30 March 2023
EMA/203468/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Epysqli

International non-proprietary name: eculizumab

Procedure No. EMEA/H/C/006036/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Quality

ADI	acceptable daily intake
AEX-HPLC	anion exchange high-performance liquid chromatography
AS	active substance
CD spectroscopy	Circular dichroism spectroscopy
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CHO	Chinese hamster ovary
CoA	certificates of analysis
DCS	differential scanning calorimetry
DLS	Dynamic Light Scattering
FP	finished product
FTIR	Fourier-transform infrared spectroscopy
HCPs	host cell proteins
H/DX-MS	Hydrogen Deuterium Exchange mass spectrometry
HILIC-UPLC	Hydrophilic interaction ultra performance liquid chromatography
icIEF	imaged capillary isoelectric focusing
INN	International Non-proprietary Name
(C)IPG	(critical) in-process gateways
IPS	in-process specification
(C)IPTs	(critical) in-process tests
LC-ESI-MS	liquid chromatography electrospray ionization and mass spectrometry
LOQ	limit of quantitation
MCB	master cell bank
MFI	flow imaging microscopy
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPQ	process performance qualification
RP-UPLC	reverse phase ultra performance liquid chromatography
SB12	company code for eculizumab
SE-HPLC	Size exclusion-high-performance liquid chromatography
SEC-MALS	Size Exclusion chromatography- Multiangle light scattering
SV-AUC	Sedimentation Velocity Analytical Ultracentrifugation
UV/Vis	ultraviolet/visible spectroscopy
WCB	working cell bank

Non-Clinical

ATC	Anatomical therapeutic chemical

CHO	Chinese hamster ovary
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FcRn	Neonatal Fc receptor
GLP	Good Laboratory Practice
INN	International non-proprietary name
IV	Intravenous
mAb	Monoclonal antibody
MAC	Membrane attack complex
mg	Milligram
MoA	Mechanism of action
No.	Number
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SA	Scientific advice
SB	Samsung Bioepis Co., Ltd.
SPR	Surface plasmon resonance
US	United States

Clinical

$\%AUC_{extrap}$	Percentage of AUCinf due to extrapolation from Tlast to infinity
λz	Terminal rate constant
ADA(s)	Anti-drug antibody(ies)
AE(s)	Adverse event(s)
AESI	AE(s) of special interest
aHUS	Atypical haemolytic uremic syndrome
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC_{inf}	AUC from time zero to infinity
AUC_{last}	AUC from time zero to the last quantifiable concentration
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beats per minute
CHF	Congestive heart failure
CI	Confidence interval
CL	Total body clearance

Cmax	Maximum serum concentration
CRP	C-reactive protein
CV%	Coefficient of variation in percent
DNA	Deoxyribonucleic acid
EAER	Exposure-adjusted event rate
ECG	Electrocardiogram
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End of study
eSource	Electronic source
ET	Early termination
EU	European Union
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
gCV%	Geometric CV%
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRR(s)	Infusion-related reaction(s)
IV	Intravenous
LDH	Lactate dehydrogenase
LSMeans	Least squares means
Max	Maximum
MedDRA®	Medical Dictionary for Regulatory Activities®
M-FAS	Modified full analysis set
Min	Minimum
NAb(s)	Neutralising antibody(ies)
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
MenACWY	Meningococcal ACWY conjugate
MenB	Meningococcal B
N. meningitidis	Neisseria meningitidis
PD	Pharmacodynamic(s)PK Pharmacokinetic(s)
PKS	PK Analysis Set
PNH	Paroxysmal nocturnal haemoglobinuria
PPS	Per Protocol Set
pRBC	Packed red blood cells

PT	Preferred term
QTcB	QT interval corrected using the Bazett's correction method
QTcF	QT interval corrected using the Fridericia's correction method
RAN	Randomised Set
RBC	Red blood cell
SAE(s)	Serious AE(s)
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SEM	Standard error of the mean
SOC	System organ class
SOP	Standard operating procedure
$t_{1/2}$	Terminal half-life
TEAE(s)	Treatment-emergent AE(s)
Tlast	Time of last measurable concentration
Tmax	Time to reach Cmax
ULN	Upper limit of normal
US	United States of America
V_z	Volume of distribution during terminal phase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis NL B.V. submitted on 22 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Epysqli, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

"Epysqli is indicated in adults and children for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1)."

