditions and any abnormal findings from assessments during the screening period which are not related to protocol-imposed intervention should not be reported as AEs; however, pre-existing conditions which worsen (i.e., increase in severity) that meet the definition of an AE during the study are to be reported as AEs.

Diagnostic and therapeutic non-invasive 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 an AE and the resulting appendectomy should be recorded as treatment of the AE.

The AEs that emerge during treatment with an IP (i.e., treatment-emergent AE [TEAE]) will be analysed for the purposes of safety analyses.

8.1.1.1. Clinically Significant Abnormality

If there are any abnormalities discovered during the laboratory tests, physical examinations, vital signs, and/or other safety assessments and the abnormality is assessed clinically significant by the Investigator, it should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening or if the abnormality is consistent with a current diagnosis (underlying disease or other AEs). If it is not specified or defined elsewhere in the protocol, clinically significant abnormality may include the events that led to an intervention, including withdrawal of the IP treatment, significant additional concomitant medication, and others evaluated as clinically significant by the Investigator.

If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be reported as an AE. If the abnormality can be characterised by a precise clinical term, the clinical term should be reported as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be reported as 'hyperkalaemia'. Observations of the same clinically significant abnormality from visit to visit should not be repeatedly reported as AEs, unless their severity, seriousness, or aetiology changes.

8.1.2. Period of Observation for Adverse Events

AEs will be reported from the time of signing the ICF until EOS.

SAEs must be reported to the Sponsor or its designated representative according to Section 8.2.2.

Unresolved AEs during the study period should be followed up until EOS. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation.

If the subject has an ongoing SAE at EOS, these cases will be followed until event resolution or stabilisation (see Section 8.2.2).

8.1.3. Reporting Adverse Events

AEs are to be reported in the eCRF and reviewed by the Investigator. When reporting an AE, a diagnosis (when possible and appropriate) rather than each individual sign and symptom should be reported.

Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 8.2.1 for SAE definition). If an AE is classified as a SAE, it must be reported to the Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2. For an SAE, a diagnosis with a description of signs and symptoms as well as other supporting information that led to the diagnosis should be described in the SAE form provided by the Sponsor (see Section 8.2.2).

8.1.4. Severity Assessment

The Investigator is responsible for assessing and reporting the severity of AEs in accordance with National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

The following general guideline can be used to describe the severity of the AE. A grading (severity) scale for each specific AE is provided in NCI-CTCAE v5.0.

Table 5. Severity Grade of NCI-CTCAE v5.0

Grade	Clinical Description of Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade	Clinical Description of Severity
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

8.1.5. Causality Assessment

The Investigator is responsible for assigning a causal relationship to each AE. The causal relationship between the IP and the AE should be defined as not related (no) or related (yes).

Events should be classified as 'related' if there is a reasonable possibility that the IP caused the AE. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Events should be classified as 'not related' if there is no reasonable possibility that the IP caused the AE.

8.1.6. Expectedness Assessment

Expectedness of AEs will be assessed by reference safety information (RSI) in IB. More detailed information on expectedness assessment will be explained in IB. The latest Soliris® SmPC [10] will be used to assess the expectedness for the reference product after database lock or emergency unblinding.

8.1.7. Withdrawal due to Adverse Events

Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons and recorded in the source documents and appropriate eCRF section. Subjects withdrawn due to an AE should be followed up until the time point specified in Section 7.2.1. When a subject withdraws from the study due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.

Subjects who discontinue the administration of IPs because of serious or significant safety issues should be followed closely until the events are fully and permanently resolved or stabilised.

8.2. Serious Adverse Events

8.2.1. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence at any dose that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,

- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly/birth defects,
- Is medically important.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. 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 hospitalisation or development of drug dependency or drug abuse.

The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious,' which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

8.2.1.1. Life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2.1.2. Hospitalisation

AEs reported from clinical studies associated with inpatient hospitalisation or prolongations of hospitalisation are considered serious. Staying at an observation unit in the emergency room for more than 24 hours qualifies for hospitalisation. Any events leading to subsequent emergency room visit for less than 24 hours should be in the discretion of the Investigator to assess serious as medically important.

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality),
- Social admission for convenience (e.g., admission of a subject who does not have a carer),
- Administrative admission (e.g., for a yearly physical exam),
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol),
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery).

Pre-planned treatments or surgical procedures should be noted in the relevant source document for the individual subject.

8.2.2. Reporting Serious Adverse Events

SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug (five half-lives of the study drug).

SAEs that occurred at or before EOS must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event.

SAEs that occurred after EOS must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event.

Date and time (wherever possible) of the Investigator becoming aware of the SAE will be recorded in the SAE form and source document properly.

In particular, if the SAE is fatal or life-threatening, the Sponsor must be notified immediately, irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. Sponsor will then follow expedited reporting procedures according to local and international regulations as appropriate.

The Investigator is obligated to pursue and provide information to the Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

All SAEs will be followed until event resolution or stabilisation (for chronic events), if possible, even when a subject is withdrawn from treatment. For chronic events that do not fully resolve until years later, the outcome should be reported as ‘resolved with sequelae’ as soon as the event has stabilised or returned to baseline. Follow-up information for the SAE should be actively sought and submitted as the information becomes available.

8.3. Adverse Events of Special Interest

8.3.1. Meningococcal Infection

Due to its mechanism of action, the use of SB12 or Soliris® increases the subject’s susceptibility to meningococcal infection (*Neisseria meningitidis*). These subjects might be at risk of disease by serogroups (particularly Y, W135, and X), although meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all subjects will be vaccinated against *Neisseria meningitidis* prior to or on Day 1. Subjects must be revaccinated later during the study if local guidelines indicate to do so. However, vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to current local guidelines and/or the discretion of the Investigator on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections have been reported in Soliris®-treated patients. All subjects should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary.

Subjects should immediately call the Investigator or seek emergency medical care, if subjects experience any of the following symptoms:

- Headache with nausea or vomiting
- Headache and a fever
- Headache with a stiff neck or stiff back
- Fever
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

Subjects should be informed of these signs and symptoms and steps taken to seek medical care immediately. Subjects who are undergoing treatment for serious meningococcal infections should discontinue SB12 or Soliris® treatment, and the Investigator must discuss the benefits and risks of SB12 or Soliris® treatment with subjects and provide them with medical instructions.

8.3.2. Other Systemic Infections

SB12 or Soliris® blocks terminal complement activation; therefore subjects may have increased susceptibility to infections, especially with encapsulated bacteria. Serious infection with *Neisseria species* (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported after Soliris® treatment. Additionally, *Aspergillus* infections have occurred in immunocompromised and neutropenic patients. Subjects should immediately call the Investigator or seek emergency medical care, if subjects experience other systemic infections.

8.3.3. Infusion-related Reactions

Administration of SB12 or Soliris® may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials, 1 (0.9%) gMG patient experienced an infusion reaction which required discontinuation of Soliris®. No PNH, aHUS, or NMOSD patients experienced an infusion reaction which required discontinuation of Soliris® in clinical trials.

Administration of SB12 or Soliris® should be performed in a setting with emergency equipment and site staff who are trained to medical emergencies.

If an infusion reaction occurs during the administration of IPs, the infusion may be slowed or stopped at the discretion of the Investigator. If the infusion is slowed, the total infusion time may not exceed 2 hours. The subject will be monitored until resolution of any observed symptoms. The majority of subjects will be resolved for symptoms and subsequently will receive further infusions. Subjects should be warned of the possibility of late onset reactions and should be instructed to contact their Investigator if these reactions occur. Subjects who experience infusion-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent infusions.

When a severe hypersensitivity reaction such as anaphylaxis occurs, the infusion should be interrupted immediately and supportive care including oxygen, epinephrine, beta-agonists, and corticosteroids should be administered with continuous vital sign monitoring by trained site staff until the symptoms are resolved.

8.4. Pregnancy

Any pregnancy, including those of female partners of male subjects treated with the IP, should be reported to the Sponsor. If the female partner of a male subject becomes pregnant, a written consent must be obtained from the female partner before collecting any pregnancy-related information. All pregnancies associated with the subject, from the time the subject receives the first dose of study drug until 5 months after the last dose of study drug should be reported to the Sponsor. Pregnancy reports should be made within 24 hours of the Investigator becoming aware of the pregnancy using the "pregnancy notification and outcome report form".

Although pregnancy is not an AE, all pregnancies must be followed up until 6-8 weeks after the outcome of the pregnancy becomes available, unless the subject is lost to follow-up. The pregnancy outcome should be notified to the Sponsor by submitting a follow-up pregnancy notification and outcome report form. If the outcome of the pregnancy meets SAE criteria then the Investigator should report this case according to the SAE reporting process (Section 8.2.2).

8.4.1. Pregnancy Prevention

In order to minimise the risk to a foetus or embryo for including women of childbearing potential in this study, female subjects of childbearing potential and male subjects with female partner of childbearing potential must agree to use at least one highly effective birth control method. The Investigator and/or designee will discuss with the subject the need to use highly effective contraception consistently and correctly and document such conversation on the subject's source documents.

Highly effective birth control method includes the following:

- Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
  - Oral, intravaginal, transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
  - Oral, injectable, implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- True abstinence

  Note: True abstinence could be considered sufficient only for subjects who do not have a partner.

Followings are not highly effective birth control method and cannot be used for this study:

- Progesterone-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, cap/diaphragm/sponge with spermicide, periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational

amenorrhoea method

8.5. Emergency Unblinding of Assigned Treatment

Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's safety by their Investigator or a regulatory body. Emergency unblinding should be decided based on the medical decision by the Investigator considering subjects safety. In general, unblinding of subjects during the conduct of the clinical study should only be performed where there are compelling medical or safety reasons to do so. The responsibility to break the treatment code in emergency situations resides solely with the Investigator.

The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual. The Sponsor must be notified immediately after a subject and/or the Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented on the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding, and the relevant IP information.

8.6. Independent Data and Safety Monitoring Board

An independent DSMB will be assigned for this study. The DSMB will consist of external experts (e.g., haematologists, clinical pharmacologists, and biostatisticians) and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the DSMB charter and in the DSMB statistical analysis plan (SAP).

In addition, an ongoing blinded review of AEs, including clinical laboratory data will be regularly and continuously undertaken by the Sponsor medical monitor and pharmacovigilance team.

9. Statistical Methods and Data Analysis

Further information on the statistical methods for this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the clinical study report (CSR).

Statistical analysis and reporting will be performed as follows:

- **Interim safety analysis for independent DSMB meeting:**

  A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP.

  The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an independent unblind statistician.

- **CSR:**

  The analysis will take place after the last subject completes the procedures at Week 58 or the corresponding visit. All study data will be analysed and reported for CSR.

9.1. Statistical Hypotheses

This is a cross-over study to demonstrate equivalence in terms of LDH between SB12 and Soliris®. The null hypothesis tested for the primary efficacy analysis is that either (1) SB12 is inferior to Soliris® or (2) SB12 is superior to Soliris® based on a pre-specified equivalence margin.

[redacted] for those who are in favour of the time-adjusted AUEC of LDH, the treatment effect will be measured by time-adjusted AUEC of LDH between two different time points in each period, from Week 14 to Week 26 and from Week 40 to Week 52. The equivalence will be declared if the 90% confidence interval (CI) of the ratio between treatment effects is entirely contained within the pre-defined equivalence margin of [0.77, 1.29].

[redacted] for those who are in favour of the LDH level at a single time point, equivalence will be declared if the 95% CI of the difference between treatments in LDH level at Week 26 is entirely contained within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study.

If normal range of LDH is gender specific, the smaller/smallest ULN will be used for the equivalence margin; otherwise ULN is not gender specific, unified ULN will be used for the equivalence margin.

9.2. Analysis Sets

The following sets will be used for the analyses performed in the study:

- Randomised Set (RAN) consists of all subjects who have received a randomisation number.
- Modified Full Analysis Set (M-FAS) consists of all RAN subjects who do not have positive result of pharmacogenetic analysis (C5 gene polymorphism). However, subjects who do not have any efficacy assessment result after randomisation and do not receive IP during the study period will be excluded from this analysis set. Following the intent-to-treat principle, subjects will be analysed according to the treatment sequence they are assigned to at randomisation.
- Per-Protocol Set for AUEC of LDH (PPS-AUEC) consists of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. In addition, subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.
- Per-Protocol Set for LDH at a single time point (PPS-single) consists of all M-FAS subjects who have LDH assessment at Week 26 without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. In addition, subjects who received different treatment in Period 1 from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.
- Safety Set (SAF) consists of all subjects who receive at least one IP during the study period. Subjects will be analysed according to the treatment received.
- PK Analysis Set (PKS) consists of all subjects in the SAF who have at least one PK sample analysed.
- PD Analysis Set (PDS) consists of all subjects in the SAF who have at least one PD sample analysed.

9.3. Subject Demographic and Baseline Characteristics

The baseline value will be defined as the last available measurement value prior to or on the date of the

initiation of study drug.

Subject demographics and baseline disease characteristics will be summarised by treatment sequence for the RAN. Continuous variables (e.g., age, weight, height) will be summarised with descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum) and categorical variables (e.g., gender, race, ethnicity) will be summarised with count and percentage.

Comparison between treatment sequences in demographics and baseline disease characteristics will be performed using the chi-square test or *F*-test as appropriate. The results of these tests will be provided including the *p*-value only for descriptive purposes and will not be used as a formal basis to determine the factors to be included in primary or secondary efficacy analysis models. If baseline imbalances are detected for any of the factors, additional analyses may be performed to adjust for these baseline differences.

Relevant medical history, transfusion history, and continuing medical conditions will be summarised by treatment sequence for the RAN.

9.4. Analysis of the Primary Objectives

[redacted] for those who are in favour of the time-adjusted AUEC of LDH, the primary efficacy analysis will be performed for the PPS-AUEC using a linear mixed model with treatment, sequence, period, and gender as fixed effects, and subject nested within sequence as a random effect. The analysis will be performed with $\log_e$-transformed time-adjusted AUEC of LDH estimating the difference in least squares means and its 90% CI, and back transformation of those values will provide the ratio of geometric means and 90% CI. The equivalence will be declared if the two-sided 90% CI of the ratio of geometric means in time-adjusted AUEC of LDH between SB12 and Soliris® lies within the pre-defined equivalence margin of [0.77, 1.29].

[redacted] for those who are in favour of the LDH level at a single time point, the primary efficacy analysis will be performed for the PPS-single using a linear mixed model with treatment, and gender as a fixed effect. The analysis will be performed with $\log_e$-transformed LDH at Week 26 estimating the difference in least squares means and its 95% CI, and the delta method will be used to provide the mean difference and 95% CI in original scale. The equivalence will be declared if the two-sided 95% CI of the mean difference in LDH level at Week 26 between SB12 and Soliris® lies within the pre-defined equivalence margin of [$-1.2 \times$ ULN, $1.2 \times$ ULN] where ULN of LDH to be specified in the central laboratory specification for this study.

No formal adjustment of Type I error rates will be performed.

For the primary analysis with the M-FAS, missing data will be imputed for subjects who drop out for the study prior to the primary analysis time point. A missing-at-random approach will assume that subjects who withdraw from a study had similar missing values to peer subjects who completed the study in that treatment sequence. This approach ensures that evidence of lack of equivalence is not diluted when there are missing data. Multiple imputation method will be used with the assumption of monotone missing pattern and regression method. For the sensitivity analyses, complete case analysis will be performed.

9.5. Analysis of the Secondary Objectives

9.5.1. Efficacy Variable Analyses

As a secondary efficacy endpoint, number of units of pRBCs transfused will be summarised descriptively by treatment sequence and treatment sequence within period and will be analysed using

Wilcoxon rank-sum test. And mean LDH profile will be presented over time.

9.5.2. Safety Analyses

All reported terms for AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be collected and classified according to NCI-CTCAE v5.0. For all AE and SAE tables, subjects will be counted once for each preferred term and each system organ class.

A TEAE will be defined as any AE with an onset date on or after the date of the initiation of study drug. AEs which are already present before the initiation of study drug and increase in severity after the initiation of study drug will be considered as TEAEs. Pre-existing AEs before the initiation of study drug with no increase in severity after the initiation of study drug will not be considered as TEAEs.

All TEAEs and SAEs will be summarised respectively by count and percentage of subjects experiencing events by system organ class, preferred term. TEAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the initiation of study drug will be listed by subject.

In addition, infection-related AEs including meningococcal infection and other systemic infection, and IRRs will also be summarised.

Duration of exposure to IP and number of IV infusion will be summarised by treatment sequence within period with descriptive statistics for the SAF. Prior and concomitant medications, and significant non-drug therapies will be summarised with count and percentage.

Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence and visit. Other safety variables will be summarised unless otherwise specified, and all safety variables will be listed.

All safety analyses will be performed using the SAF. Additional analyses will be performed for the subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator if needed. For example, AEs and concomitant medications will be analysed based on the actual switched treatment.

9.5.3. Pharmacokinetic Analyses

PK analysis will be performed for the PKS. C_{trough} will be summarised with descriptive statistics by treatment sequence, period, and time point.

9.5.4. Immunogenicity Analyses

ADA and NAb results (e.g., ‘positive’ or ‘negative’) will be summarised with count and percentage by treatment sequence and visit. In addition, incidence of overall ADA will be summarised by treatment sequence and period.

Immunogenicity analyses will be performed using the SAF.

9.5.5. Pharmacodynamic Analyses

PD analysis will be performed for the PDS. The absolute values, and change from baseline in terminal complement activities will be summarised by treatment sequence and visit. PD data for each subject will also be listed.

9.6. Sample Size Calculations

The equivalence margin for the mean difference of LDH at Week 26 is derived from two historical

studies with Soliris®. In TRIUMPH study, the mean (SD) of LDH at Week 26 is 327.3 (432.9) U/L and 2,418.9 (930.6) U/L for eculizumab and non-eculizumab arms, respectively. PNH registry study reported the mean of LDH at 6 months is 352.1 (224.0) U/L and 1,201.0 (815.6) U/L for eculizumab and non-eculizumab arms, respectively.

Table 6. LDH Level from Reference Studies

	Eculizumab		Non-eculizumab		Note
	N	Mean (SD)	N	Mean (SD)	
TRIUMPH study (2006)[a]	41	327.3 (432.9)	44	2,418.9 (930.6)	Results at Week 26
International PNH registry (2016)	38	352.1 (224.0)	102	1,201.0 (815.6)	Results at 6 months
Meta-analysis for mean difference with 95% CIs	−1,152.5 [−1,303.4, −1,001.7]				

[a] SD for TRIUMPH study was derived from the standard error in the reference paper.

A meta-analysis with fixed-effect model estimates −1,152.5 U/L of LDH mean at Week 26 with a 95% CI [−1,303.4, −1,001.7]. The [redacted] of upper limit of 95% CI was approximately [redacted] U/L, which implies that at least [redacted] treatment effect is obtained to preserve the treatment effect over placebo if the [redacted] U/L was statistically chosen as the equivalence limit.

In the clinical study, LDH detection level or normal range of LDH would depend on the specification of laboratory parameters chosen for the study. Therefore, it is not likely to be clinically meaningful to propose any specific LDH level as the equivalence margin without the consideration of normal range of LDH level.

[redacted]

Therefore, the equivalence margin will be [−1.2 × ULN, 1.2 × ULN] for the comparison with the 95% CI of the mean difference in LDH at Week 26 where ULN of LDH to be specified in the central laboratory specification for this study. For sample size calculation, [−268 U/L, 268 U/L] is chosen to be 23 subjects per treatment sequence with the assumptions of no mean difference and common SD of 270 U/L at the overall 5% significance level. Assuming a 5% loss from randomised subjects after 26 weeks, a sample size of 25 subjects per treatment sequence (overall sample size of 50) will give 23 completers per treatment sequence after 26 weeks, which is estimated to give 80% power to detect the equivalence within the margin of 268 U/L.

The nQuery Advisor® option two-group *t*-tests (two one-sided test [TOST]) of equivalence in means (equal n's) gives the following statement to estimate the n per group to show the equivalence: "*When the sample size in each group is 23, a two group design will have 80% power to reject both the null hypothesis that the test mean minus the standard mean is below −268 and the null hypothesis that the test mean minus the standard mean is above 268 i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 270 and that each test is made at the 2.5% level.*"

For calculation of the equivalence margin for time-adjusted AUEC of LDH, mean and coefficient of

variation (%CV) were referred from TRIUMPH study. The mean (%CV) of AUEC of LDH at Week 26 is 81,140.0 U/L × day (142.45%) and 429,874.1 U/L × day (33.49%) for eculizumab and non-eculizumab arms, respectively.

From the results in the reference study, mean ratio of AUEC of LDH is estimated to be 0.19 with a 90% CI [0.1308, 0.2724]. The upper limit of the equivalence margin is calculated as [redacted] where it preserves at least [redacted] of eculizumab treatment effect over the placebo, but [redacted] the equivalence margin will be [0.77, 1.29] for the comparison with the 90% CI of mean ratio of time-adjusted AUEC of LDH.

With the given equivalence margin of [0.77, 1.29], 22 subjects per treatment sequence was calculated with the assumptions of the mean ratio of 1, common %CV of 42% at the overall 10% significance level. Assuming a 10% loss from randomised subjects after 52 weeks, a sample size of 25 subjects per treatment sequence (overall sample size of 50) will give 22 completers per treatment sequence after 52 weeks, which is estimated to give 80% power to detect the equivalence within the margin of [0.77, 1.29].

The nQuery Advisor® option two-group *t*-tests (TOST) of equivalence for ratio of means (log-scale) gives the following statement to estimate the n per group to show the equivalence: "*When the sample size in each sequence group is 22 (and the total sample size is 44), a crossover design will have 80% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 0.77 and the null hypothesis that the ratio of test mean to the standard mean is above 1.29; i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two treatments are equivalent, assuming that the expected ratio of means is 1, the Crossover ANOVA, √MSE (ln scale) is [redacted] (the SD differences, σ (ln scale) is [redacted]), that data will be analyzed in the natural log scale using t-tests for differences in means, and that each t-test is made at the 5% level.*"

Therefore, the sample size of 50 allows enough power to detect the equivalence in both situations.

10. Data Collection and Management

10.1. Data Confidentiality

Information about study subjects will be kept confidential. Study information will be labelled with a code number, and will not include the subject's name, hospital number or other information that could identify them. A list linking the code and the subject's name will be kept in the site files as required by ICH-GCP to protect the subject's confidentiality.

The coded information will be sent to the Sponsor (or designee) who will analyse it and report the study results both to regulatory and ethical authorities. The Sponsor may also place data on public websites or publish journal articles based upon these results. Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research into complement inhibitor. Such data sharing practices will be covered by confidentiality agreements. No-one outside the investigational site will have access to subject-identifiable information.

10.2. Monitoring

The Sponsor has engaged the services of a contract research organisation (CRO) to perform all monitoring functions within this clinical study. The monitors will work in accordance with the CRO SOPs and have the same rights and responsibilities as monitors from the Sponsor. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each investigational site and inform the Sponsor about any problems relating to facilities, technical equipment or investigational site staff. During the study,

monitors will check that written informed consent has been obtained correctly from all subjects and that data are recorded correctly and completely. Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions. Monitors will verify adherence to the protocol at the investigational site. All PDs will be reported to the Sponsor via the monitoring visit reports. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted at regular intervals according to ICH-GCP. The monitor will provide written reports to the Sponsor on each occasion they contact with the Investigator regardless of whether it is by phone or in person.

Further details on the monitoring processes and the level of source data verification to be performed will be outlined in the monitoring plan.

10.3. Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs and its revisions, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP or 15 years from completion of the study. These documents should be retained for a longer period if required by the applicable regulatory requirements or the investigational sites, institution or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for the same period of time. These documents may be transferred to another responsible party, deemed acceptable by the Sponsor, and who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records and obtain written permission to do so.

10.4. Future Use of Stored Specimens and Data

The Sponsor or designated representative can store PK, immunogenicity, PD, and/or pharmacogenetic samples for maximum 15 years after the end of the clinical study. The Sponsor or designated representative should operate under the same regulations related to and take the same responsibility to save personal data. The sample may be used for additional assay to be performed if considered scientific relevant or requested by regulatory authorities in order to have the possibility to perform the assay.

10.5. Database Management and Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy.

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the medical records.

Data must be entered into eCRFs in English by the designated investigational site staffs in a timely manner. Forms should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the eCRF must be carried out by the Investigator or a designated investigational site staffs. These changes may be made either on the initiative of the investigational site staffs or in response to monitoring or data queries. Any changes to

written data must be made using ICH-GCP corrections and any change to electronic data should be made in a system which can provide an audit trail. Monitors and clinical data managers will review the eCRF for accuracy and can generate queries to the investigational site staffs for resolution. Corrections will be recorded in an audit trail that records the original information, the corrected information, and identification of the person making the changes, date of correction made and reason for change. The Investigator must sign and date the eCRF pages as indicated.

Medical/surgical history and underlying diseases and AEs will be coded using the MedDRA®. Concomitant medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE). The versions of coding dictionaries used will be stated in the CSR.

10.6. Quality Control and Quality Assurance

During the conduct of the study, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH-GCP are being followed. The monitors may review source documents to confirm that the data recorded are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities, the Sponsor's monitors and auditors' direct access to source documents to perform this verification. The investigational site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that the Investigators and their relevant personnel are available during the monitoring visit, possible audits and/or regulatory inspection(s) and that sufficient time is devoted to the process.

10.7. Protocol Deviation

PDs will be pre-defined prior to subject enrolment and documented separately named as "protocol deviation definition list" which includes category (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, non-compliance with treatment), deviation description, severity (major or minor), time point for PDs. Major PDs are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

PDs will be reviewed and confirmed prior to database lock to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock .