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Soliris 300 mg concentrate for solution for infusion
- Marketing authorisation holder: Alexion Europe SAS
- Date of authorisation: 20-06-2007
- Marketing authorisation granted by: European Union
- Marketing authorisation number: EU/1/07/393/001

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
12 October 2017	EMA/CHMP/SAWP/634958/2017	*Dr Serena Marchetti and Dr Karin Janssen van Doorn*
12 November 2020	EMA/CHMP/SAWP/580824/2020	*Dr Ferran Torres and Dr Monique Wakelkamp*

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the quality similarity assessment plan for the purpose of CTA and MAA.
- Proposed C5 inhibition assay as the QC release potency assay for the purpose of CTA and MAA.
- *In vitro* study plan and the non-clinical approach without conducting *in vivo* non-clinical for the purpose of CTA and MAA.
- Appropriateness of the Phase I study design to demonstrate similarity in PK profiles between SB12 and Soliris, and to investigate similarity in PD profiles between SB12 and Soliris.
- Statistical justifications to establish similarity in PK profiles between SB12 and Soliris.
- Acceptability of the clinical Phase III study design to demonstrate similarity in efficacy, safety, PK and immunogenicity between SB12 and Soliris.
- Acceptability of the proposed overall development plan to support authorisation of SB12 for all other indications for which Soliris is authorised.
- Proposal of using both EU and US Soliris in the reference arm of the pivotal clinical Phase III study due to scarcity reasons of EU Soliris, provided that the applicant can establish an acceptable bridge between EU and US Soliris.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	22 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 October 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	17 October 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 October 2022

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 December 2022
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection of FP manufacturer was conducted' between 22-26 August 2022. The outcome of the inspection carried out was issued on 09/01/2023.	22 August 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 February 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 February 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Epysqli on	30 March 2023
The CHMP adopted a report on similarity of Epysqli with Aspaveli on	30 March 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

PNH is a rare, chronic, life-threatening blood disorder associated with anaemia due to haemolysis. Haemolysis can result in a range of debilitating consequences such as severe fatigue, chest pain, and transfusion dependence, all of which contribute to the heavy disease burden and reduced quality of life (QoL) these patients experience. Even with C5 inhibitor treatment, 72% of patients with PNH remain anaemic and 36% require 1 or more transfusions per year (McKinley et al. 2017). If left untreated, PNH can cause severe and potentially fatal complications for patients.

2.1.2. Epidemiology

PNH has an annual incidence of 1-10 new cases per 1 million individuals. The median age of diagnosis is in the early thirties; it affects men and women in equal proportions and has no clear ethnic or geographic preferences (Stern and Connell 2019).

2.1.3. Clinical presentation, diagnosis

PNH is associated with a high burden of disease. The most prevalent symptoms are fatigue (80%), dyspnea (64%), and hemoglobinuria (62%). PNH commonly results in clinically significant hematologic consequences from chronic hemolysis including a marked increase in risk of thromboembolism, which may ultimately lead to target organ damage and death (Schrezenmeier et al. 2014).

2.1.4. Management

To most effectively manage PNH, both IVH and EVH need to be controlled. This is reflected in improvements across the following key markers of disease activity: haemoglobin level, LDH level, ARC, bilirubin level, transfusion requirements, and FACIT-Fatigue score. The C5 inhibitors eculizumab and ravulizumab have increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements; however, C5 inhibitors do not control EVH. In many patients treated with C5 inhibitors, although LDH is largely controlled, ARC and bilirubin levels remain elevated, indicative of ongoing haemolysis. Pegcetacoplan (Aspaveli) has been recently approved and binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

2.2. About the product

Samsung Bioepis has developed SB12 as a proposed similar biological medicinal product to Soliris.