11. Ethics Considerations and Administrative Procedures

11.1. Institutional Review Boards and Independent Ethics Committees

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the IRB/IEC.

The Investigator must provide the Sponsor with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the investigational site. The Investigator will supply documentation to the Sponsor relating to the annual renewal of the protocol from the IRB/IEC and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC on a regular basis and in accordance with the timelines required locally. Upon completion of the study, the Investigator will provide the ethics committee with a report on the outcome of the study if required by local regulations.

11.2. Ethical Conduct of the Study

This study will be conducted and informed consent will be obtained from each subject according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for ICH-GCP and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

11.3. Written Informed Consent

The written informed consent will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject enters into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP. The Investigator will provide each subject with a copy of the signed and dated ICF and this will be documented on the subject's source document.

11.4. Investigator Information

11.4.1. Investigator Obligations

This study will be conducted in accordance with the ICH-GCP, the ethical principles that have their origin in the Declaration of Helsinki (2013) and local laws and regulations.

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. The Investigator must obtain the informed consent of each subject to whom IP is administered.

11.4.2. Training of Investigational Site Personnel

Before the first subject is enrolled into the study, the Sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational site staff and will also train them in any study-specific procedures.

The Investigator will ensure that appropriate training relevant to the study is given to all investigational site staff and that any new information relevant to the performance of this study is forwarded to the investigational site staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other investigational site staff).

11.4.3. Protocol Signatures

The Investigator must sign the Investigator signature page of this protocol prior to starting recruitment for the study. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH-GCP and applicable regulatory requirements. The study will not be able to start at any investigational site where the Investigator has not signed the protocol.

11.4.4. Financing and Insurance

Samsung Bioepis is the Sponsor of this study and will be providing the finances to cover the operation of the study. Details of financial agreements are provided in the clinical trial agreement with the investigational sites and in contracts with other companies involved in the running of the study.

The Sponsor has obtained suitable insurance for this study. A copy of the insurance details will be provided to each Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.

12. Publication Policy

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human subjects. The Sponsor will register and maintain the information of clinical studies on a public registry program. The Sponsor is committed to the public disclosure of the results from clinical studies through posting on public clinical study data banks. The Sponsor will comply with the guidelines of regulatory authorities with regards to public registration and disclosure of clinical study data.

13. Extended Supply

After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years starting from Week 52 to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.

Before entering an extended supply, the Investigator will review the subject status including reduction of PNH disease activity, such as improvement of symptoms or laboratory parameters, during eculizumab treatment to decide if the subject will benefit from participation in extended supply. Once subjects are considered to benefit from extended supply, subjects will be asked if he/she would like to receive an extended supply. For receiving an extended supply, subjects should agree with signing ICF for extended supply and with required activities including refraining from pregnancy, maintaining a highly effective contraceptive method, and receiving meningococcal vaccination (if required by local regulations) to ensure subject's safety during extended supply.

During extended supply, Investigators will treat subjects with 900 mg of SB12 every 14 ± 2 days for up to 2 years (104 weeks). SB12 will be packaged and labelled using open label and dispensed through the IWRS. Investigators should ensure the compliance and accountability of SB12 during the course of extended supply. Any PC must be reported to Sponsor.

SAEs that occur during this phase must be reported to the Sponsor, which will be reported to regulatory authorities by the Sponsor according to local/national requirements via expedited reporting and periodic reporting such as Development Safety Update Report (DSUR) or Periodic Safety Update Report (PSUR). Pregnancy should also be reported until 5 months after the last SB12 treatment. Other particular activities will not be imposed and no data collection or reporting will occur for extended supply.

Discontinuation of study treatment can be decided if unacceptable toxicity, pregnancy, other complement inhibitor use or lack of efficacy occurs, or at the discretion of the Investigator or by subject’s consent withdrawal. Specific study procedures are not required for subjects who have discontinued prematurely except for SAEs reporting and pregnancy reporting.

During the period of extended supply, the Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the IRB/IEC. The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator’s care; and for the control of drugs under investigation.

The Investigators must maintain essential study documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP or 15 years from completion of the extended supply, if applicable.

Investigational sites participation may be discontinued if the Sponsor, Investigator or IRB/IEC consider necessary. Extended supply may be terminated by the Sponsor if medically or ethically indicated, and in such cases will be promptly notified to the Investigator. In any case, health authorities and IRB/IEC will be informed for the action in accordance with applicable regulations.

14. References

[1] Hillmen P, Lewis S, Bessler M, et al. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995; 333 (19): 1253-8.

[2] Moyo V, Mukhina G, Garrett E, et al. Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. *Br J Haematol.* 2004; 126 (1): 133-8.

[3] Nishimura J, Kanakura Y, Ware R, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine (Baltimore).* 2004; 83 (3): 193-207.

[4] Sharma V. Paroxysmal nocturnal hemoglobinuria: pathogenesis, testing, and diagnosis. *Clin Adv Hematol Oncol*. 2013; 11 Suppl 13 (9): 2-8.

[5] Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005; 106 (12): 3699-709.

[6] Hartmann R, Jenkins D, Mckee L, et al. Paroxysmal nocturnal hemoglobinuria: clinical and laboratory studies relating to iron metabolism and therapy with androgen and iron. *Medicine (Baltimore)*. 1966; 45 (5): 331-63.

[7] Hill A, Hillmen P, Richards S, et al. Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria. *Blood*. 2005; 106 (7): 2559-65.

[8] Hillmen P, Young N, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006; 355 (12): 1233-43.

[9] Brodsky R, Young N, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2008; 111 (4): 1840-7.

[10] Soliris® EPAR – Product Information. EMA (Jul 01, 2020). Retrieved Jul 13, 2020 from https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf

[11] Guideline on similar biological medicinal products monoclonal antibodies. EMA. (May 2012). EMA/CHMP/BMWP/403543/2010. Retrieved Jun 04, 2018 from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

[12] Rother RP, Bell L, Hillmen P, et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005; 293 (13): 1653-62.

[13] Hill A, Rother R, Wang X, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2010; 149 (3): 414-25.

[14] Weitz I. Thrombosis in Paroxysmal Nocturnal Hemoglobinuria – insights into the role of complement in thrombosis. *Thromb Res.* 2010; 125 Suppl 2: S106-7.

[15] Helley D, de Latour R, Porcher R, et al. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Haematologica*. 2010; 95 (4): 574-81.

[16] Hillmen P, Muus P, Dührsen U, et al. Effect of the complement inhibitor eculizumab on

thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007; 110 (12): 4123-8.

[17] The Most Expensive Prescription Drugs in the World. Kathlyn Stone. (Updated Aug 26, 2018/Dec 11, 2017/Apr 24, 2017). Retrieved Oct 04, 2018 from https://www.thebalance.com/the-8-most-expensive-prescription-drugs-in-the-world-2663232

[18] Devalet B, Mullier F, Chatelain B, et al. Pathophysiology, diagnosis, and treatment of paroxysmal nocturnal hemoglobinuria: a review. *Eur J Haematol*. 2015; 95 (3): 190-8.

[19] de Latour R, Mary J, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood*. 2008; 112 (8): 3099-106.

[20] Kato G, McGowan V, Machado R, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood*. 2006; 107 (6): 2279-85.

[21] Soliris® Prescribing Information. FDA (Nov 20, 2020). Retrieved Nov 26, 2020 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125166s434lbl.pdf

APPENDIX A. Paroxysmal Nocturnal Haemoglobinuria Symptoms Subject Questionnaire

Following signs and symptoms are associated with PNH.

If you have had the symptom in the past 7 days, please circle the number below that describe your severity for each sign or symptom.

1) Fatigue

0	1	2	3	4	5	6	7	8	9	10
None										Severe

2) Haemoglobinuria (discolouration of urine)

0	1	2	3	4	5	6	7	8	9	10
None										Severe

3) Chest pain

0	1	2	3	4	5	6	7	8	9	10
None										Severe

4) Abdominal pain

0	1	2	3	4	5	6	7	8	9	10
None										Severe

5) Dyspnoea (shortness of breath)

0	1	2	3	4	5	6	7	8	9	10
None										Severe

6) Dysphagia

0	1	2	3	4	5	6	7	8	9	10
None										Severe

7) Erectile dysfunction (if applicable)

0	1	2	3	4	5	6	7	8	9	10
None										Severe

Protocol Signature Pages

SIGNATURE PAGE

Declaration of Sponsor Representative

Protocol Title: A Phase III Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in Subjects with Paroxysmal Nocturnal Haemoglobinuria

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Representative

Name: [redacted]

Institution: Samsung Bioepis Co., Ltd.

Signature: [redacted] Date: Nov 27, 2020
(MMM DD, YYYY)

SIGNATURE PAGE

Declaration of the Coordinating Investigator

Protocol Title: A Phase III Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in Subjects with Paroxysmal Nocturnal Haemoglobinuria

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Coordinating Investigator

Name: [redacted]

Institution: [redacted]

Signature: [redacted] Date: 27 Nov 2020
(MMM DD, YYYY)

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: A Phase III Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in Subjects with Paroxysmal Nocturnal Haemoglobinuria

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Principal Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____
(MMM DD, YYYY)

CHANGE HISTORY OF PROTOCOL AMENDMENT

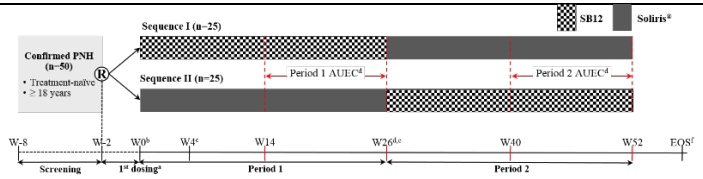
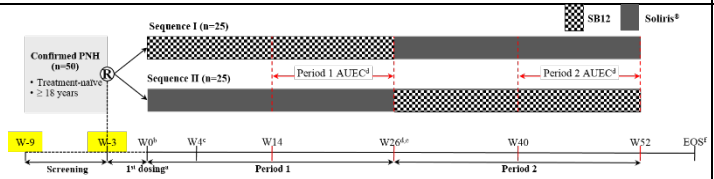
Amendment 1: Version 2.0, Oct 08, 2018

<table>
<tr><th>Section Affected</th><th>Original Content</th><th>Amended/New Content</th><th>Rationale</th></tr>
<tr><td>SYNOPSIS
Exclusion Criteria</td><td>4. Abnormal haematological parameters at Screening defined as the following:

a. Absolute neutrophil count (ANC) ≤ 500/mm^3

b. Platelet count < 80,000/mm^3</td><td>4. Abnormal haematological parameters at Screening defined as the following:

a. Absolute neutrophil count (ANC) ≤ 500/mm^3

b. Platelet count < <s>80,000</s> 70,000/mm^3</td><td>To change platelet count criteria</td></tr>
<tr><td>Figure 1</td><td> 
</td><td> 
</td><td>To extend the period from randomisation to initiation of study drug taking account of IP shipment</td></tr>
<tr><td>Figure 1 Footnote</td><td>a. Randomisation will trigger the shipping of study drugs to investigational site. The initiation of study drug should be done within 14 days of randomisation.</td><td>a. Randomisation will trigger the shipping of study drugs to investigational site. The initiation of study drug should be done within <s>14</s> 21 days of randomisation.</td><td>To extend the period from randomisation to initiation of study drug taking account of IP shipment</td></tr>
<tr><td>Table 1</td><td>
<table>
<tr><th>Assessments</th><th colspan="3">Study Period</th></tr>
<tr><td>Study Visit</td><td rowspan="2">Scree -ning</td><td rowspan="2">Randomi -sation</td><td rowspan="2">…</td></tr>
<tr><td>Week</td></tr>
<tr><td>Day (± Visit Window)</td><td>−56 to −15</td><td>−14 to −1</td><td>…</td></tr>
</table>
</td><td>
<table>
<tr><th>Assessments</th><th colspan="3">Study Period</th></tr>
<tr><td>Study Visit</td><td rowspan="2">Scree -ning</td><td rowspan="2">Randomi -sation</td><td rowspan="2">…</td></tr>
<tr><td>Week</td></tr>
<tr><td>Day (± Visit Window)</td><td><s>−56 to −15</s>
−63 to −22</td><td><s>−14 to −1</s>
−21 to −1</td><td>…</td></tr>
</table>
</td><td>To extend the period from randomisation to initiation of study drug taking account of IP</td></tr>
</table>

Section Affected	Original Content	Amended/New Content	Rationale
			shipment
Table 1 Footnote	4. All screening procedures must be completed and reviewed within 42 days prior to randomisation. All eligibility criteria must be reviewed and confirmed prior to randomisation. The initiation of study drug (Day 1) should be done within 14 days of randomisation.	4. All screening procedures must be completed and reviewed within 42 days prior to randomisation. All eligibility criteria must be reviewed and confirmed prior to randomisation. The initiation of study drug (Day 1) should be done within **~~14~~ 21 days** of randomisation.	To extend the period from randomisation to initiation of study drug taking account of IP shipment
Table 1 Footnote	8. Both white blood cell (WBC) and red blood cell (RBC) clone size will be measured by flow cytometry prior to dosing at Screening, Day 1, and Week 52. (…)	8. Both white blood cell (WBC) and red blood cell (RBC) clone size will be measured by flow **cytometry ~~prior to dosing~~ at Screening~~,~~ and prior to dosing at Day 1~~,~~ and Week 52.** (…)	To clarify the meaning because no dosing will be done at Screening
Table 1 Footnote	11. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, nucleated RBC, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean platelet volume (MPV), and red cell distribution width (RDW). (…)	11. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, and nucleated RBC**~~, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean platelet volume (MPV), and red cell distribution width (RDW)~~.** (…)	To remove several haematology test parameters
Table 2 Footnote	5. Both WBC and RBC clone size will be measured by flow cytometry prior to dosing at Screening, Day 1, and Week 52. (…)	5. Both WBC and RBC clone size will be measured by flow cytometry **~~prior to dosing~~ at Screening~~,~~ and prior to dosing at Day 1~~,~~ and Week 52**. (…)	To clarify the meaning because no dosing will be done at Screening
Table 2 Footnote	8. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC	8. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC	To remove several haematology test parameters

Section Affected	Original Content	Amended/New Content	Rationale
	count, nucleated RBC, MCH, MCHC, MCV, MPV, and RDW. (…)	count, and nucleated RBC~~, MCH, MCHC, MCV, MPV, and RDW~~. (…)	
LIST OF ABBREVIA-TIONS	MCH Mean corpuscular haemoglobin MCHC Mean corpuscular haemoglobin concentration MCV Mean corpuscular volume MPV Mean platelet volume RDW Red cell distribution width	~~MCH~~ ~~Mean corpuscular haemoglobin~~ ~~MCHC~~ ~~Mean corpuscular haemoglobin concentration~~ ~~MCV~~ ~~Mean corpuscular volume~~ ~~MPV~~ ~~Mean platelet volume~~ ~~RDW~~ ~~Red cell distribution width~~	To remove several haematology test parameters
LIST OF STUDY STAFF	Clinical Research Scientist [redacted] Safety Physician [redacted]	Clinical Research Scientist [redacted] Safety Physician [redacted]	Administrative change due to study staff change
4.3. Exclusion Criteria	4. Abnormal haematological parameters at Screening defined as the following: a. Absolute neutrophil count (ANC) ≤ 500/mm^3 b. Platelet count < 80,000/mm^3	4. Abnormal haematological parameters at Screening defined as the following: a. Absolute neutrophil count (ANC) ≤ 500/mm^3 b. Platelet count < ~~**80,000**~~ **70,000**/mm^3	To change platelet count criteria
Table 4. Parameters for Clinical Laboratory	**Haematology**: WBC count; RBC count; Mean corpuscular haemoglobin (MCH)	**Haematology**: • WBC count; • RBC count; ~~• Mean corpuscular haemoglobin~~	To remove several haematology test parameters

Section Affected	Original Content	Amended/New Content	Rationale
Tests	Haemoglobin Haematocrit Platelet count Differential WBC count Nucleated RBC Mean corpuscular haemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Mean platelet volume (MPV) Red cell distribution width (RDW)	• Haemoglobin • Haematocrit • Platelet count • Differential WBC count • Nucleated RBC ~~• Mean corpuscular haemoglobin concentration (MCHC)~~ ~~• Mean corpuscular volume (MCV)~~ ~~• Mean platelet volume (MPV)~~ ~~• Red cell distribution width (RDW)~~	
6.2.3. Physical Examinations	Physical examination including height and weight will be performed before IP administration at Screening and physical examination including weight at the visits specified in Table 1 and Table 2. (…)	Physical examination including height and weight will be performed ~~before IP administration~~ at Screening and physical examination including weight **before IP administration** at the visits specified in Table 1 and Table 2. (…)	To clarify the meaning because no dosing will be done at Screening
7.1.1.1. Screening Visit (D−63 to D−22)	**7.1.1.1. Screening Visit (D−56 to D−15)**	**7.1.1.1. Screening Visit (~~D−56~~ D−63 to ~~D−15~~ D−22)**	To extend the period from randomisation to initiation of study drug taking account of IP shipment

Section Affected	Original Content	Amended/New Content	Rationale
7.1.1.1. Screening Visit (D−63 to D−22)	• Review of laboratory results - Haematology: Haemoglobin, haematocrit, RBC count, total WBC count including differential count, platelet count, nucleated RBC, MCH, MCHC, MCV, MPV, and RDW	• Review of laboratory results - Haematology: Haemoglobin, haematocrit, RBC count, total WBC count including differential count, platelet count, **and** nucleated RBC~~, MCH, MCHC, MCV, MPV, and RDW~~	To remove several haematology test parameters
7.1.1.1. Screening Visit (D−63 to D−22)	• Review of laboratory results - Urinalysis: Protein, blood, leukocytes, nitrite, ketone, glucose, pH, specific gravity, bilirubin, urobilinogen, appearance, and colour (if urinalysis result is abnormal, urine microscopic examination will be performed)	• Review of laboratory results - Urinalysis: Protein, blood, **leukocytes esterase**, nitrite, ketone, glucose, pH, specific gravity, bilirubin, urobilinogen, appearance, and colour (if urinalysis result is abnormal, urine microscopic examination will be performed)	To change urinalysis parameter to be consistent with Table 4
7.1.1.1. Screening Visit (D−63 to D−22)	• Review of laboratory results	• Review of laboratory results - **Others: Ferritin, vitamin B_{12}, and folate**	To add laboratory tests to be consistent with Table 1
8.3.2. Other Systemic Infections	SB12 or Soliris® blocks terminal complement activation; therefore subjects may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, aspergillus infections have occurred in immunocompromised and neutropenic patients. Subjects should immediately call the Investigator or seek emergency medical care, if subjects experience other systemic infections.	SB12 or Soliris® blocks terminal complement activation; therefore subjects may have increased susceptibility to infections, especially with encapsulated bacteria. **Serious infection with *Neisseria species* (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported after Soliris® treatment.** Additionally, aspergillus infections have occurred in immunocompromised and neutropenic patients. Subjects should immediately call the Investigator or seek emergency medical care, if subjects experience other systemic infections.	To add the updated safety information according to the latest version of regulatory document
13.	[17] The Most Expensive Prescription Drugs in the World. Kathlyn Stone. (Updated Dec 11, 2017/Apr 24, 2017). Retrieved	[17] The Most Expensive Prescription Drugs in the World. Kathlyn Stone. (Updated **Aug 26, 2018/~~Dec 11, 2017~~**/Apr 24,	To refer the latest

Section Affected	Original Content	Amended/New Content	Rationale
References	Mar 09, 2018 from https://www.thebalance.com/the-8-most-expensive-prescription-drugs-in-the-world-2663232	2017). Retrieved ~~**Mar 09, 2018**~~ **Oct 04, 2018** from https://www.thebalance.com/the-8-most-expensive-prescription-drugs-in-the-world-2663232	information
13. References	[21] Soliris® Prescribing Information. FDA (Feb 28, 2018). Retrieved Apr 25, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s426lbl.pdf	[21] Soliris® Prescribing Information. FDA (~~**Feb 28**~~ **Jul 25**, 2018). Retrieved ~~**Apr 25**~~ **Oct 04**, 2018 from ~~**https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s426lbl.pdf**~~ **https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s047s048lbl.pdf**	To refer the latest version of regulatory document

Amendment 2: Version 3.0, Dec 12, 2018

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Exclusion Criteria	N/A	**7. History of serious thrombotic event (e.g., stroke, myocardial infarction, pulmonary embolism, etc.)**	To add exclusion criteria
SYNOPSIS Secondary Endpoints	Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and end of study (EOS) • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS	Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and end of study (EOS)**/early termination (ET)** • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS**/ET**	To add time point to be consistent with Table 2
SYNOPSIS Statistical Methods	PK analyses PK analysis will be performed for the PK Analysis Set (PKS). Serum trough concentration will be summarised descriptively by treatment sequence, period, and time point.	PK analyses PK analysis will be performed for the PK Analysis Set (PKS). ~~**Serum trough concentration**~~ **C_{trough}** will be summarised descriptively by treatment sequence, period, and time point.	To apply abbreviation
Figure 1 Footnote	® = Randomisation; AUEC = Area under the Effect Curve; EOS = End of Study	® = Randomisation; AUEC = Area under the Effect Curve; EOS = End of Study; **PNH = Paroxysmal Nocturnal Haemoglobinuria; W = Week**	To add abbreviations
2.2.2. Secondary Endpoints	Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and end of study (EOS)	Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and end of study (EOS)**/early termination (ET)**	To add time point to be consistent with Table 2

Section Affected	Original Content	Amended/New Content	Rationale
	• Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS	• Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS/**ET**	
3.2.1. Scientific Rationale for Study Design	(…) [redacted] for analysis of haemolysis reduction as measured by AUEC of LDH between two different time points in each period, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52. [redacted], for analysis of haemolysis reduction as measured by the LDH level at single time point, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of the LDH level (U/L) at Week 26.	(…) [redacted], for analysis of haemolysis reduction as measured by AUEC of LDH between two different time points in each period, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52. [redacted], for analysis of haemolysis reduction as measured by the LDH level at single time point, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of the LDH level (U/L) at Week 26	To add phrase to be consistent within the document
4.3. Exclusion Criteria	N/A	**7. History of serious thrombotic event (e.g., stroke, myocardial infarction, pulmonary embolism, etc.)**	To add exclusion criteria
5.1.1. Dosing and Treatment Schedule	SB12 or Soliris® will be administered up to Week 52 (a total of 29 administrations of IP) unless they are early discontinued from study treatment. • 600 mg every 7 ± 2 days for the first 4 weeks, followed by • 900 mg for the fifth dose 7 ± 2 days later, then • 900 mg every 14 ± 2 days thereafter	SB12 or Soliris® will be administered up to Week 52 (a total of 29 administrations of IP) unless they are early discontinued from study treatment. • 600 mg every 7 ± 2 days for the first 4 weeks, followed by • 900 mg for the fifth dose 7 ± 2 days later, then • 900 mg every 14 ± 2 days thereafter	To clarify dosing and treatment schedule

Section Affected	Original Content	Amended/New Content	Rationale
	In case a dosing is delayed, next dosing visit date should not be altered. The subject receiving SB12 or Soliris® therapy may require dose adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN after prior LDH reduction to < 1.5 × ULN on treatment. (…)	~~**In case a dosing is delayed, next dosing visit date should not be altered.**~~ **In case previous IP administration was out of window, next visit schedule should be adjusted to keep intervals of IP administration as indicated above.** The subject receiving SB12 or Soliris® therapy may require dose adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN **combined with sign or symptom of intravascular haemolysis** after prior LDH reduction to < 1.5 × ULN on treatment. (…)	
5.2.5. Treatment Compliance and Investigation-al Product Accountabili-ty	(…) Unless otherwise notified, empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy SOP for clinical study drugs. All unused IPs should be returned to the Sponsor or designated vendor unless local destruction site is approved by the Sponsor. If destruction is authorised at the investigational site, the Investigator must ensure that the materials are destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IPs must be adequately documented.	(…) Unless otherwise notified, empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy SOP for clinical study drugs. All unused IPs should be returned to the Sponsor or designated vendor unless local destruction site is approved by the Sponsor. If destruction is authorised at the investigational site, the Investigator must ensure that the materials are destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IPs must be adequately documented. **In case of expanded access of SB12 to subjects, the**	To add IP accountability during additional SB12 provision

Section Affected	Original Content	Amended/New Content	Rationale
		Investigator is responsible for maintaining the SB12 records which include information on amounts delivered, dispensed, and returned/destroyed; for ensuring proper storage conditions are maintained and documented including details of dates, quantities, batch numbers, expiry dates; ensuring the SB12 is only used as specified by the expanded access; for reconciling all SB12 received from the Sponsor. Further details will be provided in a guideline for expanded access.	
5.3. Concomitant Medication or Treatment	All medication including both prescription and non-prescription drugs, and any procedures undertaken during the study period (from the study informed consent has been signed to EOS/early termination [ET] visit) should be recorded in the subject's source documents and eCRF. (…)	All medication including both prescription and non-prescription drugs, and any procedures undertaken during the study period (from the study informed consent has been signed to EOS/ ~~**early termination [ET]**~~ visit) should be recorded in the subject's source documents and eCRF. (…)	To apply abbreviation
7.1.3. Treatment Period	All procedures and assessments will be performed at the visits specified in Table 1 and Table 2. Samples for laboratory assessments will be collected before IP administration. (…)	All procedures and assessments will be performed at the visits specified in Table 1 and Table 2. Samples for laboratory assessments will be collected before IP administration **on same day or up to 2 days prior, unless otherwise specified**. (…)	To clarify the window for sample collection
7.2.1. Subject Discontinuation from Study Treatment	(…) The Investigator should discuss with the medical monitor prior to discontinuing a subject's study treatment in case of the following criteria, but not limited to: • Conditions or intercurrent illness that preclude compliance with the protocol in terms of their safety or well-being	(…) The Investigator should discuss with the medical monitor prior to discontinuing a subject's study treatment in case of the following criteria, but not limited to: • Conditions or intercurrent illness that preclude compliance with the protocol in terms of their safety or well-being	To clarify the meaning of lack of subject's compliance

Section Affected	Original Content	Amended/New Content	Rationale
	• Lack of efficacy (e.g., C5 gene polymorphism) **Note**: If the LDH level is not changed after the initiation of study drug (lack of efficacy), the Investigator and medical monitor and/or Sponsor should discuss to determine how to manage this case including whether or not to perform pharmacogenetic analysis (C5 gene polymorphism). • Unacceptable toxicity • Lack of subject's compliance (e.g., a subject who missed two consecutive doses, lost to follow-up) **Note**: Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject. • Investigator discretion or other reasons (…)	• Lack of efficacy (e.g., C5 gene polymorphism) **Note**: If the LDH level is not changed after the initiation of study drug (lack of efficacy), the Investigator and medical monitor and/or Sponsor should discuss to determine how to manage this case including whether or not to perform pharmacogenetic analysis (C5 gene polymorphism). • Unacceptable toxicity • Lack of subject's compliance (e.g., ~~**a subject who missed two consecutive doses,**~~ **repeated delay in study treatment and** lost to follow-up) **Note**: Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject. • Investigator discretion or other reasons (…)	
7.2.1. Subject Discontinuation from Study Treatment	Any subject who discontinues SB12 or Soliris® should be monitored for at least 8 weeks after last study drug to detect serious haemolysis and other reactions. If serious haemolysis occurs after SB12 or Soliris® discontinuation, consider the following procedures and/or treatments: • Blood transfusion (pRBCs) or exchange transfusion if the PNH RBCs are > 50% of the total RBCs by flow cytometry	Any subject who discontinues SB12 or Soliris® should be monitored for at least 8 weeks after last study drug to detect serious haemolysis and other reactions. If serious haemolysis occurs after SB12 or Soliris® discontinuation, consider the following procedures and/or treatments: • Blood transfusion (pRBCs) or exchange transfusion if the PNH RBCs are > 50% of the total RBCs by flow cytometry	To add the additional information for SB12 provision

Section Affected	Original Content	Amended/New Content	Rationale
	• Anticoagulation • Corticosteroids • Complement inhibitors	• Anticoagulation • Corticosteroids • Complement inhibitors **According to the Investigator's medical judgement, if complement inhibitor should be administered again due to serious haemolysis and other reactions which occur within 8 weeks after completion of the study treatment with SB12 or Soliris®, the Investigator should discuss with Sponsor for an expanded access of SB12 to such subjects. Accordingly, the Sponsor will provide SB12 to those subjects as an expanded access up to 1 year period, where applicable, in accordance with relevant local regulations and/or law.**	
8.1.2. Period of Observation for Adverse Events	(…) However, SAEs that are considered to be related to the IP can be collected until 10.5 weeks from the last dose of study drug (five half-lives of the study drug). SAEs that occurred after EOS visit or ET visit and that are considered to be related to the IP must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see Section 8.2.2). Unresolved AEs during the study period should be followed up until the EOS and recorded in the eCRF. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. (…)	(…) However, SAEs **must ~~that are considered to be related to the IP can~~** be collected until 10.5 weeks from the last dose of study drug (five half-lives of the study drug). SAEs that occurred after EOS visit or ET visit **~~and that are considered to be related to the IP~~** must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see Section 8.2.2). Unresolved AEs during the study period should be followed up until the EOS and recorded in the eCRF. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. (…)	To expand the collection scope of SAE from serious adverse reaction to serious adverse event.