SB12 and Soliris have identical primary structure and the active substance for both products is eculizumab, a humanised monoclonal antibody.

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA25

Eculizumab contains human constant regions and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions.

Eculizumab 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.

The claimed therapeutic indication is similar to the indication of Soliris for the treatment of PNH as the market exclusivity period for Soliris's PNH indication ended in June 2019:

> SB12 is indicated in adults and children for the treatment of Paroxysmal nocturnal haemoglobinuria (PNH).
>
> Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).

Soliris is also indicated in the treatment of atypical haemolytic uremic syndrome (aHUS), refractory generalised myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive, and neuromyelitis optica spectrum disorder (NMOSD), but these indications are still protected by orphan exclusivity. For this MAA of SB12, the applicant intends to claim PNH, which is one of the indications granted for Soliris in the EU.

2.3. Type of application and aspects on development

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as concentrate for solution for infusion, containing 300 mg of eculizumab as active substance.

Other ingredients are: sodium dihydrogen phosphate monohydrate disodium hydrogen phosphate heptahydrate, trehalose dihydrate, polysorbate 80 and water for injections.

The product is available in a vial (Type I glass) with a stopper (coated chlorinated butyl rubber), and a seal (aluminium) with flip-off cap (polypropylene).

2.4.2. Active substance

2.4.2.1. General information

The INN name of the active substance of Epysqli (company code SB12) is eculizumab. SB12 is a full-length IgG2/4 kappa isotype antibody composed of two identical light chains (214 amino acid residues) and two heavy chains (448 residues) with a total molecular weight of 148 kDa. One N-linked glycosylation site is located at Asn298 on each heavy chain. Eculizumab binds to the human C5 complement protein and inhibits C5 cleavage to C5a and C5b, preventing the generation of the terminal complement complex C5b-9 and thus blocking complement-mediated cell lysis and activation (intravascular haemolysis).

SB12 has been developed as a biosimilar to the reference product Soliris, originally approved in the EU in June 2007 (EMEA/H/C/000791).

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls
The SB12 active substance is manufactured in Patheon facility in Woolloongabba, Australia. All relevant manufacturing, testing and cell bank storage sites have been listed, GMP compliance for all listed sites is confirmed.

The active substance (AS) manufacturing is well described: the up-stream process begins with thawing of a vial of the working cell bank, which is a Chinese Hamster Ovary cell line transfected with SB12 expression vector. After thawing of the WCB vial, the culture is serially expanded in cell mass and volume for inoculation into the production bioreactor.

The down-stream process starts with the affinity chromatography step: Harvested cell culture fluid is initially captured and purified by affinity chromatography. The eluate is collected and undergoes a low pH virus inactivation step before being further purified in series of chromatography. Subsequently, the product is passed through a series of filters for virus reduction, concentrated and buffer exchanged using tangential flow filtration. The final ultrafiltration pool is formulated with formulation buffer, and then filtered into AS bags. The filled AS bags are stored frozen.

Flow charts providing a high level overview of the manufacturing process as well as detailed narrative descriptions of the individual steps were included. Process controls (e.g. those impacting critical process parameters) as well as performance parameters (e.g. in-process tests) have been indicated in the manufacturing process description. Definitions of these process and performance parameters was provided in the dossier.

The batch and scales have been appropriately defined. One batch of AS is filled into multiple bags.

Control of materials
The raw and starting materials are briefly presented. Tabulated overviews of compendial and non-compendial materials used in the manufacturing process are shown. For the non-compendial materials in-house tests will be performed; for the majority of non-compendial materials the applicant indicates to perform testing in order to verify the manufacturer CoA certificates of analysis (CoAs). For non-compendial raw materials used in SB12 AS manufacturing process Certificates of analysis (CoAs) have been provided. Microbial control of cell culture reagents was sufficiently described.