Section Affected	Original Content	Amended/New Content	Rationale
8.1.3. Reporting Adverse Events	(…) Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 8.2.1 for SAE definition). If an AE is classified as an SAE, it must be reported to the Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2. For an SAE, a diagnosis with a description of signs and symptoms as well as other supporting information that led to the diagnosis should be described in the SAE form provided by the Sponsor (see Section 8.2.2).	Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 8.2.1 for SAE definition). If an AE is classified as an SAE, it must be reported to the Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2. For an SAE, a diagnosis with a description of signs and symptoms as well as other supporting information that led to the diagnosis should be described in the SAE form provided by the Sponsor (see Section 8.2.2). **If the subject who received the additional SB12 provision according to Section 7.2.1 has an AE, it must be reported to the Sponsor or its designated representative using the paper AE report form. If the AE is classified as a SAE, it must be reported to Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see Section 8.2.2).**	To add the safety reporting during additional SB12 provision
8.2.2. Reporting Serious Adverse Events	SAEs that occurred at or before EOS visit or ET visit must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred after EOS visit or ET visit and that are considered to be related to the IP must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. (…)	**SAEs must be collected until 10.5 weeks from the last dose of study drug (five half-lives of the study drug).** SAEs that occurred at or before EOS visit or ET visit must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred after EOS visit or ET visit ~~**and that are considered to be related to the IP**~~ must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. **SAEs that occurred from the subject who received the**	To clarify the reporting period for SAEs and add the safety reporting during additional SB12 provision

Section Affected	Original Content	Amended/New Content	Rationale
		additional SB12 must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. (…)	
9.1. Statistical Hypotheses	(…) [redacted], the treatment effect will be measured by AUEC of LDH between two different time points in each period, from Week 14 to Week 26 and from Week 40 to Week 52. The equivalence will be declared if the 90% confidence interval (CI) of the ratio between treatment effects is entirely contained within the pre-defined equivalence margin of [0.77, 1.29]. [redacted], equivalence will be declared if the 95% CI of the difference between treatments in LDH level at Week 26 is entirely contained within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study.	(…) [redacted] **for those who are in favour of the AUEC of LDH**, the treatment effect will be measured by AUEC of LDH between two different time points in each period, from Week 14 to Week 26 and from Week 40 to Week 52. The equivalence will be declared if the 90% confidence interval (CI) of the ratio between treatment effects is entirely contained within the pre-defined equivalence margin of [0.77, 1.29]. [redacted] **for those who are in favour of the LDH level at a single time point**, equivalence will be declared if the 95% CI of the difference between treatments in LDH level at Week 26 is entirely contained within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study.	To add phrase to be consistent within the document
9.5.3. Pharmacokin-etic Analyses	PK analysis will be performed for the PKS. Serum trough concentration will be summarised with descriptive statistics by treatment sequence, period, and time point.	PK analysis will be performed for the PKS. ~~**Serum trough concentration**~~ **C_{trough}** will be summarised descriptively by treatment sequence, period, and time point.	To apply abbreviation
13.	[10] Soliris® EPAR – Product Information. EMA (Jan 18, 2018). Retrieved Apr 25, 2018 from	[10] Soliris® EPAR – Product Information. EMA (~~**Jan 18**~~ **Oct 24**, 2018). Retrieved ~~**Apr 25**~~ **Dec 11**, 2018 from	To refer the latest version of

Section Affected	Original Content	Amended/New Content	Rationale
References	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000791/WC500054208.pdf	~~http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000791/WC500054208.pdf~~ **https://www.ema.europa.eu/documents/product-information/soliris-epar-product-information_en.pdf**	regulatory document
All Sections	N/A	All sections were updated to follow consistent usage of punctuation.	Administrative update irrelevant to study design and/or procedures

Amendment 3: Version 4.0, Nov 29, 2019

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Planned Study Period	After Screening, the duration of study participation will be 60 weeks per subject including 52-week treatment period and 8-week post-treatment follow-up period.	After Screening, the duration of study participation will be ~~60 weeks per subject including~~ 52-week **randomised** treatment period and ~~8-week post-treatment follow-up~~ **an extension** period **of up to 2 years**.	To reflect the changes due to 2-year extension period
SYNOPSIS Study Design	This is a randomised Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26.	This **multicentre Phase III study is composed of the Main Part and Extension Part.** **The Main Part** is a randomised ~~Phase III~~, double-blind **period~~, multicentre, cross-over study~~** to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. **The Extension Part is an open-label, single-arm, 2-year extension period to provide SB12 in subjects with PNH for an extended duration under an ethical basis.** **For the Main Part**, **subjects** ~~Subjects~~ will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. **End of the Main Part is defined as completion of pre-dose activities at Week 52. Subjects who complete the Main Part will enter the Extension Part. For the Extension Part, all subjects will receive SB12 for 2 years.**	To reflect the changes due to 2-year extension period
SYNOPSIS Inclusion Criteria	3. Presence of the PNH white blood cell (WBC) clone ≥ 10% by high-sensitivity flow cytometry at Screening.	3. Presence of the PNH white blood cell (WBC) clone**, with a granulocyte or monocyte clone size of** ≥ 10% by high-sensitivity flow cytometry at Screening.	To clarify the inclusion criteria

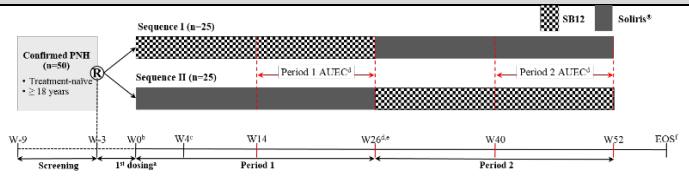
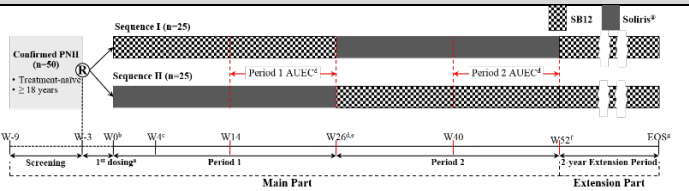
Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Exclusion Criteria	4. Abnormal haematological parameters at Screening defined as the following: a. Absolute neutrophil count (ANC) ≤ 500/mm^3 b. Platelet count < 70,000/mm^3	4. Abnormal haematological parameters at Screening defined as the following: a. Absolute neutrophil count (ANC) ≤ ~~**500/mm^3**~~ **0.5 × 10^3/µL** b. Platelet count < ~~**70,000/mm^3**~~ **70 × 10^3/µL**	To change the unit of haematology parameters
SYNOPSIS Exclusion Criteria	6. History of bone marrow transplantation.	6. History of ~~**bone marrow**~~ **haematopoietic stem cell** transplantation.	To clarify the exculsion criteria
SYNOPSIS Exclusion Criteria	10. Concomitant use of any of the following medications is prohibited if the following conditions apply. b. Warfarin with an unstable international normalized ratio (INR) for at least 4 weeks prior to initiation of study drug (Day 1).	10. Concomitant use of any of the following medications is prohibited if the following conditions apply. b. Warfarin with an unstable international ~~**normalized**~~ **normalised** ratio (INR) for at least 4 weeks prior to initiation of study drug (Day 1) **at the discretion of the Investigator.**	To clarify the exculsion criteria
SYNOPSIS Investigation-al Products	• Dose regimen: 600 mg every 7 days for the first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 14 ± 2 days until Week 52 (maintenance phase).	• Dose regimen: 600 mg every 7 days for the first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 14 ± 2 days ~~**until Week 52**~~**, thereafter** (maintenance phase).	To reflect the changes due to 2-year extension period
SYNOPSIS Main Criteria for Evaluation	**Primary endpoints** • LDH level (U/L) at Week 26 • Area under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52	**Primary endpoints** • LDH level (U/L) at Week 26 • ~~**Area**~~ **Time-adjusted area** under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52	To clarify the primary endpoint

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Main Criteria for Evaluation	**Secondary endpoints** Efficacy endpoints • LDH profile over time • Number of units of pRBCs transfused throughout the study duration for each period Safety endpoints • Incidence of adverse events (AEs) and serious AEs (SAEs) • Incidence of infection-related AEs - Meningococcal infection - Other systemic infections • Incidence of infusion-related reactions (IRRs) (…) Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and end of study (EOS)/early termination (ET) • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS/ET	**Secondary endpoints** Efficacy endpoints • LDH profile ~~over time~~ **during the Main Part** • Number of units of pRBCs transfused ~~throughout the study duration for each period~~ **during the Main Part** Safety endpoints • Incidence of adverse events (AEs) ~~and serious AEs (SAEs)~~ • **Incidence of serious AEs (SAEs)** • Incidence of infection-related AEs - Meningococcal infection - Other systemic infections • Incidence of infusion-related reactions (IRRs) (…) **During the Extension Part, only SAEs will be collected.** Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ~~end of study (EOS)/~~early termination (ET) • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ~~EOS/~~ET	To reflect the changes in secondary endpoints due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Statistical Methods	Efficacy analyses [redacted] for those who are in favour of the AUEC of LDH, the primary efficacy analysis will be performed for the PPS-AUEC using a linear mixed model with treatment, subject, sequence, and period as fixed effects and, subject nested within sequence as a random effect. The analysis will be performed with $\log_e$-transformed AUEC of LDH estimating the difference in least squares means and its 90% confidence interval (CI), and back transformation of those values will provide the ratio of geometric means and 90% CI. The equivalence will be declared if the two-sided 90% CI of the ratio of geometric means in AUEC of LDH between SB12 and Soliris® lies within the pre-defined equivalence margin of [0.77, 1.29]. [redacted] for those who are in favour of the LDH level at a single time point, the primary efficacy analysis will be performed for the PPS-single using a linear mixed model with treatment as a fixed effect. (…) (…) As a secondary efficacy endpoint, the number of units of pRBCs transfused will be analysed using Wilcoxon rank-sum test for each period. And mean LDH profile will be presented over time. Safety analyses Safety analyses will be performed for the Safety Set (SAF).	Efficacy analyses [redacted] for those who are in favour of the **time-adjusted** AUEC of LDH, the primary efficacy analysis will be performed for the PPS-AUEC using a linear mixed model with treatment, ~~**subject,**~~ sequence, ~~**and**~~ period**, and gender** as fixed effects, and subject nested within sequence as a random effect. The analysis will be performed with $\log_e$-transformed **time-adjusted** AUEC of LDH estimating the difference in least squares means and its 90% confidence interval (CI), and back transformation of those values will provide the ratio of geometric means and 90% CI. The equivalence will be declared if the two-sided 90% CI of the ratio of geometric means in **time-adjusted** AUEC of LDH between SB12 and Soliris® lies within the pre-defined equivalence margin of [0.77, 1.29]. [redacted] or those who are in favour of the LDH level at a single time point, the primary efficacy analysis will be performed for the PPS-single using a linear mixed model with treatment**, and gender** as a fixed effect. (…) **If normal range of LDH is gender specific, the smaller/smallest ULN will be used for the equivalence margin; otherwise ULN is not gender specific, unified ULN will be used for the equivalence margin.** (…)	To clarify the primary endpoint and efficacy/safety analysis To reflect the local amendment To reflect changes in the statistical methods due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	All reported terms for AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be collected and classified according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AE data will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term, treatment sequence, and period. (…) Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence, period, and time point. (…) <u>Immunogenicity analyses</u> The immunogenicity analyses will be performed for the SAF. ADA and NAb results will be summarised with count and percentage by treatment sequence, period, and time point. The incidence of overall ADA will be summarised by treatment sequence and period. <u>Sample size</u> (…) For calculation of the equivalence margin for AUEC of LDH, mean and coefficient of variation (%CV) were referred from TRIUMPH study. The mean (%CV) of AUEC of LDH at Week 26 is 81140.0 U/L × day (142.45%) and 429874.1 U/L × day (33.49%) for eculizumab and non-eculizumab arms, respectively.	As a secondary efficacy endpoint, the number of units of pRBCs transfused **during the Main Part** will be analysed using Wilcoxon rank-sum test for each period. And mean LDH profile **during the Main Part** will be presented over time. <u>Safety analyses</u> Safety analyses will be performed ~~**for**~~ **in** the Safety Set ~~**(SAF)**~~ **for the Main Part (SAF1) and Safety Set for the Extension Part (SAF2).** All reported terms for AEs will be coded using ~~**the latest version of**~~ Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be collected and classified according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AE data **reported during the Main Part** will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term, treatment sequence, and period **for the SAF1.** (…) Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence, period, and time point **for the SAF1**. (…) **All SAEs reported during the Extension Part will be summarised by count and percentage of subjects experiencing events by system organ class and preferred term for the SAF2.** <u>Immunogenicity analyses</u>	

Section Affected	Original Content	Amended/New Content	Rationale
	From the results in the reference study, mean ratio of AUEC of LDH is estimated to be 0.19 with a 90% CI [0.1308, 0.2724]. The upper limit of the equivalence margin is calculated as [redacted] where it preserves at least [redacted] of eculizumab treatment effect over the placebo, but [redacted] the equivalence margin will be [0.77, 1.29] for the comparison with the 90% CI of mean ratio of AUEC of LDH. (…)	The immunogenicity analyses will be performed for the ~~SAF~~ **SAF1**. ADA and NAb results will be summarised with count and percentage by treatment sequence, period, and time point. The incidence of overall ADA will be summarised by treatment sequence and period. <u>Sample size</u> (…) For calculation of the equivalence margin for **time-adjusted** AUEC of LDH, mean and coefficient of variation (%CV) were referred from TRIUMPH study. The mean (%CV) of AUEC of LDH at Week 26 is 81140.0 U/L × day (142.45%) and 429874.1 U/L × day (33.49%) for eculizumab and non-eculizumab arms, respectively. From the results in the reference study, mean ratio of AUEC of LDH is estimated to be 0.19 with a 90% CI [0.1308, 0.2724]. The upper limit of the equivalence margin is calculated as [redacted] where it preserves at least [redacted] of eculizumab treatment effect over the placebo, but [redacted] the equivalence margin will be [0.77, 1.29] for the comparison with the 90% CI of mean ratio of **time-adjusted** AUEC of LDH. (…)	

Section Affected	Original Content	Amended/New Content	Rationale
Figure 1			To reflect the changes due to 2-year extension period
Figure 1 Footnote	® = Randomisation; AUEC = Area under the Effect Curve; EOS = End of Study; PNH = Paroxysmal Nocturnal Haemoglobinuria; W = Week c. From Week 4, 900 mg of SB12 or Soliris® every 14 ± 2 days up to Week 52 (…) f. EOS visit is defined as 8 weeks after the last dose of SB12 or Soliris®.	® = Randomisation; AUEC = Area under the Effect Curve; EOS = End of Study; **n = No. of Subjects;** PNH = Paroxysmal Nocturnal Haemoglobinuria; W = Week c. From Week 4, 900 mg of SB12 or Soliris® every 14 ± 2 days up to Week ~~52~~ **50. During the Extension Part, SB12 will be given to all subjects.** (…) f. ~~**EOS visit**~~ **Completion of pre-dose activities at Week 52** is defined as **end of the Main Part** ~~**8 weeks after the last dose of SB12 or Soliris®**~~**.** g. **EOS is defined as the date of last subject's last visit in the Extension Part.**	To add abbreviations To reflect the changes due to 2-year extension period
Table 1	Table 1. Schedule of Activities (Period 1, before Cross-over)	Table 1. Schedule of Activities (**Main Part**: Period 1, before Cross-over)	To reflect the changes due to 2-year extension period
Table 1 Footnote	4. All screening procedures must be completed and reviewed within 42 days prior to randomisation. All eligibility criteria must be reviewed and confirmed prior to randomisation. The initiation of study drug (Day 1) should be done within 21 days of randomisation.	4. All screening procedures must be completed and reviewed within 42 days prior to randomisation. All eligibility criteria **not dependent on Day 1** must be reviewed and confirmed prior to randomisation. The initiation of study drug (Day 1) should be done within 21 days of randomisation. **Eligibility criteria that are dependent on**	To clarify the randomisation process including eligibility confirmation process

Section Affected	Original Content	Amended/New Content	Rationale
		Day 1 should be checked at Day 1 and if found in violation then should be withdrawn according to discontinuation criteria.	
Table 1 Footnote	7. Females of childbearing potential only. Serum pregnancy test at Screening and EOS (or 8 weeks after the last dose of study drug in case of early termination [ET]); urine pregnancy test at other applicable visits.	7. Females of childbearing potential only. Serum pregnancy test at Screening and ~~**EOS (or**~~ 8 weeks after the last dose of study drug in case of early termination ~~**[ET])**~~ **(ET) during the Main Part**; urine pregnancy test at other applicable visits **before study drug administration**.	To reflect the changes due to 2-year extension period and clarify the timeframe
Table 1 Footnote	10. LDH will be measured at pre-dose on each visit and will also be measured throughout the study period if the suspected sign or symptom of breakthrough haemolysis occurs .	10. LDH will be measured at pre-dose on each visit and will also be measured ~~**throughout the study period**~~ if the suspected sign or symptom of breakthrough haemolysis occurs.	To reflect the changes due to 2-year extension period
Table 1 Footnote	11. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, and nucleated RBC. (…)	11. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, ~~**and**~~ nucleated RBC**, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean platelet volume (MPV), and red cell distribution width (RDW)**. (…)	To add several haematology parameters
Table 1 Footnote	12. Blood sample for PK analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PK samples will also be collected throughout the	12. Blood sample for PK analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK analysis, blood sample should be re-collected on actual dosing day and be used	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	study period if the suspected sign or symptom of breakthrough haemolysis occurs.	for analysis. PK samples will also be **collected ~~throughout the study period~~** if the suspected sign or symptom of breakthrough haemolysis occurs.	
Table 1 Footnote	13. Blood sample for PD (terminal complement activity) analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PD analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PD samples will also be collected throughout the study period if the suspected sign or symptom of breakthrough haemolysis occurs.	13. Blood sample for PD (terminal complement activity) analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PD analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PD samples will also be collected **~~throughout the study period~~** if the suspected sign or symptom of breakthrough haemolysis occurs.	To reflect the changes due to 2-year extension period
Table 1 Footnote	14. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS/ET. Blood samples should be collected at the same day of study drug administration except for EOS/ET. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis.	14. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and **~~EOS~~**/ET. Blood samples should be collected at the same day of study drug administration except for **~~EOS~~**/ET **visit**. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis.	To reflect the changes due to 2-year extension period
Table 1 Footnote	19. Adverse events (AEs) will be collected from the time of signing the informed consent until EOS (or 8 weeks after the last dose of study drug in case of ET).	19. Adverse events (AEs) will be collected from the time of signing the informed consent until **~~EOS~~ end of the Main Part** (or 8 weeks after the last dose of study drug in case of ET **during the Main Part**).	To reflect the changes due to 2-year extension period

<table>
<tr><th>Section Affected</th><th>Original Content</th><th>Amended/New Content</th><th>Rationale</th></tr>
<tr><td>Table 1 Footnote</td><td>20. Previous medications (within 4 weeks prior to Screening except immunosuppressant, 8 weeks prior to Screening for immunosuppressant) will be recorded and concomitant medications will be recorded throughout the study period.</td><td>20. Previous medications (within 4 weeks prior to Screening except immunosuppressant, 8 weeks prior to Screening for immunosuppressant) will be recorded and concomitant medications will be recorded <s>throughout the study period</s> until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part).</td><td>To reflect the changes due to 2-year extension period</td></tr>
<tr><td>Table 1 Footnote</td><td>21. Transfusion record will be collected from the time of signing the informed consent until EOS (or 8 weeks after the last dose of study drug in case of ET).</td><td>21. Transfusion record will be collected from the time of signing the informed consent until <s>EOS</s> end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part).</td><td>To reflect the changes due to 2-year extension period</td></tr>
<tr><td>Table 2</td><td>Table 2. Schedule of Activities (Period 2 and EOS/ET, after Cross-over)</td><td>Table 2. Schedule of Activities (Main Part: Period 2 <s>and EOS/ET</s>, after Cross-over)</td><td>To reflect the changes due to 2-year extension period</td></tr>
<tr><td>Table 2</td><td>
<table>
<tr><th>Assessments</th><th colspan="2">Study Period</th></tr>
<tr><td>Study Visit</td><td>29</td><td>EOS/ET[20]</td></tr>
<tr><td>Week</td><td>52</td><td>60</td></tr>
<tr><td>Day (± Visit Window)</td><td>365 (±2)</td><td>421 (±7)</td></tr>
<tr><td>IP administration[15]</td><td>✓</td><td></td></tr>
</table>
</td><td>
<table>
<tr><th>Assessments</th><th colspan="2">Study Period</th></tr>
<tr><td>Study Visit</td><td>29</td><td><s>EOS/ET</s>[20] ET[21]</td></tr>
<tr><td>Week</td><td>52[20]</td><td><s>60</s>
8 (±1) weeks after the last dose of study drug</td></tr>
<tr><td>Day (± Visit Window)</td><td>365 (±2)</td><td><s>421 (±7)</s></td></tr>
<tr><td>IP administration[15]</td><td>✓</td><td></td></tr>
</table>
</td><td>To reflect the changes due to 2-year extension period</td></tr>
<tr><td>Table 2 Footnote</td><td>EOS = End of Study;</td><td><s>EOS = End of Study;</s></td><td>To reflect the changes due to 2-year extension period</td></tr>
</table>

Section Affected	Original Content	Amended/New Content	Rationale
Table 2 Footnote	4. Females of childbearing potential only. Serum pregnancy test at Screening and EOS (or 8 weeks after the last dose of study drug in case of ET); urine pregnancy test at other applicable visits.	4. Females of childbearing potential only. Serum pregnancy test at Screening and ~~**EOS (or**~~ 8 weeks after the last dose of study drug in case of ET~~)~~ **during the Main Part**; urine pregnancy test at other applicable visits **before study drug administration.**	To reflect the changes due to 2-year extension period and clarify the timeframe
Table 2 Footnote	7. LDH will be measured at pre-dose on each visit and will also be measured throughout the study period if the suspected sign or symptom of breakthrough haemolysis occurs .	7. LDH will be measured at pre-dose on each visit and will also be measured ~~**throughout the study period**~~ if the suspected sign or symptom of breakthrough haemolysis occurs.	To reflect the changes due to 2-year extension period
Table 2 Footnote	8. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, and nucleated RBC. (…)	8. Parameters included in haematology test are WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential WBC count, ~~**and**~~ nucleated RBC**, MCH, MCHC, MCV, MPV, and RDW.** (…)	To add several haematology parameters
Table 2 Footnote	9. Blood sample for PK analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PK samples will also be collected throughout the study period if the suspected sign or symptom of breakthrough haemolysis occurs.	9. Blood sample for PK analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PK samples will also be collected ~~**throughout the study period**~~ if the suspected sign or symptom of breakthrough haemolysis occurs.	To reflect the changes due to 2-year extension period
Table 2 Footnote	10. Blood sample for PD (terminal complement activity) analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52. Blood samples should be collected at the same day of study drug administration. If the administration of IPs is delayed for	10. Blood sample for PD (terminal complement activity) analysis will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 26, 28, 30, 32, 36, 40, and 52. Blood samples should be collected at the same day of study drug	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	any reasons after pre-dose blood sampling for PD analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PD samples will also be collected throughout the study period if the suspected sign or symptom of breakthrough haemolysis occurs.	administration. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PD analysis, blood sample should be re-collected on actual dosing day and be used for analysis. PD samples will also be collected ~~**throughout the study period**~~ if the suspected sign or symptom of breakthrough haemolysis occurs.	
Table 2 Footnote	11. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS/ET. Blood samples should be collected at the same day of study drug administration except for EOS/ET. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis.	11. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ~~**EOS**~~/ET. Blood samples should be collected at the same day of study drug administration except for ~~**EOS**~~/ET **visit**. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis.	To reflect the changes due to 2-year extension period
Table 2 Footnote	17. Adverse events (AEs) will be collected from the time of signing the informed consent until EOS (or 8 weeks after the last dose of study drug in case of ET).	17. Adverse events (AEs) will be collected from the time of signing the informed consent until ~~**EOS**~~ **end of the Main Part** (or 8 weeks after the last dose of study drug in case of ET **during the Main Part**).	To reflect the changes due to 2-year extension period
Table 2 Footnote	18. Concomitant medications will be recorded throughout the study period.	18. Concomitant medications will be recorded ~~**throughout the study period**~~ **until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part).**	To reflect the changes due to 2-year extension period
Table 2 Footnote	19. Transfusion record will be collected from the time of signing the informed consent until EOS (or 8 weeks after the last dose of study drug in case of ET).	19. Transfusion record will be collected from the time of signing the informed consent until ~~**EOS**~~ **end of the Main Part** (or 8 weeks after the last dose of study drug in case of ET **during the Main Part**).	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
Table 2 Footnote	20. EOS visit or ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®.	20. ~~**EOS visit or ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®**~~ **End of the Main Part is defined as completion of pre-dose activities at Week 52.**	To reflect the changes due to 2-year extension period
Table 2 Footnote	N/A	21. **ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®, which may be up to Week 58**.	To reflect the changes due to 2-year extension period
Table 3	N/A	**Table 3. Schedule of Activities (Extension Part: 2-year Extension Period)** **Assessments** / **Study Period** **Week** 52 54 56 58 60 62 64 … 140 142 144 148 150 152 154 **End of the Extension Part**[1] SB12 administration[2] ✓ ✓ ✓ ✓ ✓ ✓ ✓ … ✓ ✓ ✓ ✓ ✓ ✓ ✓ Serious adverse events[2] Continuously	To reflect the changes due to 2-year extension period
Table 3 Footnote	N/A	**1. From Week 52, SB12 will be administered bi-weekly via IV infusion for 35 ± 10 minutes for all subjects.** **2. Only SAEs will be collected during the Extension Part from start of study treatment at Week 52.** 3. **End of the Extension Part is defined as 8 weeks after the last dose of SB12. Prematurely discontinued subjects do not require any specific study procedures as done in the Main Part.**	To reflect the changes due to 2-year extension period
LIST OF ABBREVIA-TIONS	IB Investigators' Brochure INR International normalized ratio N/A N/A SAF Safety Set	IB ~~**Investigators'**~~ **Investigator's** Brochure INR International ~~**normalized**~~ **normalised** ratio **MCH Mean corpuscular haemoglobin** **MCHC Mean corpuscular haemoglobin concentration** **MCV Mean corpuscular volume**	To revise/add abbreviations according to updated contents

Section Affected	Original Content	Amended/New Content	Rationale
		MFDS **Ministry of Food and Drug Safety** **MPV** **Mean platelet volume** **NMOSD** **Neuromyelitis optica spectrum disorder** **RDW** **Red cell distribution width** SAF**1** Safety Set **for the Main Part** **SAF2** **Safety Set for the Extension Part**	
LIST OF STUDY STAFF	**Sponsor:** **Samsung Bioepis Co., Ltd.** 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea Tel: +82 (32) 455 3114 Fax: +82 (32) 455 6799 Clinical Development Lead [redacted] Statistician [redacted]	**Sponsor:** **Samsung Bioepis Co., Ltd.** 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea Tel: +82 (32) 455 **6114** ~~**3114**~~ ~~**Fax: +82 (32) 455 6799**~~ Clinical Development Lead [redacted] Statistician [redacted]	Administrative change
1.1. Paroxysmal Nocturnal Haemoglobi-	(…) Soliris® (eculizumab, Alexion Pharmaceuticals, Inc.) is a humanised monoclonal antibody that blocks terminal	(…) Soliris® (eculizumab, Alexion Pharmaceuticals, Inc.) is a humanised monoclonal antibody that blocks terminal	To refer the latest information

Section Affected	Original Content	Amended/New Content	Rationale
nuria	complement by binding to C5 and is the only approved therapy for PNH.	complement by binding to C5 and is the ~~only~~ approved therapy for PNH.	
1.2. Overview of SB12	SB12 has been developed as a similar biological medicinal product to Soliris® (eculizumab, Alexion Pharmaceuticals, Inc.). Soliris® is currently indicated for the treatment of patients with PNH, atypical haemolytic uremic syndrome (aHUS), and refractory generalised myasthenia gravis (gMG) [10]. (…)	SB12 has been developed as a similar biological medicinal product to Soliris® (eculizumab, Alexion Pharmaceuticals, Inc.). Soliris® is currently indicated for the treatment of patients with PNH, atypical haemolytic uremic syndrome (aHUS), ~~and~~ refractory generalised myasthenia gravis (gMG)**, and neuromyelitis optica spectrum disorder (NMOSD)** [10**; 21**]. (…)	To refer the latest version of regulatory document
1.2.2. Clinical Pharmacolog -y of SB12	As clinical studies using SB12 have not been conducted up to date, clinical data is currently not available. Based on biosimilarity between SB12 and Soliris®, which was demonstrated through extensive quality and non-clinical similarity exercise, a Phase I study will be conducted in healthy subjects to compare the pharmacokinetic (PK), safety, tolerability, immunogenicity, and pharmacodynamic (PD) profiles and a Phase III study will be conducted in subjects with PNH to compare the efficacy, safety, pharmacokinetics, and immunogenicity of SB12 to Soliris®. Information on the safety of SB12 based on the product information of Soliris® and non-clinical exercise is presented in the Investigators' Brochure (IB). The safety results of the Phase I study will be updated when the results become available.	~~**As clinical studies using SB12 have not been conducted up to date, clinical data is currently not available.**~~ Based on biosimilarity between SB12 and Soliris®, which was demonstrated through extensive quality and non-clinical similarity exercise, a Phase I study ~~**will be**~~ **was** conducted in healthy subjects to compare the pharmacokinetic (PK), safety, tolerability, immunogenicity, and pharmacodynamic (PD) profiles and a Phase III study will be conducted in subjects with PNH to compare the efficacy, safety, pharmacokinetics, and immunogenicity of SB12 to Soliris®. Information on the safety of SB12 based on the product information of Soliris® ~~**and**~~ **,** non-clinical**, and clinical** exercise is presented in the ~~**Investigators'**~~ **Investigator's** Brochure (IB). ~~**The safety results of the Phase I study will be updated when the results become available.**~~	To reflect updated study progress (Phase I study completion)
1.3.2. Clinical Data of Soliris®	In 40 patients with PNH, a 1-compartmental model was used to estimate PK parameters after multiple doses. Mean clearance was 0.31 ± 0.12 mL/hr/kg, mean volume of distribution was 110.3 ± 17.9 mL/kg, and mean elimination half-life was 11.3 ± 3.4 days. Based on these data, the onset of steady state is predicted to be approximately 49-56 days.	In 40 patients with PNH, a 1-compartmental model was used to estimate PK parameters after multiple doses. Mean clearance was 0.31 ± 0.12 mL/hr/kg, mean volume of distribution was 110.3 ± 17.9 mL/kg, and mean elimination half-life was 11.3 ± 3.4 days~~.~~ ~~**Based on these data, the onset of**~~ **The** steady state is ~~**predicted to be approximately 49-56 days**~~ **achieved by 4 weeks using the**	To refer the latest version of regulatory document

Section Affected	Original Content	Amended/New Content	Rationale
	(…)	**PNH adult dosing regimen**. (…)	
1.5.1. Known Potential Risks	According to Soliris® Summary of Product Characteristics (SmPC) [10], supportive safety data were collected from 29 completed and one ongoing clinical studies that included 1,407 patients exposed to eculizumab in ten disease populations, including PNH, aHUS, and refractory gMG. (…) (…) (…) Subjects will have a safety follow-up at the end of study (EOS) visit 8 weeks after the last dose of study drug. An independent Data and Safety Monitoring Board (DSMB) will convene at pre-specified intervals to conduct interim monitoring of accumulating safety data. Following each data review, the DSMB will make recommendations regarding the conduct of the study, including continuation of the study without modifications, termination of the study for safety reasons, or modification of the study design for safety reasons.	According to Soliris® Summary of Product Characteristics (SmPC) [10], supportive safety data were collected from ~~29~~ **30** completed and one ongoing clinical studies that included ~~1,407~~ **1,503** patients exposed to eculizumab in ~~ten~~ **complement-medicated** disease populations, including PNH, aHUS, ~~and~~ refractory gMG**, and NMOSD**. (…) (…) (…) Subjects will have a safety follow-up ~~at the end of study (EOS) visit~~ **until** 8 weeks after the last dose of study drug. An independent Data and Safety Monitoring Board (DSMB) will convene at pre-specified intervals to conduct interim monitoring of accumulating safety data. Following each data review, the DSMB will make recommendations regarding the conduct of the study, including continuation of the study without modifications, **modification of the protocol, pausing of subject enrolment until the resolution of issues, or** termination of the study for safety reasons~~, or modification of the study design for safety reasons~~.	To refer the latest version of regulatory document To reflect the changes due to 2-year extension period To further clarify the DSMB actions
1.5.2. Known Potential Benefits	Soliris® is the only approved therapy for PNH and is indicated for the treatment patients with aHUS and gMG [10]. The drug is highly effective in stopping intravascular haemolysis, eliminating or decreasing the need for RBC transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH [7; 8; 9]. (…)	Soliris® is the ~~only~~ approved therapy for PNH and is indicated for the treatment patients with aHUS**,** ~~and~~ gMG**, and NMOSD** [10**; 21**]. The drug is highly effective in stopping intravascular haemolysis, eliminating or decreasing the need for RBC transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH [7; 8; 9]. (…)	To refer the latest version of regulatory document

Section Affected	Original Content	Amended/New Content	Rationale
2.2.1. Primary Endpoints	**Primary endpoints** • LDH level (U/L) at Week 26 • Area under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52	**Primary endpoints** • LDH level (U/L) at Week 26 • ~~Area~~ **Time-adjusted area** under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52	To clarify the primary endpoint
2.2.2. Secondary Endpoints	**Secondary endpoints** Efficacy endpoints • LDH profile over time • Number of units of pRBCs transfused throughout the study duration for each period Safety endpoints • Incidence of AEs and serious AEs (SAEs) • Incidence of infection-related AEs - Meningococcal infection - Other systemic infections • Incidence of infusion-related reactions (IRRs) (…) Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS/early termination (ET) • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and EOS/ET	**Secondary endpoints** Efficacy endpoints • LDH profile ~~over time~~ **during the Main Part** • Number of units of pRBCs transfused ~~throughout the study duration for each period~~ **during the Main Part** Safety endpoints • Incidence of AEs ~~and serious AEs (SAEs)~~ • **Incidence of serious AEs (SAEs)** • Incidence of infection-related AEs - Meningococcal infection - Other systemic infections • Incidence of infusion-related reactions (IRRs) (…) **During the Extension Part, only SAEs will be collected.** Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ~~EOS/~~early termination (ET)	To reflect the changes in secondary endpoints due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
		• Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ~~**EOS**~~/ET	
3.1. Overview of Study Design	This is a randomised Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. (…) IPs will be given until Week 52. Details of assessment that will be conducted and treatment that will be administered are presented in Table 1 and Table 2. The last assessment will be done at Week 60 or 8 weeks after the last dose of study drug.	This **multicentre Phase III study is composed of the Main Part and Extension Part.** **The Main Part** is a randomised ~~**Phase III**~~, double-blind **period**~~**, multicentre, cross-over study**~~ to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. **The Extension Part is an open-label, single-arm, 2-year extension period to provide SB12 in subjects with PNH for an extended duration under an ethical basis.** (…) ~~**IPs**~~ **SB12 or Soliris®** will be given until Week ~~**52**~~ **50**. **End of the Main Part is defined as completion of pre-dose activities at Week 52. Subjects who complete the Main Part will enter the Extension Part.** **For the Extension Part, all subjects will receive SB12 for 2 years.** Details of assessment that will be conducted and treatment that will be administered are presented in Table 1**, and** Table 2**, and Table 3.** The last assessment **for the Main Part** will be ~~**done**~~ **performed** at **pre-dose of** Week ~~**60**~~ **52** or 8 weeks after the last dose of study drug **in case of ET during the Main Part** . **The last assessment for the Extension Part will be performed at 8 weeks after the last dose of SB12.**	To reflect the changes due to 2-year extension period
3.2.1. Scientific Rationale for	(…) [redacted], for	(…) [redacted], for	To clarify the primary endpoint and reflect the

Section Affected	Original Content	Amended/New Content	Rationale
Study Design	analysis of haemolysis reduction as measured by AUEC of LDH between two different time points in each period, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52. [redacted], for analysis of haemolysis reduction as measured by the LDH level at single time point, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of the LDH level (U/L) at Week 26.	analysis of haemolysis reduction as measured by **time-adjusted** AUEC of LDH between two different time points in each period, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of **time-adjusted** AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52. [redacted]s, for analysis of haemolysis reduction as measured by the LDH level at single time point, the primary objective is to demonstrate comparable clinical efficacy of SB12 and Soliris® in terms of the LDH level (U/L) at Week 26.	local amendment
3.2.3. Rationale for Pharmacokin-etic Assessments	A randomised, three-arm, parallel, single-dose Phase I PK study will be conducted in healthy subjects to demonstrate similarity in PK profiles of SB12, European Union (EU) sourced Soliris®, and US sourced Soliris®. However, since target-mediated clearance of eculizumab can be more accurately investigated in patients, additional PK assessments will be performed in this Phase III study to provide supportive evidence to PK similarity.	A randomised, three-arm, parallel, single-dose Phase I PK study ~~**will be**~~ **was** conducted in healthy subjects to demonstrate similarity in PK profiles of SB12, European Union (EU) sourced Soliris®, and US sourced Soliris®. However, since target-mediated clearance of eculizumab can be more accurately investigated in patients, additional PK assessments will be performed in this Phase III study to provide supportive evidence to PK similarity.	To reflect updated study progress (Phase I study completion)
3.3. Duration of Study Participation	After Screening, the duration of study participation will be 60 weeks per subject including 52-week treatment period and 8-week post-treatment follow-up period	After Screening, the duration of study participation will be ~~**60 weeks per subject including**~~ 52-week **randomised** treatment period and ~~**8-week post-treatment follow-up**~~ **an extension** period **of up to 2 years**.	To reflect the changes due to 2-year extension period
3.5. End of Study Definition	A subject is considered to have completed the study if he or she has completed all study treatment including the last visit or the last scheduled procedure shown in Table 2. The EOS is defined as completion of the last scheduled visit shown in Table 2. The	A subject is considered to have completed the **each part of** study if he or she has completed all study treatment including the last visit or the last scheduled procedure shown in Table 2 **and Table 3**. ~~**The EOS is defined as completion of the last**~~	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	end of this clinical study is defined as completion of the last subject's EOS.	~~**scheduled visit shown in Table 2**~~. The end of ~~**this clinical study**~~ **the Main Part** is defined as completion of ~~**the last subject's EOS**~~ **pre-dose activities at Week 52 for subjects. The end of the Extension Part is defined as 8 weeks after the last dose of SB12.** **The end of study (EOS) is defined as the date of last subject's last visit in the Extension Part.**	
4.2. Inclusion Criteria	3. Presence of the PNH white blood cell (WBC) clone ≥ 10% by high-sensitivity flow cytometry at Screening.	3. Presence of the PNH white blood cell (WBC) clone**, with a granulocyte or monocyte clone size of** ≥ 10% by high-sensitivity flow cytometry at Screening.	To clarify the inclusion criteria
4.3. Exclusion Criteria	4. Abnormal haematological parameters at Screening defined as the following: a. Absolute neutrophil count (ANC) ≤ 500/mm^3 b. Platelet count < 70,000/mm^3	4. Abnormal haematological parameters at Screening defined as the following: a. Absolute neutrophil count (ANC) ≤ ~~**500/mm^3**~~ **0.5 × 10^3/µL** b. Platelet count < ~~**70,000/mm^3**~~ **70 × 10^3/µL**	To change the unit of haematology parameters
4.3. Exclusion Criteria	6. History of bone marrow transplantation.	6. History of ~~**bone marrow**~~ **haematopoietic stem cell** transplantation.	To clarify the exculsion criteria
4.3. Exclusion Criteria	10. Concomitant use of any of the following medications is prohibited if the following conditions apply. b. Warfarin with an unstable international normalized ratio (INR) for at least 4 weeks prior to initiation of study drug (Day 1).	10. Concomitant use of any of the following medications is prohibited if the following conditions apply. b. Warfarin with an unstable international ~~**normalized**~~ **normalised** ratio (INR) for at least 4 weeks prior to initiation of study drug (Day 1) **at the discretion of the Investigator.**	To clarify the exculsion criteria

Section Affected	Original Content	Amended/New Content	Rationale
5.1.1. Dosing and Treatment Schedule	SB12 or Soliris® will be administered up to Week 52 (a total of 29 administrations of IP) unless they are early discontinued from study treatment. • 600 mg every 7 ± 2 days for the first 4 weeks, followed by • 900 mg for the fifth dose 7 ± 2 days later, then • 900 mg every 14 ± 2 days thereafter In case previous IP administration was out of visit window, next visit schedule should be adjusted to keep intervals of IP administration as indicated above. The subject receiving SB12 or Soliris® therapy may require dose adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. Once the above event has occurred, the Investigator should inform the medical monitor and/or Sponsor immediately.	~~**SB12 or Soliris® will be administered up to Week 52 (a total of 29 administrations of IP) unless they are early discontinued from study treatment.**~~ **Dosing and treatment schedule of SB12 or Soliris® should be kept as follows:** • 600 mg every 7 ± 2 days for the first 4 weeks, followed by • 900 mg for the fifth dose **(Week 4)** 7 ± 2 days later, then • 900 mg every 14 ± 2 days thereafter ~~**In case previous IP administration was out of visit window, next visit schedule should be adjusted to keep intervals of IP administration as indicated above.**~~ **The treatment schedule is dependent on the previous treatment date rather than the absolute (i.e., fixed) number of days from Day 1. In other words, the next 7 ± 2 days or 14 ± 2 days treatment schedule described above is re-scheduled every time based on the date when the previous treatment is given.** The subject receiving SB12 or Soliris® therapy may require ~~**dose**~~ **dosing interval** adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. **For subjects whose dosing interval is adjusted to**	To clarify dosing and treatment schedule To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
		12 days in Period 1 of the Main Part, it is recommended that the dosing interval be switched back to 14 days after switching IP at Week 26. Once the above event has occurred, the Investigator should inform the medical monitor and/or Sponsor immediately **during the Main Part, but in the Extension Part, the event can be managed at the discretion of the Investigator**.	
5.1.3. Blinding	This study is double-blinded. Subjects, Investigators, and other study personnel will remain blinded to the treatment sequence assignment throughout the study period after randomisation. (…)	~~**This**~~ **The Main Part of this** study is double-blinded. Subjects, Investigators, and other study personnel will remain blinded to the treatment sequence assignment ~~**throughout the study period**~~ **until end of the Main Part** after randomisation. (…)	To reflect the changes due to 2-year extension period
5.2.1. Identify of Investigation -al Product	The IPs will be supplied to investigational site in one carton containing a single vial. These IP vials will be packed and labelled in a double-blinded manner for clinical use. (…)	The IPs will be supplied to investigational site in one carton containing a single vial. These IP vials will be packed and labelled in a double-blinded manner for ~~**clinical use**~~ **the Main Part**. For the Extension Part, SB12 will also be supplied to investigational site in one carton containing a single vial. These SB12 vials will be packed and labelled using open label for the Extension Part. (…)	To reflect the changes due to 2-year extension period
5.2.2. Formulation, Packaging, and Labelling	Eculizumab (SB12 or Soliris®) will be supplied for use as a concentrate for solution for infusion (300 mg per vial for SB12, EU sourced Soliris®). (…). SB12 or Soliris® will be pre-packaged and labelled in a double-blinded form. (…)	Eculizumab (SB12 or Soliris®) will be supplied for use as a concentrate for solution for infusion (300 mg per vial for SB12, ~~**EU sourced**~~ Soliris®). (…). SB12 or Soliris® will be pre-packaged and labelled in a double-blinded form **for the Main Part. For the Extension Part, SB12 will be packaged and labelled using open label**. (…)	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
5.2.4. Preparation and Administrati -on of Investigation -al Products	(…) Dilution should be performed in accordance with good particles rules, particularly for the respect of asepsis. Withdraw the total amount of SB12 or Soliris® from the vials using a sterile syringe. Transfer the recommended dose to an infusion bag. Dilute SB12 or Soliris® to a final concentration of 5 mg/mL by addition to the infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection, sodium chloride 4.5 mg/mL (0.45%) solution for injection, or 5% dextrose in water, as the diluent. (…)	(…) Dilution should be performed in accordance with good ~~**particles**~~ **practices** rules, particularly for the respect of asepsis. Withdraw the total amount of SB12 or Soliris® from the vials using a sterile syringe. Transfer the recommended dose to an infusion bag. Dilute SB12 or Soliris® to a final concentration of 5 mg/mL by addition to the infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection, sodium chloride 4.5 mg/mL (0.45%) solution for injection, or 5% dextrose in water, as the diluent. (…)	To correct editorial error
5.2.5. Treatment Compliance and Investigation -al Product Accountabili -ty	(…) (…) At the completion or termination of the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their resolution must be documented. Unless otherwise notified, empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy SOP for clinical study drugs. (…) In case of expanded access of SB12 to subjects, the Investigator is responsible for maintaining the SB12 records which include information on amounts delivered, dispensed, and returned/destroyed; for ensuring proper storage conditions are maintained and documented including details of dates, quantities, batch numbers, expiry dates; ensuring the SB12 is only used as specified by the expanded access; for reconciling all SB12	(…) (…) At the completion or termination of **each part of** the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their resolution must be documented. ~~**Unless otherwise notified,**~~ **To avoid accidental unblinding, used drug kits (**empty vials ~~**and,**~~ vials with residual materials**, and cartons)** should be ~~**kept for inspection**~~ **promptly discarded after the infusion bag is prepared** and ~~**accountability by the study monitor prior to their**~~ **in accordance with the local** destruction ~~**or handled per local pharmacy**~~ SOP/**policies** for clinical study drugs. (…) ~~**In case of expanded access of SB12 to subjects, the Investigator is responsible for maintaining the SB12 records which include information on amounts delivered, dispensed, and returned/destroyed; for ensuring proper storage**~~	To reflect the changes due to 2-year extension period To revise according to latest pharmacy manual

Section Affected	Original Content	Amended/New Content	Rationale
	received from the Sponsor. Further details will be provided in a guideline for expanded access.	~~conditions are maintained and documented including details of dates, quantities, batch numbers, expiry dates; ensuring the SB12 is only used as specified by the expanded access; for reconciling all SB12 received from the Sponsor. Further details will be provided in a guideline for expanded access.~~ **For the Extension Part, compliance will be assessed by the subject's source documents. All dosing information should be recorded in the subject's source documents.**	
5.3. Concomitant Medication or Treatment	All medication including both prescription and non-prescription drugs, and any procedures undertaken during the study period (from the study informed consent has been signed to EOS/ET visit) should be recorded in the subject's source documents and eCRF. (…) (…)	All medication including both prescription and non-prescription drugs, and any procedures undertaken ~~during the study period (from the study informed consent has been signed to EOS/ET visit)~~ **between 4 weeks prior to Screening (except for immunosuppressant) and end of the Main Part** should be recorded in the subject's source documents and eCRF. (…) (…)	To reflect the changes due to 2-year extension period
5.3.1. Permitted Concomitant Medications or Treatment	The following concomitant medications are allowed if on a stable dose (only for chronic administration) during the study treatment period (up to Week 52). However, for the subject's welfare, medications can be adjusted after discussion between the Investigator and medical monitor and/or Sponsor. (…)	The following concomitant medications are allowed if **given** on a stable dose (only for chronic administration) during the ~~study treatment period (up to Week 52)~~ **Main Part**. However, for the subject's welfare, medications can be adjusted after discussion between the Investigator and medical monitor and/or Sponsor. (…)	To reflect the changes due to 2-year extension period
5.3.2. Prohibited Concomitant Medications	Immunosuppressant except for cyclosporine is prohibited including but not limited to: (…)	Immunosuppressant except for cyclosporine is prohibited **during the Main Part** including but not limited to: (…)	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
or Treatment			
6.1.2. Breakthroug -h Haemolysis	The Investigator and/or designee will record the breakthrough haemolysis in the source documents and eCRF during the study period.	The Investigator and/or designee will record the breakthrough haemolysis in the source documents and eCRF during the ~~**study period**~~ **Main Part**.	To reflect the changes due to 2-year extension period
6.1.3. Transfusions	(…) It is recommended that the transfusion would be performed within 48 hours of the haemoglobin assessment. Transfusion record will be collected from the signing of the informed consent until EOS (or 8 weeks after the last dose of study drug in case of ET). Anaemia-related signs or symptoms, haemoglobin value, number of units of pRBCs will be documented on the source documents and eCRF.	(…) It is recommended that the transfusion would be performed within 48 hours of the haemoglobin assessment. **The decision to give a transfusion may be based on either local or central laboratory haemoglobin values.** Transfusion record will be collected from the signing of the informed consent until ~~**EOS**~~ **end of the Main Part** (or 8 weeks after the last dose of study drug in case of ET **during the Main Part**). Anaemia-related signs or symptoms, haemoglobin value, number of units of pRBCs will be documented on the source documents and eCRF.	To clarify the guide for transfusion To reflect the changes due to 2-year extension period
6.1.4. Major Adverse Vascular Events	The description of MAVEs, anatomical site, method of diagnosis, date of diagnosis, and outcome will be recorded in the source documents and eCRF as medical history and AEs throughout the study period. The MAVE is defined as following; • Thrombophlebitis/deep vein thrombosis, pulmonary embolus, cerebrovascular accident, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, mesenteric vein thrombosis,	The description of MAVEs, anatomical site, method of diagnosis, date of diagnosis, and outcome will be recorded in the source documents and eCRF as ~~**medical history and**~~ AEs ~~**throughout the study period**~~ **during the Main Part**. The MAVE is defined as following; Thrombophlebitis/deep vein thrombosis, pulmonary embolus, ~~**cerebrovascular accident**~~ **cerebral arterial/venous occlusion**, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, mesenteric vein thrombosis, portal vein	To reflect the changes due to 2-year extension period To update MAVE definition

Section Affected	Original Content	Amended/New Content	Rationale
	portal vein thrombosis (Budd-Chiari syndrome), acute mesenteric ischaemia, etc.	thrombosis (Budd-Chiari syndrome), acute mesenteric ischaemia, etc.	
6.1.5. Paroxysmal Nocturnal Haemolgobi-nuria-related Symptoms	The PNH-related symptom questionnaire will be completed by subjects. The questionnaire will be provided to subjects before IP administration at the visits specified in Table 1 and Table 2; at Screening, Weeks 0 (Day 1), 4, 14, 26, 30, 40, and 52. (…)	The PNH-related symptom questionnaire will be completed by subjects. The questionnaire ~~**will be provided to**~~ **should be completed by** subjects before IP administration at the visits specified in Table 1 and Table 2; at Screening, Weeks 0 (Day 1), 4, 14, 26, 30, 40, and 52. (…)	To clarify the study procedure
6.2.1. Adverse Events	All AEs will be recorded from the timing of the signed informed consent until EOS or 8 weeks after the last dose of study drug in case of ET. Further description on monitoring and reporting of AEs is presented in Section 8.	All AEs will be recorded ~~**from the timing of the signed informed consent until EOS or 8 weeks after the last dose of study drug in case of ET. Further description on monitoring and reporting of AEs is presented in**~~ **according to** Section 8.	To reduce redundant wording and simplify the paragraph
6.2.2. Clinical Laboratory Evaluations	(…) If other laboratory tests not listed below are performed as per local practice and found to be abnormal, it is recommended that the Investigator uses their best clinical judgement to determine if the abnormal values would affect subjects' safety while participating in the study. It is highly recommended to test the abnormal parameter by central laboratory as well, if available. (…)	(…) If ~~**other**~~ laboratory tests ~~**not listed below**~~ are performed as per local practice and found to be abnormal, it is recommended that the Investigator uses their best clinical judgement to determine if the abnormal values would affect subjects' safety while participating in the study. It is highly recommended to test the abnormal parameter by central laboratory as well, if available. (…)	To clarify the study procedure
Table 5	**Haematology** • WBC count • RBC count • Haemoglobi	**Haematology** • WBC count • RBC count • **Mean corpuscular haemoglobin**	To add several haematology parameters

Section Affected	Original Content	Amended/New Content	Rationale
	n • Haematocrit • Platelet count • Differential WBC count • Nucleated RBC	• Haemoglobin • Haematocrit • Platelet count • Differential WBC count • Nucleated RBC • **Mean corpuscular haemoglobin (MCH)** • **Mean corpuscular haemoglobin concentration (MCHC)** • **Mean corpuscular volume (MCV)** • **Mean platelet volume (MPV)** • **Red cell distribution width (RDW)**	
Table 5 Footnote	[1] Pregnancy test will performed for women of childbearing potential (serum or urine). Serum pregnancy test will be performed at Screening and EOS and urine pregnancy test will be performed at other applicable visits.	[1] Pregnancy test will **be** performed for women of childbearing potential (serum or urine). Serum pregnancy test will be performed at Screening and ~~**EOS**~~ **8 weeks after the last dose of study drug in case of ET during the Main Part** and urine pregnancy test will be performed at other applicable visits **before study drug administration**.	To reflect the changes due to 2-year extension period and clarify the timeframe
6.3.1. Pharmacokin-etic Assessments	(…) The Sponsor or its designated representative will store PK samples after the end of the clinical study for several years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).	(…) The Sponsor or its designated representative will store PK samples after the end of the clinical study for ~~**several**~~ **maximum 15** years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by	To clarify the sample storage period

Section Affected	Original Content	Amended/New Content	Rationale
		regulatory authorities or failure of first analysis [see Section 10.4]).	
6.3.2. Immunogeni-city assessments	(…) Blood samples should be collected at the same day of study drug administration except for EOS/ET. Subjects' samples may be used for immunogenicity testing assay method development and/or method validation. (…) The Sponsor or its designated representative will store immunogenicity samples after the end of clinical study for several years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).	(…) Blood samples should be collected at the same day of study drug administration except for ~~**EOS/**~~ET **visit**. Subjects' samples may be used for immunogenicity testing assay method development and/or method validation. (…) The Sponsor or its designated representative will store immunogenicity samples after the end of **the** clinical study for ~~**several**~~ **maximum 15** years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).	To reflect the changes due to 2-year extension period To clarify the sample storage period
6.3.3. Pharmacody-namic Assessments	(…) Complement activity will be measured by the validated method by the Sponsor or its designated representative. If the IP administration is delayed for any reasons after blood sample for PD is collected, blood sample for PD analysis should be repeated on actual dosing day and be used for anlaysis. In all cases, the exact date and time of the PD sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for PD samples are described in the laboratory manual. The Sponsor or its designated representative will store PD samples after the end of the clinical study for several years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).	(…) Complement activity will be measured **within the secured sample stability period** by the validated method by the Sponsor or its designated representative. If the IP administration is delayed for any reasons after blood sample for PD is collected, blood sample for PD analysis should be repeated on actual dosing day and be used for ~~**anlaysis**~~ **analysis**. In all cases, the exact date and time of the PD sampling and IP administration must be carefully recorded in the source documents and eCRF. Detail instructions of handling, storage, and shipment for PD samples are described in the laboratory manual. The Sponsor or its designated representative will store PD samples after the end of the clinical study for ~~**several**~~ **maximum 15** years in order to have the possibility to repeat the	To reflect agency comments To clarify the sample storage period

Section Affected	Original Content	Amended/New Content	Rationale
		assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).	
6.3.4. Pharmacoge-netic Assessments	(…) Genetic variants in C5 is associated with poor response to eculizumab since C5 mutation causes the structural change in binding site of eculizumab, resulting in less suppression of complement-mediated haemolysis. These blood samples can be used for extraction and analysis of DNA in order to investigate the mutational status of the subjects including, but not limited to C5 protein. The analysis will be performed during or after the study for subjects who present poor response to study drug, or only if scientifically appropriate and data required. (…)	(…) Genetic variants in C5 is associated with poor response to eculizumab since C5 mutation causes the structural change in binding site of eculizumab, resulting in less suppression of complement-mediated haemolysis. These blood samples can be used for extraction and analysis of DNA in order to investigate the mutational status of the subjects including, but not limited to C5 ~~protein~~. The analysis will be performed during or after the study for subjects who present poor response to study drug, or only if scientifically appropriate and data required. (…) **The Sponsor or its designated representative will store pharmacogenetic samples after the end of the clinical study for maximum 15 years in order to have the possibility to repeat the assay already performed (e.g., re-analysis requested by regulatory authorities or failure of first analysis [see Section 10.4]).**	To add the sample storage period and clarify the meaning
7.1. Study Flow and Visit Schedule	During this study, efficacy, safety, PK, immunogenicity, and PD assessments will be performed. The complete schedule of activities is outlined in Table 1 and Table 2.	During this study, efficacy, safety, PK, immunogenicity, and PD assessments will be performed. The complete schedule of activities is outlined in Table 1**,** ~~**and**~~ Table 2**, and Table 3.**.	To reflect the changes due to 2-year extension period
7.1.1.1. Screening Visit (D−63 to D−22)	• Review of laboratory results - Haematology: Haemoglobin, haematocrit, RBC count, total WBC count including differential count, platelet count, and nucleated RBC	• Review of laboratory results - Haematology: Haemoglobin, haematocrit, RBC count, total WBC count including differential count, platelet count, ~~**and**~~ nucleated RBC**, MCH, MCHC, MCV, MPV, and RDW**	To add several haematology parameters

Section Affected	Original Content	Amended/New Content	Rationale
7.1.1.2. Vaccination for *Neisseria meningitidis*	(…) To reduce the risk of meningococcal infection, all subjects must be vaccinated against Neisseria meningitidis prior to or on Day 1 in accordance with current local guidelines or Soliris® SmPC. Vaccines against serogroups A, C, Y, W135, and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. In case subjects were vaccinated against meningococcal infection within 3 years prior to Day 1, which is properly documented, vaccination for this study could be omitted. For the information including formulation, preparation, and storage of vaccine, refer to the prescribing information in SmPC of vaccine. (…)	(…) To reduce the risk of meningococcal infection, all subjects must be vaccinated against Neisseria meningitidis prior to or on Day 1 in accordance with current local guidelines or Soliris® SmPC. Vaccines against serogroups A, C, Y, W135, and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. In case subjects were vaccinated against meningococcal infection within 3 years prior to Day 1, which is properly documented, vaccination for this study could be omitted. For the information including formulation, preparation, and storage of vaccine, refer to the prescribing information in SmPC of vaccine. **Subjects must be revaccinated later during the study if local guidelines indicate to do so .** (…)	To add guide for re-vaccination
7.1.3. Randomised Treatment Period	**7.1.3. Treatment Period** All procedures and assessments will be performed at the visits specified in Table 1 and Table 2. Samples for laboratory assessments will be collected before IP administration on same day or up to 2 days prior, unless otherwise specified. Laboratory assessments will be performed at central laboratory. Detail instructions of collecting, processing, storing, and shipping for blood samples are described in the laboratory manual. Laboratory reports will be available to the Investigator in a timely manner for clinical management of subjects during treatment period.	**7.1.3. Randomised Treatment Period** **The Investigator should check if the subject does not meet the discontinuation criteria before the initiation of study drug at Day 1.** All procedures and assessments will be performed at the visits specified in Table 1 and Table 2**, ~~Samples for laboratory assessments will be collected~~ and** before IP administration on same day or up to 2 days prior, unless otherwise specified. Laboratory assessments will be performed at central laboratory. Detail instructions of collecting, processing, storing, and shipping for blood samples are described in the laboratory	To reflect the changes due to 2-year extension period and clarify the eligibility re-confirmation process

Section Affected	Original Content	Amended/New Content	Rationale
	(…)	manual. Laboratory reports will be available to the Investigator in a timely manner for clinical management of subjects during **randomised** treatment period. (…)	
7.1.3.1. Randomised Treatment Period 1 (before Cross-over)	**7.1.3.1. Treatment Period 1 (before Cross-over)** • AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded throughout the study period.	**7.1.3.1. Randomised Treatment Period 1 (before Cross-over)** • AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded ~~**throughout the study period**~~.	To reflect the changes due to 2-year extension period
7.1.3.2. Visit 16 (Week 26/Day 183)	Each subject will cross-over from the treatment initially assigned to another treatment at Visit 16 (Week 26) and IPs will be given until Visit 29 (Week 52). (…)	Each subject will cross-over from the treatment initially assigned to another treatment at Visit 16 (Week 26) and IPs will be given until Visit ~~**29**~~ **28** (Week ~~**52**~~ **50**). (…)	To reflect the changes due to 2-year extension period
7.1.3.3. Randomised Treatment Period *2* (*after* Cross-over)	**7.1.3.3. Treatment Period 2 (after Cross-over)** • AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded throughout the study period.	**7.1.3.3. Randomised Treatment Period 2 (after Cross-over)** • AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded ~~**throughout the study period**~~.	To reflect the changes due to 2-year extension period
7.1.3.4. Early Termination Visit	**7.1.3.4. End of Study/Early Termination Visit (Week 60/Day 421)** EOS visit and ET visit is defined as 8 weeks (± 7 days) after the last dose of study drug.	**7.1.3.4. ~~End of Study/~~Early Termination Visit ~~(Week 60/Day 421)~~** ~~**EOS visit and**~~ ET visit is defined as 8 weeks (± 7 days) after the last dose of study drug **during the randomised treatment period**. **This includes when the subject does not enroll into the extension period (i.e., discontinue at Week 52 without study drug administration).**	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
7.1.4. Unscheduled Visits	If a sign or symptom of breakthrough haemolysis is suspected, an unscheduled visit should be occurred and samples should be collected for LDH, PK, and PD assessment for central laboratory at that time. Additionally, other unscheduled visits are permitted at the discretion of the Investigator. Any tests, procedures, or assessments performed at the unscheduled visits must be recorded in the source documents and eCRF.	If a sign or symptom of breakthrough haemolysis is suspected **during randomised treatment period**, an unscheduled visit should be occurred and samples should be collected for LDH, PK, and PD assessment for central laboratory at that time. Additionally, other unscheduled visits are permitted at the discretion of the Investigator. Any tests, procedures, or assessments performed at the unscheduled visits must be recorded in the source documents and eCRF.	To reflect the changes due to 2-year extension period
7.1.5. Extension Period	N/A	**After the randomised treatment period, all subjects who have completed the Main Part will enter the extension period and receive SB12 from Week 52 for 2 years.** • **SB12 administrations by IV infusion for 35 ± 10 minutes (900 mg every 14 ± 2 days)** • **SAEs will be assessed and recorded.** **Discontinuation of study treatment can be decided at the discretion of the Investigator or by subject's consent withdrawal. Specific study procedures are not required for subjects who have discontinued prematurely. SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug (Section 8.2.2).**	To reflect the changes due to 2-year extension period
7.2.1. Subject Discontinuation from Study Treatment	The study treatment must be discontinued for a subject in the event of the following: • Consent withdrawal by subject - (...) • Pregnancy (…) • Other complement inhibitor use The Investigator should discuss with the medical monitor prior to	The study treatment must be discontinued for a subject in the event of the following: • Consent withdrawal by subject - (...) • Pregnancy (…) • **Unblinding the study treatment to the Investigator or subject (i.e., breaking the double-blind).**	To add/revise the discontinuation criteria

Section Affected	Original Content	Amended/New Content	Rationale
	discontinuing a subject's study treatment in case of the following criteria, but not limited to: • Conditions or intercurrent illness that preclude compliance with the protocol in terms of their safety or well-being • Lack of efficacy (e.g., C5 gene polymorphism) **Note**: (…) • Unacceptable toxicity • Lack of subject's compliance (e.g., repeated delay in study treatment and lost to follow-up) **Note**: (…) • Investigator discretion or other reasons	• Other complement inhibitor use ~~The~~ **During the Main Part, the** Investigator should discuss with the medical monitor prior to discontinuing a subject's study treatment in case of the following criteria, but not limited to: • Conditions or intercurrent illness that preclude compliance with the protocol in terms of their safety or well-being • Lack of efficacy (e.g., C5 gene polymorphism) **Note**: (…) • Unacceptable toxicity **including meningococcal infection or anaphylaxis** • **Serious protocol deviations including l**~~L~~ack of subject's compliance (e.g., repeated delay in study treatment and lost to follow-up) **that preclude continuation fot the study** **Note**: (…) • Investigator discretion or other reasons	
7.2.1. Subject Discontinuation from Study Treatment	Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. Only subjects who discontinue from the study at any time post-Day 1 (after the initiation of study drug) will be required to have an ET visit. The data to be collected at the 8 weeks after the last dose of study drug are described in the Section 7.1.3.4. Every effort will be employed to keep subjects who discontinued from study treatment to undertake the scheduled ET visit procedures.	**For the Extension Part, discontinuation of study treatment can be decided at the discretion of the Investigator or by subject's consent withdrawal**. Discontinuation from study treatment does not mean **immediate** discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. ~~**Only subjects**~~ **Subjects** who discontinue from the study at any time post-Day 1 (after the initiation of study drug) will be required to have an ET visit. The data to be collected at the 8 weeks after	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	(…) Any subject who discontinues SB12 or Soliris® should be monitored for at least 8 weeks after last study drug to detect serious haemolysis and other reactions. If serious haemolysis occurs after SB12 or Soliris® discontinuation, consider the following procedures and/or treatments: • Blood transfusion (pRBCs) or exchange transfusion if the PNH RBCs are > 50% of the total RBCs by flow cytometry • Anticoagulation • Corticosteroids • Complement inhibitors According to the Investigator's medical judgement, if complement inhibitor should be administered again due to serious haemolysis and other reactions which occur within 8 weeks after completion of the study treatment with SB12 or Soliris®, the Investigator should discuss with Sponsor for an expanded access of SB12 to such subjects. Accordingly, the Sponsor will provide SB12 to those subjects as an expanded access up to 1 year period, where applicable, in accordance with relevant local regulations and/or law.	the last dose of study drug are described in the Section 7.1.3.4. Every effort will be employed to keep subjects who discontinued from study treatment to undertake the scheduled ET visit procedures. **For the Extension Part, specific study procedures are not required for subjects who have discontinued the study treatment prematurely and the subject will discontinue from the study once the study treatment is permanently discontinued. SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug in such cases (Section 8.2.2). Once study treatment is discontinued during the Extension Part, it is recommended to inform the Sponsor, if occurs.** (…) Any subject who discontinues SB12 or Soliris® should be monitored for at least 8 weeks after last **dose of** study drug to detect serious haemolysis and other reactions. If serious haemolysis occurs after SB12 or Soliris® discontinuation, consider the following procedures and/or treatments: • Blood transfusion (pRBCs) or exchange transfusion if the PNH RBCs are > 50% of the total RBCs by flow cytometry • Anticoagulation • Corticosteroids • Complement inhibitors ~~**According to the Investigator's medical judgement, if complement inhibitor should be administered again due to serious haemolysis and other reactions which occur within 8 weeks after completion of the study treatment with SB12 or**~~	

Section Affected	Original Content	Amended/New Content	Rationale
		~~**Soliris®, the Investigator should discuss with Sponsor for an expanded access of SB12 to such subjects. Accordingly, the Sponsor will provide SB12 to those subjects as an expanded access up to 1 year period, where applicable, in accordance with relevant local regulations and/or law.**~~	
8.1.1. Definition of Adverse Event	(…) All AEs during the period of observation (as specified in Section 8.1.2) including the events that occurred prior to administration of an IP should be reported as an AE in the AE section of the eCRF. (…)	(…) All AEs during the period of observation (as specified in Section 8.1.2) including the events that occurred prior to administration of an IP should be reported as an AE ~~**in the AE section of the eCRF**~~. (…)	To reflect the changes due to 2-year extension period
8.1.1.1. Clinically Significant Abnormality	(…) If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be reported as an AE in the eCRF. If the abnormality can be characterised by a precise clinical term, the clinical term should be reported as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be reported as 'hyperkalaemia.' Observations of the same clinically significant abnormality from visit to visit should not be repeatedly reported as AEs in the eCRF, unless their severity, seriousness, or aetiology changes.	(…) If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be reported as an AE ~~**in the eCRF**~~. If the abnormality can be characterised by a precise clinical term, the clinical term should be reported as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be reported as 'hyperkalaemia~~.~~**'.** Observations of the same clinically significant abnormality from visit to visit should not be repeatedly reported as AEs ~~**in the eCRF**~~, unless their severity, seriousness, or aetiology changes.	To reflect the changes due to 2-year extension period
8.1.2. Period of Observation for Adverse Events	AEs will be reported from the time of signing the ICF until EOS visit or ET visit. However, SAEs must be collected until 10.5 weeks from the last dose of study drug (five half-lives of the study drug). SAEs that occurred after EOS visit or ET visit must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator	AEs will be reported from the time of signing the ICF until ~~**EOS visit**~~ **end of the Main Part (**or ET visit **of the Main Part). Only SAEs will be collected during the Extension Part from start of study treatment at Week 52.** ~~**However, SAEs must be collected until 10.5 weeks from the last dose of study drug (five half-lives of the study drug).**~~ SAEs ~~**that occurred after EOS visit or ET visit**~~ must be	To reflect the changes in AE/SAE reporting period due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	becoming aware of the event (see Section 8.2.2). Unresolved AEs during the study period should be followed up until the EOS and recorded in the eCRF. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. If the subject has an ongoing SAE at the EOS, these cases will be followed until event resolution or stabilisation (see Section 8.2.2).	reported to the Sponsor or its designated representative ~~**using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see**~~ **according to** Section 8.2.2~~**)**~~. Unresolved AEs during the ~~**study period**~~ **Main Part** should be followed up until **end of** the ~~**EOS**~~ **Main Part** and recorded ~~**in the eCRF**~~. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. If the subject has an ongoing SAE at **8 weeks after** the **last dose of study drug** ~~**EOS**~~, these cases will be followed until event resolution or stabilisation (see Section 8.2.2).	
8.1.3. Reporting Adverse Events	(…) If the subject who received the additional SB12 provision according to Section 7.2.1 has an AE, it must be reported to the Sponsor or its designated representative using the paper AE report form. If the AE is classified as an SAE, it must be reported to Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see Section 8.2.2).	(…) ~~**If the subject who received the additional SB12 provision according to Section 7.2.1 has an AE, it must be reported to the Sponsor or its designated representative using the paper AE report form. If the AE is classified as an SAE, it must be reported to Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see Section 8.2.2).**~~	To reflect the changes in AE reporting due to 2-year extension period
8.1.7. Withdrawal due to Adverse Events	Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons and recorded in the source documents and appropriate eCRF section. Subjects withdrawn due to an AE should be followed up until the time point specified in the protocol. When a subject withdraws from the study due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.	Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons and recorded in the source documents and appropriate eCRF section. Subjects withdrawn due to an AE should be followed up until the time point specified in ~~**the protocol**~~ **Section 7.2.1.** When a subject withdraws from the study due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.	To specify the reference section

Section Affected	Original Content	Amended/New Content	Rationale
	(…)	(…)	
8.2.2. Reporting Serious Adverse Events	SAEs must be collected until 10.5 weeks from the last dose of study drug (five half-lives of the study drug). SAEs that occurred at or before EOS visit or ET visit must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred after EOS visit or ET visit must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred from the subject who received the additional SB12 must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. (…) The Investigator is obligated to pursue and provide information to the Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on eCRF. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and	SAEs must be collected until ~~10.5~~ **8** weeks **(± 7 days)** from the last dose of study drug (five half-lives of the study drug). SAEs that occurred ~~**at or before EOS visit**~~ **until end of the Main Part (**or ET visit **of the Main Part)** must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred after ~~**EOS visit or ET visit**~~ **end of the Main Part** must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. ~~**SAEs that occurred from the subject who received the additional SB12 must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event.**~~ (…) The Investigator is obligated to pursue and provide information to the Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. ~~**This information may be more detailed than that captured on eCRF.**~~ In general, this will include a description of the SAE, which should be provided in sufficient detail so as	To align the SAE reporting period with the safety follow-up oeriod (8 weeks) To reflect the changes in SAE reporting due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative. (…)	to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative. (…)	
8.3.1. Meningococ-cal Infection	Due to its mechanism of action, the use of SB12 or Soliris® increases the subject's susceptibility to meningococcal infection (*Neisseria meningitidis*). These subjects might be at risk of disease by serogroups (particularly Y, W135, and X), although meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all subjects will be vaccinated against *Neisseria meningitidis* prior to or on Day 1. However, vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to current local guidelines and/or the discretion of the Investigator on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections have been reported in Soliris®-treated patients. All subjects should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. (…) Subjects should be informed of these signs and symptoms and steps taken to seek medical care immediately. The Investigator must discuss the benefits and risks of SB12 or Soliris® treatment with subjects and provide them with medical	Due to its mechanism of action, the use of SB12 or Soliris® increases the subject's susceptibility to meningococcal infection (*Neisseria meningitidis*). These subjects might be at risk of disease by serogroups (particularly Y, W135, and X), although meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all subjects will be vaccinated against *Neisseria meningitidis* prior to or on Day 1. **Subjects must be revaccinated later during the study if local guidelines indicate to do so.** However, vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to current local guidelines and/or the discretion of the Investigator on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections have been reported in Soliris®-treated patients. All subjects should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. (…) Subjects should be informed of these signs and symptoms and steps taken to seek medical care immediately. **Subjects who are undergoing treatment for serious meningococcal**	To add guide for re-vaccination To clarify the paragraph based on the regulatory document

Section Affected	Original Content	Amended/New Content	Rationale
	instructions.	**infections should discontinue SB12 or Soliris® treatment, and the ~~The~~** Investigator must discuss the benefits and risks of SB12 or Soliris® treatment with subjects and provide them with medical instructions.	
8.3.3. Infusion-related Reaction	Administration of SB12 or Soliris® may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis), though immune reactions within 48 hours of Soliris® administration did not differ from placebo arm in PNH, aHUS, refractory gMG, and other studies conducted with Soliris®. In clinical trials no PNH, aHUS, or refractory gMG patients experienced an infusion reaction which required discontinuation of Soliris®. (…)	Administration of SB12 or Soliris® may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis), though immune reactions within 48 hours of Soliris® administration did not differ from placebo arm in PNH, aHUS, refractory gMG, **NMOSD,** and other studies conducted with Soliris®. In clinical trials no PNH, aHUS, **~~or~~** refractory gMG**, or NMOSD** patients experienced an infusion reaction which required discontinuation of Soliris®. (…)	To refer the latest version of regulatory document
8.5. Emergency Unblinding of Assigned Treatment	(…) If IWRS is not working at emergency situation, Investigator can contact the Sponsor representative to unblind the treatment. Still, the Sponsor representative is not entitled to stall or reject unblinding and provides treatment code to the Investigator in a manual way.	(…) ~~**If IWRS is not working at emergency situation, Investigator can contact the Sponsor representative to unblind the treatment. Still, the Sponsor representative is not entitled to stall or reject unblinding and provides treatment code to the Investigator in a manual way.**~~	Deleted as the process is no longer applicable. IWRS problems can be solved within IWRS framework.
8.6. Independent Data and Safety Monitoring Board	An independent DSMB will be assigned for this study. The DSMB will consist of external experts (i.e., haematologists, clinical pharmacologists, and biostatisticians) and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the DSMB charter and in the DSMB statistical analysis plan (SAP).	An independent DSMB will be assigned for this study. The DSMB will consist of external experts (**~~i.e.,~~ e.g.,** haematologists, clinical pharmacologists, and biostatisticians) and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the DSMB charter and in the DSMB statistical analysis plan (SAP).	To clarify the DSMB activities and safety monitoring process

Section Affected	Original Content	Amended/New Content	Rationale
	In addition, an ongoing blinded review of AEs, including clinical laboratory data will be regularly and continuously undertaken by the Sponsor medical monitor.	In addition, an ongoing blinded review of AEs, including clinical laboratory data will be regularly and continuously undertaken by the Sponsor medical monitor **and pharmacovigilance team**.	
9. Statistical Methods and Data Analysis	Further information on the statistical methods for this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the final clinical study report (CSR). Statistical analysis and reporting will be performed as follows: • **Interim safety analysis for independent DSMB meeting:** A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document and included in the DSMB charter. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP. The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an independent unblind statistician. • **Final CSR:** The final analysis will take place after the last subject completes the procedures at Week 60 or the corresponding visit. All study data will be analysed and reported for final CSR.	Further information on the statistical methods for this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the ~~**final**~~ clinical study report (CSR). Statistical analysis and reporting will be performed as follows: • **Interim safety analysis for independent DSMB meeting:** A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document ~~**and included in the DSMB charter**~~. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP. The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an independent unblind statistician. • ~~**Final**~~ **Main Part CSR:** The ~~**final**~~ analysis will take place after the last subject completes the procedures at Week ~~**60**~~ **52** or the corresponding visit. All study data will be analysed and reported for ~~**final**~~ **the Main Part** CSR. • **Extension Part CSR:** **A separate SAP for analyses of 2-year extension period will be prepared describing the methodology and**	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
		presentation of results. The analysis will take place after the last subject completes the procedures of 2-year extension period.	
9.1. Statistical Hypotheses	(…) [redacted] or those who are in favour of the AUEC of LDH, the treatment effect will be measured by AUEC of LDH between two different time points in each period, from Week 14 to Week 26 and from Week 40 to Week 52. The equivalence will be declared if the 90% confidence interval (CI) of the ratio between treatment effects is entirely contained within the pre-defined equivalence margin of [0.77, 1.29]. [redacted] for those who are in favour of the LDH level at a single time point, equivalence will be declared if the 95% CI of the difference between treatments in LDH level at Week 26 is entirely contained within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study.	(…) [redacted] for those who are in favour of the **time-adjusted** AUEC of LDH, the treatment effect will be measured by **time-adjusted** AUEC of LDH between two different time points in each period, from Week 14 to Week 26 and from Week 40 to Week 52. The equivalence will be declared if the 90% confidence interval (CI) of the ratio between treatment effects is entirely contained within the pre-defined equivalence margin of [0.77, 1.29]. [redacted] for those who are in favour of the LDH level at a single time point, equivalence will be declared if the 95% CI of the difference between treatments in LDH level at Week 26 is entirely contained within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study. **If normal range of LDH is gender specific, the smaller/smallest ULN will be used for the equivalence margin; otherwise ULN is not gender specific, unified ULN will be used for the equivalence margin.**	To clarify the primary endpoint and reflect the local amendment
9.2. Analysis Sets	The following sets will be used for the analyses performed in the study:	The following sets will be used for the analyses performed in the study:	To reflect the changes in analysis set due to 2-year

Section Affected	Original Content	Amended/New Content	Rationale
	• (…) • Safety Set (SAF) consists of all subjects who receive at least one IP during the study period. Subjects will be analysed according to the treatment received. • PK Analysis Set (PKS) consists of all subjects in the SAF who have at least one PK sample analysed. • PD Analysis Set (PDS) consists of all subjects in the SAF who have at least one PD sample analysed.	• (…) • Safety Set **for the Main Part** (SAF**1**) consists of all subjects who receive at least one IP during the ~~**study**~~ **randomised treatment** period. Subjects will be analysed according to the treatment received. • **Safety Set for the Extension Part (SAF2) consists of all subjects who receive at least one IP during the extension period** • PK Analysis Set (PKS) consists of all subjects in the SAF**1** who have at least one PK sample analysed. • PD Analysis Set (PDS) consists of all subjects in the SAF**1** who have at least one PD sample analysed.	extension period
9.4. Analysis of the Primary Objectives	[redacted] for those who are in favour of the AUEC of LDH, the primary efficacy analysis will be performed for the PPS-AUEC using a linear mixed model with treatment, subject, sequence, and period as fixed effects and subject nested within sequence as a random effect. The analysis will be performed with $\log_e$-transformed AUEC of LDH estimating the difference in least squares means and its 90% CI, and back transformation of those values will provide the ratio of geometric means and 90% CI. The equivalence will be declared if the two-sided 90% CI of the ratio of geometric means in AUEC of LDH between SB12 and Soliris® lies within the pre-defined equivalence margin of [0.77, 1.29]. [redacted] for those who are in favour of the LDH level at a single time point, the primary	[redacted] for those who are in favour of the **time-adjusted** AUEC of LDH, the primary efficacy analysis will be performed for the PPS-AUEC using a linear mixed model with treatment~~**, subject**~~, sequence, **period,** and ~~**period**~~ **gender** as fixed effects**,** and subject nested within sequence as a random effect. The analysis will be performed with $\log_e$-transformed **time-adjusted** AUEC of LDH estimating the difference in least squares means and its 90% CI, and back transformation of those values will provide the ratio of geometric means and 90% CI. The equivalence will be declared if the two-sided 90% CI of the ratio of geometric means in **time-adjusted** AUEC of LDH between SB12 and Soliris® lies within the pre-defined equivalence margin of [0.77, 1.29]. [redacted]	To clarify the efficacy analysis and reflect the local amendment

Section Affected	Original Content	Amended/New Content	Rationale
	efficacy analysis will be performed for the PPS-single using a linear mixed model with treatment as a fixed effect. The analysis will be performed with $\log_e$-transformed LDH at Week 26 estimating the difference in least squares means and its 95% CI, and the delta method will be used to provide the mean difference and 95% CI in original scale. The equivalence will be declared if the two-sided 95% CI of the mean difference in LDH level at Week 26 between SB12 and Soliris® lies within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study. (…)	for those who are in favour of the LDH level at a single time point, the primary efficacy analysis will be performed for the PPS-single using a linear mixed model with treatment**, and gender** as a fixed effect. The analysis will be performed with $\log_e$-transformed LDH at Week 26 estimating the difference in least squares means and its 95% CI, and the delta method will be used to provide the mean difference and 95% CI in original scale. The equivalence will be declared if the two-sided 95% CI of the mean difference in LDH level at Week 26 between SB12 and Soliris® lies within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] where ULN of LDH to be specified in the central laboratory specification for this study. (…)	
9.5.1. Efficacy Variable Analyses	As a secondary efficacy endpoint, number of units of pRBCs transfused will be analysed using Wilcoxon rank-sum test for each period. And mean LDH profile will be presented over time.	As a secondary efficacy endpoint, number of units of pRBCs transfused **during the Main Part** will be analysed using Wilcoxon rank-sum test for each period. And mean LDH profile **during the Main Part** will be presented over time.	To reflect the changes due to 2-year extension period
9.5.2. Safety Analyses for the Main Part	**9.5.2. Safety Analyses** (…) All TEAEs and SAEs will be summarised respectively by count and percentage of subjects experiencing events by system organ class, preferred term, treatment sequence, and period. SAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the initiation of study drug will be listed by subject. In addition, infection-related AEs including meningococcal	**9.5.2. Safety Analyses for the Main Part** (…) All TEAEs and SAEs **reported during the randomised treatment period** will be summarised respectively by count and percentage of subjects experiencing events by system organ class, preferred term, treatment sequence, and period. SAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the initiation of study drug will be listed by subject.	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
	infection and other systemic infection, and IRRs will also be summarised. Duration of exposure to IP and number of IV infusion will be summarised by treatment sequence and period with descriptive statistics for the SAF. Prior and concomitant medications, and significant non-drug therapies will be summarised by treatment sequence and period with count and percentage. (…) All safety analyses will be performed using the SAF.	In addition, infection-related AEs including meningococcal infection and other systemic infection, and IRRs **reported during the randomised treatment period** will also be summarised. Duration of exposure to IP and number of IV infusion **during the randomised treatment period** will be summarised by treatment sequence and period with descriptive statistics for the SAF**1**. Prior and concomitant medications, and significant non-drug therapies will be summarised by treatment sequence and period with count and percentage. (…) All safety analyses will be performed using the SAF**1**.	
9.5.3. Safety Analyses for the Extension Part	N/A	**9.5.3. Safety Analyses for the Extension Part** **All reported terms for SAEs will be coded using MedDRA®. SAEs reported during the Extension Part will be summarised and listed for the SAF2.** **Duration of exposure to IP and number of IV infusion during the Extension Part will be summarised with descriptive statistics for the SAF2.**	To reflect the changes due to 2-year extension period
9.5.5. Immunogenicity Analyses	(…) Immunogenicity analyses will be performed using the SAF.	(…) Immunogenicity analyses will be performed using the SAF**1**.	To reflect the changes due to 2-year extension period
9.6. Sample Size	(…) For calculation of the equivalence margin for AUEC of LDH,	(…) For calculation of the equivalence margin for **time-adjusted**	To clarify the primary endpoint

Section Affected	Original Content	Amended/New Content	Rationale
Calculation	mean and coefficient of variation (%CV) were referred from TRIUMPH study. The mean (%CV) of AUEC of LDH at Week 26 is 81140.0 U/L × day (142.45%) and 429874.1 U/L × day (33.49%) for eculizumab and non-eculizumab arms, respectively. From the results in the reference study, mean ratio of AUEC of LDH is estimated to be 0.19 with a 90% CI [0.1308, 0.2724]. The upper limit of the equivalence margin is calculated as [redacted] where it preserves at least [redacted] of eculizumab treatment effect over the placebo, but [redacted] the equivalence margin will be [0.77, 1.29] for the comparison with the 90% CI of mean ratio of AUEC of LDH. (…)	AUEC of LDH, mean and coefficient of variation (%CV) were referred from TRIUMPH study. The mean (%CV) of AUEC of LDH at Week 26 is 81140.0 U/L × day (142.45%) and 429874.1 U/L × day (33.49%) for eculizumab and non-eculizumab arms, respectively. From the results in the reference study, mean ratio of **time-adjusted** AUEC of LDH is estimated to be 0.19 with a 90% CI [0.1308, 0.2724]. The upper limit of the equivalence margin is calculated as [redacted] where it preserves at least [redacted] of eculizumab treatment effect over the placebo, but [redacted] the equivalence margin will be [0.77, 1.29] for the comparison with the 90% CI of mean ratio of AUEC of LDH. (…)	
10.2 Monitoring	(…) (…) Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions. Monitors will verify adherence to the protocol at the investigational site. All PDs will be reported to the Sponsor via the monitoring visit reports. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained. Monitoring visits will be conducted at regular intervals according to ICH-GCP. The monitor will provide written reports to the Sponsor on each occasion they make contact with the Investigator regardless of whether it is by phone or in person. (…)	(…) (…) Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions **for the Main Part and IP infusion date/time at Week 52**. Monitors will verify adherence to the protocol at the investigational site. All PDs will be reported to the Sponsor via the monitoring visit reports. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained. Monitoring visits will be conducted at regular intervals according to ICH-GCP. The monitor will provide written reports to the Sponsor on each occasion they ~~**make**~~ contact with the Investigator regardless of whether it is by phone or in person (…)	To reflect the changes due to 2-year extension period

Section Affected	Original Content	Amended/New Content	Rationale
10.5. Database Management and Coding	Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy. (…)	Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy. **The eCRF will be used only during the Main Part and IP infusion date/time at Week 52.** (…)	To reflect the changes due to 2-year extension period
10.6. Quality Control and Quality Assurance	During the conduct of the study, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH-GCP are being followed. The monitors may review source documents to confirm that the data recorded in the eCRF are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities, the Sponsor's monitors and auditors' direct access to source documents to perform this verification. The investigational site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that the Investigators and their relevant personnel are available during the monitoring visit and possible audits or inspections and that sufficient time is devoted to the process.	During the conduct of the study, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH-GCP are being followed. The monitors may review source documents to confirm that the data recorded ~~**in the eCRF**~~ are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities, the Sponsor's monitors and auditors' direct access to source documents to perform this verification. The investigational site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that the Investigators and their relevant personnel are available during the monitoring visit**,** ~~**and**~~ possible audits **and**/or ~~**inspections**~~ **regulatory inspection(s)** and that sufficient time is devoted to the process.	To reflect the changes due to 2-year extension period
10.7. Protocol Deviation	(…) PDs will be reviewed and confirmed prior to database lock to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock.	(…) PDs will be reviewed and confirmed prior to database lock **for the Main Part** to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock **for the Main Part**.	To reflect the changes due to 2-year extension period

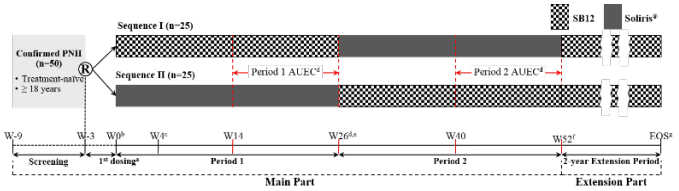
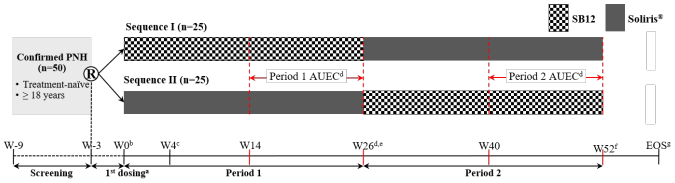
Section Affected	Original Content	Amended/New Content	Rationale
13. References	[10] Soliris® EPAR – Product Information. EMA (Oct 24, 2018). Retrieved Dec 11, 2018 from https://www.ema.europa.eu/documents/product-information/soliris-epar-product-information_en.pdf	[10] Soliris® EPAR – Product Information. EMA (~~**Oct 24, 2018**~~ **Sep 04, 2019**). Retrieved ~~**Dec 11, 2018**~~ **Sep 09, 2019** from https://www.ema.europa.eu/documents/product-information/soliris-epar-product-information_en.pdf	To refer the latest version of regulatory document
13. References	[21] Soliris® Prescribing Information. FDA (Jul 25, 2018). Retrieved Oct 04, 2018 from **https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s047s048lbl.pdf**	[21] Soliris® Prescribing Information. FDA (~~**Jul 25, 2018**~~ **Jun 27, 2019**). Retrieved ~~**Oct 04, 2018**~~ **Jul 09, 2019** from ~~**https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s047s048lbl.pdf**~~ **https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s431lbledt.pdf**	To refer the latest version of regulatory document
Protocol Signature Pages	**Sponsor Representative** Name: [redacted]	**Sponsor Representative** Name: [redacted]	Administrative change
Protocol Signature Pages	**Declaration of the Global Principal/Coordinating Investigator** (…) **Global Principal/Coordinating Investigator**	**Declaration of the ~~Global Principal/~~Coordinating Investigator** (…) **~~Global Principal/~~Coordinating Investigator**	To use the terminology as defined by GCP

Amendment 4: Version 5.0, Aug 21, 2020

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Planned Study Period	After Screening, the duration of study participation will be 52-week randomised treatment period and an extension period of up to 2 years.	After Screening, the duration of study participation will be **58 weeks per subject including ~~52-week randomised treatment period and an extension period of up to 2 years~~. 50 weeks of treatment and 8 weeks of post-treatment follow-up. After completion of study treatment, subjects may be entered into an extended supply of up to 2 years.**	To update study design/process in order to minimize the risk of COVID-19 pandemic
SYNOPSIS Study Design	This multicentre Phase III study is composed of the Main Part and Extension Part. The Main Part is a randomised, double-blind period to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. The Extension Part is an open-label, single-arm, 2-year extension period to provide SB12 in subjects with PNH for an extended duration under an ethical basis. For the Main Part, subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. End of the Main Part is defined as completion of pre-dose activities at Week 52. Subjects who complete the Main Part will enter the Extension Part. For the Extension Part, all subjects will receive SB12 for 2 years.	This ~~**multicentre Phase III study is composed of the Main Part and Extension Part**~~. ~~**The Main Part**~~ is a randomised, **Phase III,** double-blind ~~**period**~~, **multicentre, cross-over study** to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. ~~**The Extension Part is an open-label, single-arm, 2-year extension period to provide SB12 in subjects with PNH for an extended duration under an ethical basis.**~~ ~~**For the Main Part, s**~~**S**ubjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. ~~**End of the Main Part is defined as completion of pre-dose activities at Week 52. Subjects who complete the Main Part will enter the Extension Part. For the Extension Part, all subjects will receive SB12 for 2 years.**~~ **After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2**	To update study design/process in order to minimize the risk of COVID-19 pandemic

		calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.	
SYNOPSIS Eligibiltiy Criteria	**Main Eligibility Criteria:**	**~~Main~~ Eligibility Criteria:**	To update study design/process in order to minimize the risk of COVID-19 pandemic
SYNOPSIS Investigation-al Products	• Dose regimen: 600 mg every 7 days for the first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 14 ± 2 days, thereafter (maintenance phase).	• Dose regimen: 600 mg every 7 days for the first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 14 ± 2 days**~~, thereafter~~ until Week 50** (maintenance phase).	To update study design/process in order to minimize the risk of COVID-19 pandemic
SYNOPSIS Main Criteria for Evaluation	**Secondary endpoints** Efficacy endpoints • LDH profile during the Main Part • Number of units of pRBCs transfused during the Main Part Safety endpoints (…) During the Extension Part, only SAEs will be collected. Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and early termination (ET) • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET	**Secondary endpoints** Efficacy endpoints • LDH profile **~~during the Main Part~~ over time** • Number of units of pRBCs transfused **~~during the Main Part~~ throughout the study period** Safety endpoints (…) **~~During the Extension Part, only SAEs will be collected.~~** Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and early termination (ET) **visit** • Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET **visit**	To update study design/process in order to minimize the risk of COVID-19 pandemic

SYNOPSIS Statistical Methods	Efficacy analyses (…) As a secondary efficacy endpoint, the number of units of pRBCs transfused during the Main Part will be analysed using Wilcoxon rank-sum test for each period. And mean LDH profile during the Main Part will be presented over time. Safety analyses Safety analyses will be performed in the Safety Set for the Main Part (SAF1) and Safety Set for the Extension Part (SAF2). (…) All AE data reported during the Main Part will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term, treatment sequence, and period for the SAF1. SAEs leading to IP discontinuation and treatment-emergent AEs (TEAEs) by causality and severity will be summarised similarly. (…) Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence, period, and time point for the SAF1. (…) All SAEs reported during the Extension Part will be summarised by count and percentage of subjects experiencing events by system organ class and preferred term for the SAF2. PK analyses PK analysis will be performed for the PK Analysis Set (PKS). C_{trough} will be summarised descriptively by treatment sequence, period, and time point.	Efficacy analyses (…) As a secondary efficacy endpoint, the number of units of pRBCs transfused ~~**during the Main Part**~~ **will be summarised descriptively by treatment sequence and treatment sequence within period and** will be analysed using Wilcoxon rank-sum test ~~**for each period**~~. And mean LDH profile ~~**during the Main Part**~~ will be presented over time. Safety analyses Safety analyses will be performed in the Safety Set **(SAF).** ~~**for the Main Part (SAF1) and Safety Set for the Extension Part (SAF2).**~~ All AE data ~~**reported during the Main Part**~~ will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term~~**, treatment sequence, and period for the SAF1**~~. ~~**SAEs**~~ **TEAEs** leading to IP discontinuation and treatment-emergent AEs (TEAEs) by causality and severity will be summarised similarly. (…) Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence~~**, period,**~~ and ~~**time point for the SAF1**~~ **visit**. (…) ~~**All SAEs reported during the Extension Part will be summarised by count and percentage of subjects experiencing events by system organ class and preferred term for the SAF2.**~~ PK analyses	To update study design/process in order to minimize the risk of COVID-19 pandemic To clarify the efficacy/safety analysis

	Immunogenicity analyses The immunogenicity analyses will be performed for the SAF1. ADA and NAb results will be summarised with count and percentage by treatment sequence, period, and time point. The incidence of overall ADA will be summarised by treatment sequence and period. PD analyses PD analysis will be performed for the PD Analysis Set (PDS). The absolute value and change from baseline in terminal complement activities will be summarised by treatment sequence, period, and time point.	PK analysis will be performed for the PK Analysis Set (PKS). C_{trough} will be summarised descriptively by treatment sequence~~, period,~~ and ~~time point~~ **visit**. Immunogenicity analyses The immunogenicity analyses will be performed for the SAF~~1~~. ADA and NAb results will be summarised with count and percentage by treatment sequence~~, period,~~ and ~~time point~~ **visit**. The incidence of overall ADA will be summarised by treatment sequence and period. PD analyses PD analysis will be performed for the PD Analysis Set (PDS). The absolute value and change from baseline in terminal complement activities will be summarised by treatment sequence~~, period,~~ and ~~time point~~ **visit**.	
Figure 1			To update study design/process in order to minimize the risk of COVID-19 pandemic
Figure 1 Footnote	d. From Week 4, 900 mg of SB12 or Soliris® every 14 ± 2 days up to Week 50. During the Extension Part, SB12 will be given to all subjects. (…) f. Completion of pre-dose activities at Week 52 is defined as end of the Main Part. g. EOS is defined as the date of last subject's last visit in the Extension Part.	d. From Week 4, 900 mg of SB12 or Soliris® every 14 ± 2 days up to Week 50. ~~During the Extension Part, SB12 will be given to all subjects.~~ (…) **f.** ~~Completion of pre-dose activities at Week 52 is defined as end of the Main Part.~~ **After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from**	To update study design/process in order to minimize the risk of COVID-19 pandemic

		study treatment and opt to participate in extended supply under an ethical basis. g. EOS is defined as **~~the date of last subject's last visit in the Extension Part.~~ either completion of safety follow-up at Week 58 or completion of ET visit (8 weeks after the last dose of SB12 or Soliris®), which may be up to Week 56.**	
Table 1	Table 1. Schedule of Activities (Main Part: Period 1, before Cross-over)	Table 1. Schedule of Activities (**~~Main Part:~~** Period 1, before Cross-over)	To update study design/process in order to minimize the risk of COVID-19 pandemic
Table 1 Footnote	7. Females of childbearing potential only. Serum pregnancy test at Screening and 8 weeks after the last dose of study drug in case of early termination (ET) during the Main Part; urine pregnancy test at other applicable visits before study drug administration. (…) 14. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET. Blood samples should be collected at the same day of study drug administration except for ET visit. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis. (…) 19. Adverse events (AEs) will be collected from the time of signing the informed consent until end of the Main Part (or	**7.** Females of childbearing potential only. Serum pregnancy test at Screening and 8 weeks after the last dose of study drug in case of early termination (ET) **~~during the Main Part~~**; urine pregnancy test at other applicable visits before study drug administration. (…) 14. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET **visit**. Blood samples should be collected at the same day of study drug administration **~~except for ET visit~~**. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis. (…) 19. Adverse events (AEs) will be collected from the time of signing the informed consent until **~~end of the Main Part~~**	To update study design/process in order to minimize the risk of COVID-19 pandemic

<table>
<tr><td></td><td>8 weeks after the last dose of study drug in case of ET during the Main Part).

20. Previous medications (within 4 weeks prior to Screening except immunosuppressant, 8 weeks prior to Screening for immunosuppressant) will be recorded and concomitant medications will be recorded until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part).

21. Transfusion record will be collected from the time of signing the informed consent until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part).</td><td><s>(or 8 weeks after the last dose of study drug in case of ET during the Main Part)</s> end of study (EOS).

20. Previous medications (within 4 weeks prior to Screening except immunosuppressant, 8 weeks prior to Screening for immunosuppressant) will be recorded and concomitant medications will be recorded until <s>end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part)</s> EOS.

21. Transfusion record will be collected from the time of signing the informed consent until <s>end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part)</s> EOS.</td><td></td></tr>
<tr><td>Table 2</td><td>Table 2. Schedule of Activities (Main Part: Period 2, after Cross-over)</td><td>Table 2. Schedule of Activities (Main Part: Period 2 and Safety Follow-up/ET, after Cross-over)</td><td>To update study design/process in order to minimize the risk of COVID-19 pandemic</td></tr>
<tr><td>Table 2</td><td>
<table>
<tr><th>Assessments</th><th>Study Period</th></tr>
<tr><td>Study Visit</td><td>ET[21]</td></tr>
<tr><td>Week</td><td rowspan="2">8 (±1) weeks after the last dose of study d rug</td></tr>
<tr><td>Day (± Visit Window)</td></tr>
</table>
</td><td>
<table>
<tr><th>Assessments</th><th colspan="2">Study Period</th></tr>
<tr><td>Study Visit</td><td>Safety Follow-up[21]</td><td>ET[22]</td></tr>
<tr><td>Week</td><td>58</td><td rowspan="2">8 (±1) weeks after the last dose of study drug</td></tr>
<tr><td>Day (± Visit Window)</td><td>407 (±7)</td></tr>
<tr><td>Adverse events[17]</td><td colspan="2">Continuously</td></tr>
<tr><td>Previous and concomitant medications[18]</td><td colspan="2">Continuously</td></tr>
<tr><td>Thrombosis record (MAVEs)</td><td colspan="2">Continuously</td></tr>
</table>
</td><td>To update study design/process in order to minimize the risk of COVID-19 pandemic</td></tr>
</table>

		Transfusion record (date and number of pRBCs)[19] — Continuously	
Table 2 Footnote	ET = Early Termination; (…) 4. Females of childbearing potential only. Serum pregnancy test at Screening and 8 weeks after the last dose of study drug in case of ET during the Main Part; urine pregnancy test at other applicable visits before study drug administration. (…) 11. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET. Blood samples should be collected at the same day of study drug administration except for ET visit. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis. (…) 17. AEs will be collected from the time of signing the informed consent until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part). 18. Concomitant medications will be recorded until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part). 19. Transfusion record will be collected from the time of signing the informed consent until end of the Main Part (or	ET = Early Termination; (…) **4.** Females of childbearing potential only. Serum pregnancy test at Screening and 8 weeks after the last dose of study drug in case of ET ~~**during the Main Part**~~; urine pregnancy test at other applicable visits before study drug administration. (…) 11. Blood sample for immunogenicity assay will be taken prior to dosing at Weeks 0, 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET **visit**. Blood samples should be collected at the same day of study drug administration ~~**except for ET visit**~~. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity assay, blood sample should be re-collected on actual dosing day and be used for analysis. (…) 17. AEs will be collected from the time of signing the informed consent until ~~**end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part)**~~ **EOS**. 18. Concomitant medications will be recorded until ~~**end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part)**~~ **EOS**. 19. Transfusion record will be collected from the time of signing the informed consent until ~~**end of the Main Part**~~	To update study design/process in order to minimize the risk of COVID-19 pandemic

	8 weeks after the last dose of study drug in case of ET during the Main Part). 20. End of the Main Part is defined as completion of pre-dose activities at Week 52. 21. ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®, which may be up to Week 58.	~~(or 8 weeks after the last dose of study drug in case of ET during the Main Part)~~ **EOS**. 20. ~~End of the Main Part is defined as completion of pre-dose activities at Week 52~~. **After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis. The Week 52 activities must be completed prior to initiation of extended supply. Subjects who are eligible to participate should provide separate informed consent prior to enter an extended supply of SB12**. 21. ~~ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®, which may be up to Week 58.~~ **Safety follow-up will be done at Week 58 for subjects who complete the study treatments until Week 50, regardless whether subject receives extended supply of SB12 or not. These activities will be conducted either by visit or by phone call on subjects' preference.** **22. ET visit is defined as 8 weeks after the last dose of SB12 or Soliris®, which may be up to Week 56. Subjects who discontinue from the study at any time post-Day 1 (after the initiation of study drug) before completion of last study treatment at Week 50 will be required to have an ET visit.**	
Table 3	**Table 7. Schedule of Activities (Extension Part: 2-year Extension Period)**	~~Table 8. Schedule of Activities (Extension Part: 2-year Extension Period)~~	To update study design/process in order to minimize the risk of COVID-

	Assessments / **Study Period** **Week** 52 54 … 152 154 **End of the Extension Part**[3] SB12 administration[1] ✓ ✓ … ✓ ✓ Serious adverse events[2] Continuously 1. From Week 52, SB12 will be administered bi-weekly via IV infusion for 35 ± 10 minutes for all subjects. 2. Only SAEs will be collected during the Extension Part from start of study treatment at Week 52. 3. End of the Extension Part is defined as 8 weeks after the last dose of SB12. Prematurely discontinued subjects do not require any specific study procedures as done in the Main Part.	~~**Assessments**~~ / ~~**Study Period**~~ ~~**Week** 52 54 … 152 154 **End of the Extension Part**[3]~~ ~~SB12 administration[1] ✓ ✓ … ✓ ✓~~ ~~Serious adverse events[2] Continuously~~ ~~1. From Week 52, SB12 will be administered bi-weekly via IV infusion for 35 ± 10 minutes for all subjects.~~ ~~2. Only SAEs will be collected during the Extension Part from start of study treatment at Week 52.~~ ~~3. End of the Extension Part is defined as 8 weeks after the last dose of SB12. Prematurely discontinued subjects do not require any specific study procedures as done in the Main Part.~~	19 pandemic
LIST OF ABBREVIA-TIONS	N/A N/A SAF1 Safety Set for the Main Part SAF2 Safety Set for the Extension Part	**COVID-19 Coronavirus Disease 2019** **DSUR Development Safety Update Report** **IgG Immunoglobulin G** **PC Product Complaints** **PSUR Periodic Safety Update Report**	To revise/add abbreviations according to updated contents

		SAF~~1~~ Safety ~~**Set for the Main Part**~~ ~~**SAF2**~~ ~~**Safety Set for the Extension Part**~~	
LIST OF STUDY STAFF	Clinical Project Manager [redacted] Clinical Development Assistant [redacted] Statistician [redacted] Project Safety Lead [redacted]	Clinical Project Manager [redacted] **Clinical Research Physician** [redacted] Clinical ~~**Development Assistant**~~ **Research Scientist** [redacted] Statistician [redacted] Project Safety Lead [redacted]	Administrative change
1.2. Overview of SB12	(…) SB12 and Soliris® have identical primary structure and the active substance for both products is eculizumab, a humanised monoclonal antibody (IgG2/4 kappa immunoglobulin) that binds to the human C5 complement protein with high affinity. Binding to this protein blocks its cleavage into C5a and C5b, thereby inhibiting terminal complement-mediated intravascular haemolysis.	(…) SB12 and Soliris® have identical primary structure and the active substance for both products is eculizumab, a humanised monoclonal antibody (**immunoglobulin G[**IgG**]**2/4 kappa ~~**immunoglobulin**~~) that binds to the human C5 complement protein with high affinity. Binding to this protein blocks its cleavage into C5a and C5b, thereby inhibiting terminal complement-mediated intravascular haemolysis.	To refer the latest information

	(…) According to the guideline International Conference on Harmonisation Q6B, characterisation of a biological therapeutic must involve its physicochemical properties, biological activities, purity, impurities, and quantity. (…)	(…) According to the guideline International ~~**Conference on**~~ **Council for** Harmonisation **(ICH)** Q6B, characterisation of a biological therapeutic must involve its physicochemical properties, biological activities, purity, impurities, and quantity. (…)	
1.5.1. Known Potential Risks	According to Soliris® Summary of Product Characteristics (SmPC) [10], supportive safety data were collected from 30 completed and one ongoing clinical studies that included 1,503 patients exposed to eculizumab in complement-mediated disease populations, including PNH, aHUS, refractory gMG and NMOSD. The most common adverse reaction was headache (occurred mostly in the initial phase) and of all meningococcal infections the most frequently reported serious adverse reaction was meningococcal sepsis.	According to Soliris® Summary of Product Characteristics (SmPC) [10], supportive safety data were collected from ~~**30**~~ **31** completed ~~**and one ongoing**~~ clinical studies that included 1,503 patients exposed to eculizumab in complement-mediated disease populations, including PNH, aHUS, refractory gMG and NMOSD. The most common adverse reaction was headache (occurred mostly in the initial phase) and ~~**of all meningococcal infections**~~ the most frequently reported serious adverse reaction was meningococcal sepsis. (…)	To refer the latest version of regulatory document
2.2.2. Secondary Endpoints	**Secondary endpoints** Efficacy endpoints • LDH profile during the Main Part • Number of units of pRBCs transfused during the Main Part Safety endpoints (…) During the Extension Part, only SAEs will be collected. Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and early termination (ET)	**Secondary endpoints** Efficacy endpoints • LDH profile ~~**during the Main Part**~~ **over time** • Number of units of pRBCs transfused ~~**during the Main Part**~~ **throughout the study period** Safety endpoints (…) ~~**During the Extension Part, only SAEs will be collected.**~~ Immunogenicity endpoints • Incidence of anti-drug antibodies (ADAs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and early termination (ET) **visit**	To update study design/process in order to minimize the risk of COVID-19 pandemic

	• Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET	• Incidence of neutralising antibodies (NAbs) at Weeks 0 (Day 1), 2, 4, 6, 10, 14, 18, 22, 26, 28, 30, 32, 36, 40, 44, 48, 52, and ET **visit**	
3.1. Overview of Study Design	This multicentre Phase III study is composed of the Main Part and Extension Part. The Main Part is a randomised, double-blind period to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. The Extension Part is an open-label, single-arm, 2-year extension period to provide SB12 in subjects with PNH for an extended duration under an ethical basis. Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects randomly assigned to treatment with SB12 or Soliris® will receive 600 mg of eculizumab IV every week for first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter. Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. SB12 or Soliris® will be given until Week 50. End of the Main Part is defined as completion of pre-dose activities at Week 52. Subjects who complete the Main Part will enter the Extension Part. For the Extension Part, all subjects will receive SB12 for 2 years. Details of assessment that will be conducted and treatment that will be administered are presented in, Table 1, Table 2, and Table 3. The last assessment for the Main Part will be performed at pre-dose of Week 52 or 8 weeks after the last dose of SB12 or Soliris® in case of ET during the Main Part. The last assessment for the Extension Part will be performed at 8 weeks after the last dose of	This ~~**multicentre Phase III study is composed of the Main Part and Extension Part.**~~ ~~**The Main Part**~~ is a randomised, **Phase III,** double-blind ~~**period**~~ **, multicentre, cross-over study** to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. ~~**The Extension Part is an open-label, single-arm, 2-year extension period to provide SB12 in subjects with PNH for an extended duration under an ethical basis.**~~ Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects randomly assigned to treatment with SB12 or Soliris® will receive 600 mg of eculizumab IV every week for first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter. Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. SB12 or Soliris® will be given until Week 50. ~~**End of the Main Part is defined as completion of pre-dose activities at Week 52. Subjects who complete the Main Part will enter the Extension Part.**~~ ~~**For the Extension Part, all subjects will receive SB12 for 2 years.**~~ Details of assessment that will be conducted and treatment that will be administered are presented in~~**,**~~ Table 1 **and** Table 2~~**, and Table 3**~~. The last assessment ~~**for the Main Part**~~ will be performed at ~~**pre-dose of**~~ Week ~~**52**~~ 58 or 8 weeks after the last	To update study design/process in order to minimize the risk of COVID-19 pandemic

	SB12.	dose of SB12 or Soliris® in case of ET ~~**during the Main Part**~~. ~~**The last assessment for the Extension Part will be performed at 8 weeks after the last dose of SB12.**~~ After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.	
3.3. Duration of Study Participation	After Screening, the duration of study participation will be 52-week randomised treatment period and an extension period of up to 2 years.	After Screening, the duration of study participation will be **58 weeks per subject including** ~~**52-week randomised treatment period and an extension period of up to 2 years**~~. **50 weeks of treatment and 8 weeks of post-treatment follow-up. After completion of study treatment, subjects may be entered into an extended supply of up to 2 years.**	To update study design/process in order to minimize the risk of COVID-19 pandemic
3.5. End of Study Definition	A subject is considered to have completed the each part of study if he or she has completed all study treatment including the last visit or the last scheduled procedure shown in Table 2 and Table 3. The end of the Main Part is defined as completion of pre-dose activities at Week 52 for subjects. The end of the Extension Part is defined as 8 weeks after the last dose of SB12. The end of study (EOS) is defined as the date of last subject's last visit in the Extension Part.	A subject is considered to have completed the ~~**each part of**~~ study if he or she has completed all study treatment ~~**including**~~ **and** the last visit or the last scheduled procedure shown in Table 2 ~~**and Table 3**~~. The ~~**end of the Main Part**~~ **end of study (EOS)** is defined as completion of ~~**pre-dose activities**~~ **safety follow-up** at Week ~~**52 for subjects. The end of the Extension Part is defined as**~~ **58 or completion of ET visit** (8 weeks after the last dose of SB12 **or Soliris®). The end of this clinical study is defined as completion of the last subject's EOS.** ~~**The end of study (EOS) is defined as the date of last subject's last visit in the Extension Part.**~~	To update study design/process in order to minimize the risk of COVID-19 pandemic
4.4. Screen Failures and Re-screening	N/A	**During Coronavirus Disease 2019 (COVID-19) pandemic circumstances, eligibility may not be confirmed at Screening due to unexpected COVID-19 related restrictions. These cases may fall into screen failures due to out of 42 days screening window or consent withdrawal related with COVID-19 concern, etc. These will be considered as**	To implement recommendations belonging to DDLs issued to address COVID-19 pandemic

		technical issue so that re-screening is applicable after COVID-19 related restrictions are relieved.	
5.1.1. Dosing and Treatment Schedule	Dosing and treatment schedule of SB12 or Soliris® should be kept as follows: • 600 mg every 7 ± 2 days for the first 4 weeks, followed by • 900 mg for the fifth dose 7 ± 2 days later, then • 900 mg every 14 ± 2 days thereafter (…) The subject receiving SB12 or Soliris® therapy may require dosing interval adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. For subjects whose dosing interval is adjusted to 12 days in Period 1 of the Main Part, it is recommended that the dosing interval be switched back to 14 days after switching IP at Week 26. Once the above event has occurred, the Investigator should inform the medical monitor and/or Sponsor immediately during the Main Part, but in the Extension Part, the event can be managed at the discretion of the Investigator.	**SB12 or Soliris® will be administered up to Week 50 (a total of 28 administrations of IP) unless they are early discontinued from study treatment.** Dosing and treatment schedule ~~**of SB12 or Soliris®**~~ should be kept as follows: • 600 mg every 7 ± 2 days for the first 4 weeks, followed by • 900 mg for the fifth dose 7 ± 2 days later, then • 900 mg every 14 ± 2 days thereafter (…) The subject receiving SB12 or Soliris® therapy may require dosing interval adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. **If a 12 or 13 day dosing interval conflicts with administrative schedules (e.g., holidays or weekends) but a shortened dosing interval is considered necessary for safety of subject, consultation with medical monitor (or Sponsor) is recommended**. For subjects whose dosing interval is adjusted to 12 days in Period 1 ~~**of the Main Part**~~, it is recommended that the dosing interval be switched back to 14 days after switching IP at Week 26. Once the above event has occurred, the Investigator should inform the medical monitor and/or Sponsor immediately ~~**during the Main Part, but in the Extension**~~	To update study design/process in order to minimize the risk of COVID-19 pandemic To add clarification of dosing interval adjustement to address DSMB feedback

		~~**Part, the event can be managed at the discretion of the Investigator**~~.	
5.1.3. Blinding	The Main Part of this study is double-blinded. Subjects, Investigators, and other study personnel will remain blinded to the treatment sequence assignment until end of the Main Part after randomisation. (…)	~~**The Main Part of t**~~**T**his study is double-blinded. Subjects, Investigators, and other study personnel will remain blinded to the treatment sequence assignment ~~**until end of the Main Part**~~ **throughout the study period** after randomisation. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
5.2.1. Identify of Investigation-al Product	The IPs will be supplied to investigational site in one carton containing a single vial. These IP vials will be packed and labelled in a double-blinded manner for the Main Part. For the Extension Part, SB12 will also be supplied to investigational site in one carton containing a single vial. These SB12 vials will be packed and labelled using open label for the Extension Part. (…)	The IPs will be supplied to investigational site in one carton containing a single vial. These IP vials will be packed and labelled in a double-blinded manner for ~~**the Main Part. For the Extension Part, SB12 will also be supplied to investigational site in one carton containing a single vial. These SB12 vials will be packed and labelled using open label for the Extension Part**~~ **clinical use**. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
5.2.2. Formulation, Packaging, and Labelling	(…) Packaging and labelling of SB12 or Soliris® will follow standard operating procedure (SOP) of the manufacturing site and regulatory requirements in each country, as well as will be in accordance with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP). SB12 or Soliris® will be pre-packaged and labelled in a double-blinded form for the Main Part. For the Extension Part, SB12 will be packaged and labelled using open label. (…)	(…) Packaging and labelling of SB12 or Soliris® will follow standard operating procedure (SOP) of the manufacturing site and regulatory requirements in each country, as well as will be in accordance with ~~**International Council for Harmonisation (**~~ICH~~)**~~-Good Clinical Practice (GCP). SB12 or Soliris® will be pre-packaged and labelled in a double-blinded form ~~**for the Main Part. For the Extension Part, SB12 will be packaged and labelled using open label**~~. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
5.2.5. Treatment Compliance and Investigation-al Product	(…) (…) At the completion or termination of each part of the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their	(…) (…) At the completion or termination of ~~**each part of**~~ the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their	To update study design/process in order to minimize the risk of COVID-19 pandemic

Accountabili-ty	resolution must be documented. (…) For the Extension Part, compliance will be assessed by the subject's source documents. All dosing information should be recorded in the subject's source documents.	resolution must be documented. (…) ~~**For the Extension Part, compliance will be assessed by the subject's source documents. All dosing information should be recorded in the subject's source documents.**~~	
5.3. Concomitant Medication or Treatment	All medication including both prescription and non-prescription drugs, and any procedures undertaken between 4 weeks prior to Screening (except for immunosuppressant) and end of the Main Part should be recorded in the subject's source documents and eCRF. (…) (…)	All medication including both prescription and non-prescription drugs, and any procedures undertaken between 4 weeks prior to Screening (except for immunosuppressant) and ~~**end of the Main Part**~~ **EOS** should be recorded in the subject's source documents and eCRF. (…) (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
5.3.1. Permitted Concomitant Medications or Treatment	The following concomitant medications are allowed if given on a stable dose (only for chronic administration) during the Main Part. However, for the subject's welfare, medications can be adjusted after discussion between the Investigator and medical monitor and/or Sponsor. (…)	The following concomitant medications are allowed if given on a stable dose (only for chronic administration) during the ~~**Main Part**~~ **study period**. However, for the subject's welfare, medications can be adjusted ~~**after**~~ **under** discussion between the Investigator and medical monitor and/or Sponsor. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic To clarify the meaning regarding permitted medications dose adjustement for subjects' welfare
5.3.2. Prohibited Concomitant Medications or Treatment	Immunosuppressant except for cyclosporine is prohibited during the Main Part including but not limited to: (…)	Immunosuppressant except for cyclosporine is prohibited during the ~~**Main Part**~~ **study period from randomisation** including but not limited to: (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic

6.1.2. Breakthroug -h Haemolysis	The Investigator and/or designee will record the breakthrough haemolysis in the source documents and eCRF during the Main Part. (…)	The Investigator and/or designee will record the breakthrough haemolysis in the source documents and eCRF during the ~~**Main Part**~~ **study period**. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
6.1.3. Transfusions	(…) Transfusion record will be collected from the signing of the informed consent until end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part). Anaemia-related signs or symptoms, haemoglobin value, number of units of pRBCs will be documented on the source documents and eCRF.	(…) Transfusion record will be collected from the signing of the informed consent until ~~**end of the Main Part (or 8 weeks after the last dose of study drug in case of ET during the Main Part)**~~ **EOS**. Anaemia-related signs or symptoms, haemoglobin value, number of units of pRBCs will be documented on the source documents and eCRF.	To update study design/process in order to minimize the risk of COVID-19 pandemic
6.1.4. Major Adverse Vascular Events	The description of MAVEs, anatomical site, method of diagnosis, date of diagnosis, and outcome will be recorded in the source documents and eCRF as AEs during the Main Part. (…)	The description of MAVEs, anatomical site, method of diagnosis, date of diagnosis, and outcome will be recorded in the source documents and eCRF as AEs during the ~~**Main Part**~~ **study period**. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
6.2.2. Clinical Laboratory Evaluations	N/A	**During COVID-19 pandemic circumstances, it may be unable to get central laboratory values in time due to COVID-19 related restrictions. For those cases, local laboratory will be allowed in addition to central laboratory for scheduled visit after randomisation until COVID-19 restrictions are relieved under discussion with Sponsor**.	To implement recommendations belonging to DDLs issued to address COVID-19 pandemic
Table 4 Footnote	[1] Pregnancy test will be performed for women of childbearing potential (serum or urine). Serum pregnancy test will be performed at Screening and 8 weeks after the last dose of study drug in case of ET during the Main Part and urine pregnancy test will be performed at other applicable visits before study drug administration.	[1] Pregnancy test will be performed for women of childbearing potential (serum or urine). Serum pregnancy test will be performed at Screening and 8 weeks after the last dose of study drug in case of ET ~~**during the Main Part**~~ and urine pregnancy test will be performed at other applicable visits before study drug administration.	To update study design/process in order to minimize the risk of COVID-19 pandemic

6.3.2. Immunogeni-city assessments	(…) Blood samples should be collected at the same day of study drug administration except for ET visit. (…) (…)	(…) Blood samples should be collected at the same day of study drug administration ~~**except for ET visit**~~. (…) (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.1. Study Flow and Visit Schedule	During this study, efficacy, safety, PK, immunogenicity, and PD assessments will be performed. The complete schedule of activities is outlined in Table 1, Table 2, and Table 3.	During this study, efficacy, safety, PK, immunogenicity, and PD assessments will be performed. The complete schedule of activities is outlined in Table 1~~,~~ **and** Table 2~~, and Table 3~~.	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.1.2. Randomisati-on	N/A	**During COVID-19 pandemic circumstances, Day 1 (1st dosing) may not be started within 21 days of randomisation due to unexpected COVID-19 related restrictions. In such cases, the subject will be monitored for safety per Investigator's discretion. Day 1 will be started after the COVID-19 related restrictions are relieved.**	To implement recommendations belonging to DDLs issued to address COVID-19 pandemic
7.1.3. Treatment Period	**7.1.3. Randomised Treatment Period** (…) Laboratory assessments will be performed at central laboratory. Detail instructions of collecting, processing, storing, and shipping for blood samples are described in the laboratory manual. Laboratory reports will be available to the Investigator in a timely manner for clinical management of subjects during randomised treatment period. (…)	**7.1.3. ~~Randomised~~ Treatment Period** (…) Laboratory assessments will be performed at central laboratory. Detail instructions of collecting, processing, storing, and shipping for blood samples are described in the laboratory manual. Laboratory reports will be available to the Investigator in a timely manner for clinical management of subjects during ~~**randomised**~~ treatment period. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.1.3.1. Randomised Treatment Period 1 (before	**7.1.3.1. Randomised Treatment Period 1 (before Cross-over)**	**7.1.3.1. ~~Randomised~~ Treatment Period 1 (before Cross-over)**	To update study design/process in order to minimize the risk of COVID-

Cross-over)			19 pandemic
7.1.3.3. Randomised Treatment Period 2 (after Cross-over)	**7.1.3.3. Randomised Treatment Period 2 (after Cross-over)**	**7.1.3.3. ~~Randomised~~ Treatment Period 2 (after Cross-over)**	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.1.3.4. Early Termination Visit	N/A	**7.1.3.4. Safety Follow-up (Week 58/Day 407)** **Safety follow-up will be done at Week 58 (± 7 days) which is 8 weeks after the last dose of SB12 or Soliris® for subjects who complete the study treatments until Week 50, regardless whether subject receives extended supply of SB12 or not to ensure subject's safety. These activities will be conducted either by visit or by phone call based on subjects' preference.** • **AEs, concomitant medications, MAVEs, and transfusion record will be assessed and recorded.**	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.1.3.5. Early Termination Visit	**7.1.3.4. Early Termination Visit** ET visit is defined as 8 weeks (± 7 days) after the last dose of study drug during the randomised treatment period. This includes when the subject does not enroll into the extension period (i.e., discontinue at Week 52 without study drug administration). (…)	**~~7.1.3.4.~~ 7.1.3.5. Early Termination Visit** ET visit is defined as 8 weeks (± 7 days) after the last dose of **~~study drug~~ SB12 or Soliris®** during the **~~randomised~~** treatment period. **~~This includes when the subject does not enroll into the extension period (i.e., discontinue at Week 52 without study drug administration).~~** (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.1.4. Unscheduled Visits	If a sign or symptom of breakthrough haemolysis is suspected during randomised treatment period, an unscheduled visit should be occurred and samples should be collected for LDH, PK, and	If a sign or symptom of breakthrough haemolysis is suspected **~~during randomised treatment period~~**, an unscheduled visit	To update study design/process in order to minimize the risk of COVID-

	PD assessment for central laboratory at that time. (…)	should be occurred and samples should be collected for LDH, PK, and PD assessment for central laboratory at that time. (…)	19 pandemic
7.1.5. Extension Period	**7.1.5. Extension Period** After the randomised treatment period, all subjects who have completed the Main Part will enter the extension period and receive SB12 from Week 52 for 2 years. • SB12 administrations by IV infusion for 35 ± 10 minutes (900 mg every 14 ± 2 days) • SAEs will be assessed and recorded. Discontinuation of study treatment can be decided at the discretion of the Investigator or by subject's consent withdrawal. Specific study procedures are not required for subjects who have discontinued prematurely. SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug (Section 8.2.2).	~~**7.1.5. Extension Period**~~ ~~**After the randomised treatment period, all subjects who have completed the Main Part will enter the extension period and receive SB12 from Week 52 for 2 years.**~~ ~~• SB12 administrations by IV infusion for 35 ± 10 minutes (900 mg every 14 ± 2 days)~~ ~~• SAEs will be assessed and recorded.~~ ~~**Discontinuation of study treatment can be decided at the discretion of the Investigator or by subject's consent withdrawal. Specific study procedures are not required for subjects who have discontinued prematurely. SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug (Section 8.2.2).**~~	To update study design/process in order to minimize the risk of COVID-19 pandemic
7.2.1. Subject Discontinuation from Study Treatment	(…) During the Main Part, the Investigator should discuss with the medical monitor prior to discontinuing a subject's study treatment in case of the following criteria, but not limited to: (…) For the Extension Part, discontinuation of study treatment can be decided at the discretion of the Investigator or by subject's consent withdrawal. Discontinuation from study treatment does not mean immediate discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. Subjects	(…) ~~**During the Main Part, t**~~The Investigator should discuss with the medical monitor prior to discontinuing a subject's study treatment in case of the following criteria, but not limited to: (…) ~~**For the Extension Part, discontinuation of study treatment can be decided at the discretion of the Investigator or by subject's consent withdrawal.**~~ Discontinuation from study treatment does not mean immediate discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. Subjects	To update study design/process in order to minimize the risk of COVID-19 pandemic

	who discontinue from the study at any time post-Day 1 (after the initiation of study drug) will be required to have an ET visit. The data to be collected at the 8 weeks after the last dose of study drug are described in the Section 7.1.3.4. Every effort will be employed to keep subjects who discontinued from study treatment to undertake the scheduled ET visit procedures. For the Extension Part, specific study procedures are not required for subjects who have discontinued the study treatment prematurely and the subject will discontinue from the study once the study treatment is permanently discontinued. SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug in such cases (Section 8.2.2). Once study treatment is discontinued during the Extension Part, it is recommended to inform the Sponsor, if occurs. (…)	who discontinue from the study at any time post-Day 1 (after the initiation of study drug) **before completion of last study treatment at Week 50** will be required to have an ET visit. The data to be collected at the 8 weeks after the last dose of study drug are described in the Section ~~7.1.3.4~~ **7.1.3.5**. Every effort will be employed to keep subjects who discontinued from study treatment to undertake the scheduled ET visit procedures. ~~**For the Extension Part, specific study procedures are not required for subjects who have discontinued the study treatment prematurely and the subject will discontinue from the study once the study treatment is permanently discontinued. SAEs must be collected until 8 weeks (± 7 days) from the last dose of study drug in such cases (Section 8.2.2). Once study treatment is discontinued during the Extension Part, it is recommended to inform the Sponsor, if occurs**~~. (…)	
8.1.2. Period of Observation for Adverse Events	AEs will be reported from the time of signing the ICF until end of the Main Part (or ET visit of the Main Part). Only SAEs will be collected during the Extension Part from start of study treatment at Week 52. (…) Unresolved AEs during the Main Part should be followed up until end of the Main Part and recorded. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. If the subject has an ongoing SAE at 8 weeks after the last dose of study drug, these cases will be followed until event resolution or stabilisation (see Section 8.2.2).	AEs will be reported from the time of signing the ICF until ~~**end of the Main Part (or ET visit of the Main Part). Only SAEs will be collected during the Extension Part from start of study treatment at Week 52**~~ **EOS**. (…) Unresolved AEs during the ~~**Main Part**~~ **study period** should be followed up until ~~**end of the Main Part and recorded**~~ **EOS**. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation. If the subject has an ongoing SAE at ~~**8 weeks after the last dose of study drug**~~ **EOS**, these cases will be followed until event resolution or stabilisation (see Section 8.2.2).	To update study design/process in order to minimize the risk of COVID-19 pandemic

8.2.2. Reporting Serious Adverse Events	(…) SAEs that occurred until end of the Main Part (or ET visit of the Main Part) must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred after end of the Main Part must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. (…)	(…) SAEs that occurred ~~**until end of the Main Part (**~~ **at** or ~~**ET visit of the Main Part)**~~ **before EOS** must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. SAEs that occurred after ~~**end of the Main Part**~~ **EOS** must be reported to the Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
9. Statistical Methods and Data Analysis	Statistical analysis and reporting will be performed as follows: (…) • **Main Part CSR:** The analysis will take place after the last subject completes the procedures at Week 52 or the corresponding visit. All study data will be analysed and reported for the Main Part CSR. • **Extension Part CSR:** A separate SAP for analyses of 2-year extension period will be prepared describing the methodology and presentation of results. The analysis will take place after the last subject completes the procedures of 2-year extension period.	Statistical analysis and reporting will be performed as follows: (…) • ~~**Main Part**~~ **CSR:** The analysis will take place after the last subject completes the procedures at Week ~~**52**~~ **58** or the corresponding visit. All study data will be analysed and reported for ~~**the Main Part**~~ CSR. • ~~**Extension Part CSR:**~~ ~~**A separate SAP for analyses of 2-year extension period will be prepared describing the methodology and presentation of results. The analysis will take place after the last subject completes the procedures of 2-year extension period.**~~	To update study design/process in order to minimize the risk of COVID-19 pandemic

9.2. Analysis Sets	The following sets will be used for the analyses performed in the study: • (…) • Safety Set for the Main Part (SAF1) consists of all subjects who receive at least one IP during the randomised treatment period. Subjects will be analysed according to the treatment received. • Safety Set for the Extension Part (SAF2) consists of all subjects who receive at least one IP during the extension period. • PK Analysis Set (PKS) consists of all subjects in the SAF1 who have at least one PK sample analysed. • PD Analysis Set (PDS) consists of all subjects in the SAF1 who have at least one PD sample analysed.	The following sets will be used for the analyses performed in the study: • (…) • Safety Set ~~**for the Main Part**~~ (SAF~~**1**~~) consists of all subjects who receive at least one IP during the ~~**randomised treatment**~~ **study** period. Subjects will be analysed according to the treatment received. • ~~**Safety Set for the Extension Part (SAF2) consists of all subjects who receive at least one IP during the extension period.**~~ • PK Analysis Set (PKS) consists of all subjects in the SAF~~**1**~~ who have at least one PK sample analysed. • PD Analysis Set (PDS) consists of all subjects in the SAF~~**1**~~ who have at least one PD sample analysed.	To update study design/process in order to minimize the risk of COVID-19 pandemic
9.5.1. Efficacy Variable Analyses	As a secondary efficacy endpoint, number of units of pRBCs transfused during the Main Part will be analysed using Wilcoxon rank-sum test for each period. And mean LDH profile during the Main Part will be presented over time.	As a secondary efficacy endpoint, number of units of pRBCs transfused ~~**during the Main Part**~~ **will be summarised descriptively by treatment sequence and treatment sequence within period and** will be analysed using Wilcoxon rank-sum test ~~**for each period**~~. And mean LDH profile ~~**during the Main Part**~~ will be presented over time.	To update study design/process in order to minimize the risk of COVID-19 pandemic To clarify the efficacy/safety analysis
9.5.2. Safety Analyses	**9.5.2. Safety Analyses for the Main Part** (…) All TEAEs and SAEs reported during the randomised treatment	**9.5.2. Safety Analyses for the Main Part** (…) All TEAEs and SAEs ~~**reported during the randomised**~~	To update study design/process in order to minimize the risk of COVID-

	period will be summarised respectively by count and percentage of subjects experiencing events by system organ class, preferred term, treatment sequence, and period. SAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the initiation of study drug will be listed by subject. In addition, infection-related AEs including meningococcal infection and other systemic infection, and IRRs reported during the randomised treatment period will also be summarised. Duration of exposure to IP and number of IV infusion during the randomised treatment period will be summarised by treatment sequence and period with descriptive statistics for the SAF1. Prior and concomitant medications, and significant non-drug therapies will be summarised by treatment sequence and period with count and percentage. Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence, period, and time point. Other safety variables will be summarised unless otherwise specified, and all safety variables will be listed. All safety analyses will be performed using the SAF1.	~~**treatment period**~~ will be summarised respectively by count and percentage of subjects experiencing events by system organ class, preferred term~~**, treatment sequence, and period**~~. ~~**SAEs**~~ **TEAEs** leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the initiation of study drug will be listed by subject. In addition, infection-related AEs including meningococcal infection and other systemic infection, and IRRs ~~**reported during the randomised treatment period**~~ will also be summarised. Duration of exposure to IP and number of IV infusion ~~**during the randomised treatment period**~~ will be summarised by treatment sequence ~~**and**~~ **within** period with descriptive statistics for the SAF~~**1**~~. Prior and concomitant medications, and significant non-drug therapies will be summarised ~~**by treatment sequence and period**~~ with count and percentage. Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence~~**, period,**~~ and ~~**time point**~~ **visit**. Other safety variables will be summarised unless otherwise specified, and all safety variables will be listed. All safety analyses will be performed using the SAF~~**1**~~.	19 pandemic To clarify the efficacy/safety analysis
9.5.3. Safety Analyses for the Extension Part	**9.5.3. Safety Analyses for the Extension Part** All reported terms for SAEs will be coded using MedDRA®. SAEs reported during the Extension Part will be summarised and listed for the SAF2. Duration of exposure to IP and number of IV infusion during the Extension Part will be summarised with descriptive statistics for the SAF2.	~~**9.5.3. Safety Analyses for the Extension Part**~~ ~~**All reported terms for SAEs will be coded using MedDRA®. SAEs reported during the Extension Part will be summarised and listed for the SAF2.**~~ ~~**Duration of exposure to IP and number of IV infusion during the Extension Part will be summarised with descriptive statistics for the SAF2.**~~	To update study design/process in order to minimize the risk of COVID-19 pandemic

9.5.4. Immunogeni-city Analyses	ADA and NAb results (e.g., 'positive' or 'negative') will be summarised with count and percentage by treatment sequence, period, and time point. In addition, incidence of overall ADA will be summarised by treatment sequence and period. Immunogenicity analyses will be performed using the SAF1.	ADA and NAb results (e.g., 'positive' or 'negative') will be summarised with count and percentage by treatment sequence~~,~~ **~~period,~~** and **~~time point~~ visit**. In addition, incidence of overall ADA will be summarised by treatment sequence and period. Immunogenicity analyses will be performed using the SAF**~~1~~**.	To clarify the efficacy/safety analysis
9.5.5. Pharmacody-namic Analyses	PD analysis will be performed for the PDS. The absolute values, and change from baseline in terminal complement activities will be summarised by treatment sequence, period, and time point. (…)	PD analysis will be performed for the PDS. The absolute values, and change from baseline in terminal complement activities will be summarised by treatment sequence**~~, period,~~** and **~~time point~~ visit**. (…)	To clarify the efficacy/safety analysis
10.2 Monitoring	(…) (…) Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions for the Main Part and IP infusion date/time at Week 52. (…) (…)	(…) (…) Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions **~~for the Main Part and IP infusion date/time at Week 52~~**. (…) (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
10.5. Database Management and Coding	(…) The eCRF will be used only during the Main Part and IP infusion date/time at Week 52. (…)	(…) **~~The eCRF will be used only during the Main Part and IP infusion date/time at Week 52~~**. (…)	To update study design/process in order to minimize the risk of COVID-19 pandemic
10.7. Protocol Deviation	(…) PDs will be reviewed and confirmed prior to database lock for the Main Part to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock for the Main Part.	(…) PDs will be reviewed and confirmed prior to database **~~lock for the Main Part~~** to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock **~~for the Main Part~~**.	To update study design/process in order to minimize the risk of COVID-19 pandemic

13. Extended Supply	N/A	**After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years starting from Week 52 to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.** **Before entering an extended supply, the Investigator will review the subject status including reduction of PNH disease activity, such as improvement of symptoms or laboratory parameters, during eculizumab treatment to decide if the subject will benefit from participation in extended supply. Once subjects are considered to benefit from extended supply, subjects will be asked if he/she would like to receive an extended supply. For receiving an extended supply, subjects should agree with signing ICF for extended supply and with required activities including refraining from pregnancy, maintaining a highly effective contraceptive method, and receiving meningococcal vaccination (if required by local regulations) to ensure subject's safety during extended supply.** **During extended supply, Investigators will treat subjects with 900 mg of SB12 every 14 ± 2 days for up to 2 years (104 weeks). SB12 will be packaged and labelled using open label and dispensed through the IWRS. Investigators should ensure the compliance and accountability of SB12 during the course of extended supply. Any PC must be reported to Sponsor.** **SAEs that occur during this phase must be reported to the Sponsor, which will be reported to regulatory authorities by the Sponsor according to local/national requirements via expedited reporting and periodic reporting such as Development Safety Update Report (DSUR) or Periodic**	To update study design/process in order to minimize the risk of COVID-19 pandemic

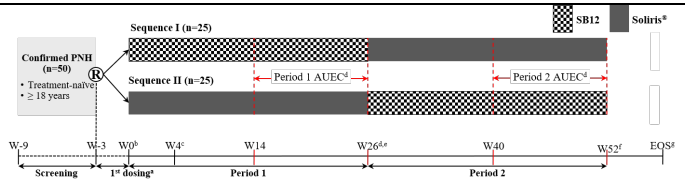
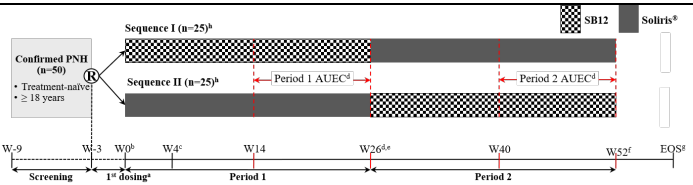
		Safety Update Report (PSUR). Pregnancy should also be reported until 5 months after the last SB12 treatment. Other particular activities will not be imposed and no data collection or reporting will occur for extended supply. **Discontinuation of study treatment can be decided if unacceptable toxicity, pregnancy, other complement inhibitor use or lack of efficacy occurs, or at the discretion of the Investigator or by subject's consent withdrawal. Specific study procedures are not required for subjects who have discontinued prematurely except for SAEs reporting and pregnancy reporting.** **During the period of extended supply, the Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the IRB/IEC. The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs under investigation.** **The Investigators must maintain essential study documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP or 15 years from completion of the extended supply, if applicable.** **Investigational sites participation may be discontinued if the Sponsor, Investigator or IRB/IEC consider necessary. Extended supply may be terminated by the Sponsor if medically or ethically indicated, and in such cases will be**	

		promptly notified to the Investigator. In any case, health authorities and IRB/IEC will be informed for the action in accordance with applicable regulations..	
14. References	[10] Soliris® EPAR – Product Information. EMA (Sep 04, 2019). Retrieved Sep 09, 2019 from https://www.ema.europa.eu/documents/product-information/soliris-epar-product-information_en.pdf	[10] Soliris® EPAR – Product Information. EMA (~~**Sep 04, 2019**~~ **Jul 01, 2020**). Retrieved ~~**Sep 09, 2019**~~ **Jul 13, 2020** from https://www.ema.europa.eu/documents/product-information/soliris-epar-product-information_en.pdf	To refer the latest version of regulatory document

Amendment 5: Version 6.0, Nov 27, 2020

Section Affected	Original Content	Amended/New Content	Rationale
SYNOPSIS Study Design	This is a randomised, Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.	This is a randomised, Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. **In special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner.** After completion of activities at Week 52, an open-label extended supply of SB12 will be provided for up to 2 calendar years to subjects who have benefited from study treatment and opt to participate in extended supply under an ethical basis.	To update study design/process in order to address a special circumstances of a shortage of the comparator
SYNOPSIS Statistical Methods	<u>Analysis sets for efficacy analyses</u> Modified Full Analysis Set (M-FAS) consists of all randomised subjects who do not have positive result of pharmacogenetic analysis (C5 gene polymorphism). However, subjects who do not have any efficacy assessment result after randomisation and do not receive IP during the study period will be excluded from this analysis set. Following the intent-to-treat principle, subjects	<u>Analysis sets for efficacy analyses</u> Modified Full Analysis Set (M-FAS) consists of all randomised subjects who do not have positive result of pharmacogenetic analysis (C5 gene polymorphism). However, subjects who do not have any efficacy assessment result after randomisation and do not receive IP during the study period will be excluded from this analysis set. Following the intent-to-treat principle, subjects	To update study design/process in order to address a special circumstances of a shortage of the comparator

	will be analysed according to the treatment sequence they are assigned to at randomisation. Per-Protocol Set for AUEC of LDH (PPS-AUEC) consists of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major protocol deviations (PDs) that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. Per-Protocol Set for LDH at a single time point (PPS-single) consists of all M-FAS subjects who have LDH assessment at Week 26 without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. (…) Safety analyses Safety analyses will be performed in the Safety Set (SAF). All reported terms for AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be collected and classified according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. All AE data will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term. TEAEs leading to IP discontinuation and treatment-emergent AEs (TEAEs) by causality and severity will be summarised similarly. Infection-related AEs including	will be analysed according to the treatment sequence they are assigned to at randomisation. Per-Protocol Set for AUEC of LDH (PPS-AUEC) consists of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major protocol deviations (PDs) that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. **In addition, subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.** Per-Protocol Set for LDH at a single time point (PPS-single) consists of all M-FAS subjects who have LDH assessment at Week 26 without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. **In addition, subjects who received different treatment in Period 1 from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.** (…) Safety analyses Safety analyses will be performed in the Safety Set (SAF). All reported terms for AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be collected and classified according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.	

	meningococcal infection and other systemic infection, and IRRs will also be summarised. Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence and visit. Other safety variables will be summarised unless otherwise specified.	All AE data will be summarised by count and percentage of subjects experiencing events by system organ class, preferred term. TEAEs leading to IP discontinuation and treatment-emergent AEs (TEAEs) by causality and severity will be summarised similarly. Infection-related AEs including meningococcal infection and other systemic infection, and IRRs will also be summarised. Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment sequence and visit. Other safety variables will be summarised unless otherwise specified. **Additional analyses will be performed for the subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator if needed. For example, AEs and concomitant medications will be analysed based on the actual switched treatment.**	
Figure 1			To update study design/process in order to address a special circumstances of a shortage of the comparator
Figure 1 Footnote	N/A	**During the treatment period, in special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner.**	To update study design/process in order to address a special circumstances of a shortage of the comparator

LIST OF STUDY STAFF	Clinical Project Manager [redacted] Clinical Development Lead [redacted] Clinical Research Physician [redacted] Clinical Research Scientist [redacted]	Clinical Project Manager [redacted] Clinical Development Lead [redacted] Clinical Research Physician [redacted] ~~**Clinical Research Scientist**~~ [redacted]	Administrative change
1.5.1. Known Potential Risks	Considering the mechanism of action of eculizumab, (…) All subjects will be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. In order to ensure the safety of subjects who participate in the study, (…)	Considering the mechanism of action of eculizumab, (…) All subjects will be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. **According to the study design, the switch of IP (cross-over) occurs during the study. The potential negative impact from this IP switch is considered to be minimal given similarity and comparability of SB12 to Soliris® and low antibody responses in Soliris® (3.4%) similar to that of placebo (4.8%) in placebo controlled studies in subjects with PNH [10].** In order to ensure the safety of subjects who participate in the study, (…)	To update risk assessment in order to address a special circumstances of a shortage of the comparator

3.1. Overview of Study Design	This is a randomised, Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects randomly assigned to treatment with SB12 or Soliris® will receive 600 mg of eculizumab IV every week for first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter. Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. SB12 or Soliris® will be given until Week 50.	This is a randomised, Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH. Subjects will be randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris®) or treatment sequence II (Soliris® to SB12). Subjects randomly assigned to treatment with SB12 or Soliris® will receive 600 mg of eculizumab IV every week for first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter. Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26. SB12 or Soliris® will be given until Week 50. **However, in special circumtances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner.**	To update study design/process in order to address a special circumstances of a shortage of the comparator
5.1.1. Dosing and Treatment Schedule	(…) The subject receiving SB12 or Soliris® therapy may require dosing interval adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. If a 12 or 13 day dosing interval conflicts with administrative schedules (e.g., holidays or weekends) but a shortened dosing interval is considered necessary for safety of subject, consultation with medical monitor (or Sponsor) is recommended. For subjects whose dosing interval is adjusted to 12 days in Period 1, it is recommended that the dosing interval be	(…) The subject receiving SB12 or Soliris® therapy may require dosing interval adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it is deemed necessary at the discretion of the Investigator; e.g., two consecutive events of elevated LDH ≥ 2 × ULN combined with sign or symptom of intravascular haemolysis after prior LDH reduction to < 1.5 × ULN on treatment. If a 12 or 13 day dosing interval conflicts with administrative schedules (e.g., holidays or weekends) but a shortened dosing interval is considered necessary for safety of subject, consultation with medical monitor (or Sponsor) is recommended. For subjects whose dosing interval is adjusted to 12 days in Period 1, it is recommended that the dosing interval be	To update study design/process in order to address a special circumstances of a shortage of the comparator

	switched back to 14 days after switching IP at Week 26. Once the above event has occurred, the Investigator should inform the medical monitor and/or Sponsor immediately.	switched back to 14 days after switching IP at Week 26. Once the above event has occurred, the Investigator should inform the medical monitor and/or Sponsor immediately. **In special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner. Rules for allocation of remaining comparators during the comparator shortage situation will be prespecified prior to execution of the potential change of IP assignment from Soliris® to SB12 in a blinded manner. This is to avoid the risk of unblinding and potential bias.**	
7.1.3. Treatment Period	The Investigator will evaluate the assessment results and manage subjects based on the medicinal judgement and/or knowledge.	The Investigator will evaluate the assessment results and manage subjects based on the medicinal judgement and/or knowledge. **In special circumstances of a shortage of the comparator, to ensure continuity of study treatment for the duration of study, the Sponsor will provide SB12 instead of Soliris® in a blinded manner. Investigators and subjects will be informed prior to the execution of the potential change of IP assignment. Subjects willing to continue the study treatment after knowing that they may receive SB12 instead of Soliris® in a blinded manner during the study, should have their agreement both documented in the source document and an ICF. If the Investigators or subjects do not agree to the potential change of IP assignment, then subjects may withdraw from the study and be closely monitored for at least 8 weeks after last dose of study drug.**	To update study design/process in order to address a special circumstances of a shortage of the comparator
8.3.3. Infusion-related Reactions	Administration of SB12 or Soliris® may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis), though immune reactions within 48 hours of Soliris® administration did not differ from placebo arm in PNH, aHUS, refractory	Administration of SB12 or Soliris® may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis)~~**, though immune reactions within 48 hours of Soliris® administration did not differ from placebo arm in PNH,**~~	To refer the latest version of regulatory document

	gMG, NMOSD, and other studies conducted with Soliris®. In clinical trials no PNH, aHUS, refractory gMG, or NMOSD patients experienced an infusion reaction which required discontinuation of Soliris®. (…)	~~aHUS, refractory gMG, NMOSD, and other studies conducted with Soliris®~~. In clinical trials**, 1 (0.9%) gMG patient experienced an infusion reaction which required discontinuation of Soliris®. ~~n~~**No PNH, aHUS, ~~refractory gMG,~~ or NMOSD patients experienced an infusion reaction which required discontinuation of Soliris® **in clinical trials.** (…)	
9.2. Analysis Sets	The following sets will be used for the analyses performed in the study: • (…) • Per-Protocol Set for AUEC of LDH (PPS-AUEC) consists of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. • Per-Protocol Set for LDH at a single time point (PPS-single) consists of all M-FAS subjects who have LDH assessment at Week 26 without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. (…)	The following sets will be used for the analyses performed in the study: • (…) • Per-Protocol Set for AUEC of LDH (PPS-AUEC) consists of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. **In addition, subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator will be excluded from this analysis set.** • Per-Protocol Set for LDH at a single time point (PPS-single) consists of all M-FAS subjects who have LDH assessment at Week 26 without any major PDs that have impact on efficacy assessment. Subjects excluded from the primary analysis will be pre-defined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. **In addition, subjects who received different treatment in Period 1 from the randomised treatment sequence due to a shortage of the comparator will be excluded from**	To update study design/process in order to address a special circumstances of a shortage of the comparator

		this analysis set. (…)	
9.5.2. Safety Analyses	(…) All safety analyses will be performed using the SAF.	(…) All safety analyses will be performed using the SAF. **Additional analyses will be performed for the subjects who received different treatment from the randomised treatment sequence due to a shortage of the comparator if needed. For example, AEs and concomitant medications will be analysed based on the actual switched treatment.**	To update study design/process in order to address a special circumstances of a shortage of the comparator
14. References	[21] Soliris® Prescribing Information. FDA (Jun 27, 2019). Retrieved Jul 09, 2019 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s431lbledt.pdf	[21] Soliris® Prescribing Information. FDA (~~**Jun 27, 2019**~~ **Nov 20, 2020**). Retrieved ~~**Jul 09, 2019**~~ **Nov 26, 2020** from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125166s434lbl.pdf	To refer the latest version of regulatory document