The compositions of the media used in the SB12 cell culture process were provided. The applicant confirms that the change notification would be made in case of change. The composition of solutions for the purification process was included in the dossier.

Raw materials of animal origin used for SB12 host cell construction and cell line development as well as materials of biological origin used during the active substance manufacturing process are listed as well. A detailed discussion on the materials of animal origin is described in the dossier.

The source, history and generation of the cell line has been appropriately described: The host cell line is Chinese hamster ovary cell line. The DNA fragments coding SB12 heavy chain and SB12 light chain were chemically synthesized based on the reference amino acid sequence of Soliris. The expression plasmid vectors were prepared and introduced into the host cells by transfection. The production cell line was generated by stable pool selection and single clone selection in chemically defined media.

The cell bank system is comprised of the master and the working cell bank. Appropriate information in accordance with ICH Q5A and Q5D on the establishment, testing/characterisation, and storage of the cell banks has been provided. A new expiry date is assigned to cell banks after periodical stability testing. The manufacturing and testing strategy in case of replacement of the working cell bank has been described. In addition to the master and the working cell bank, an end of production cell bank for

SB12 was generated and tested to characterise the stability of cell line at the end of its usable life cycle. Finally, stability of the SB12 cell substrate was confirmed by genetic and phenotypic analysis methods.

Control of critical steps and intermediates
The process control strategy is generally endorsed. The control of the active substance manufacturing process is described in the dossier: The process controls are divided into process parameters (inputs) and performance parameters (outputs). Key and critical process parameters as well as in-process gateways, critical in-process gateways (CIPGs), in-process tests (IPTs), and critical in-process tests (CIPTs) have been defined. For each individual manufacturing step, process and performance parameters with their respective action ranges and/or in-process specifications are outlined. The initially proposed control strategy of host cell proteins (HCPs) was not accepted and consequently implementation of a release specification was requested. To address the concern an in-process specification (IPS) and a revised action range was set. This improved control strategy can be accepted. A brief description of the used HCP assay was given. The method has been validated according to ICH Guideline Q2 (R1).

Process validation and/or verification
Process validation included a number of studies which investigated a) process performance qualification (PPQ) of both the cell culture and the purification process, b) impurity clearance to show that the intended purification process is able to reduce the impurities to acceptable levels in accordance with the pre-determined acceptance criteria, c) hold times for process intermediates, d) resin lifetime to demonstrate that the chromatography column resins are capable of maintaining acceptable performance characteristics over extensive cycling, and e) the shipping qualification.

Several PPQ batches had been produced, and met the acceptance criteria. Based on the results of the process validation, the manufacturing process is considered validated for active substance commercial manufacturing. However, a single batch was terminated due to the presence of microbial contaminants. Since there was no breach of GMP practice with low possibility of recurrence and immediate detection of the event was performed, the risk category was determined as low with the requirement of an investigation for root cause analysis. A detailed summary of the conducted root cause investigation of this microbial contamination during process validation has been submitted. Based on the investigation results, it was concluded that there was no process or product impact due to termination of the certain batch. An alternative batch was started as a replacement batch and met all pre-determined specification.

The clearance studies of process-related impurities involved studies for cell derived impurities (HCP, host cell DNA), cell-culture process derived impurities, and impurities derived from the downstream purification process (protein A leachate). Impurity clearance was validated by using direct measurements of the impurities in process intermediates for the PPQ batches, or by using scale-down spiking models. The overall clearance factor for certain impurities was calculated and the lowest detected log reduction value (LRV) was considered effective in impurity reduction. Presented data from PPQ batches and clearance studies of process-related impurities demonstrated that their levels are well below their acceptable daily intake (ADI).

Resins lifetime studies to evaluate the performance of chromatography resins used in the purification process were performed at laboratory scale based on the scale-down models to determine appropriate resin lifetimes without any potential product loss and impact on process performance and product quality. In addition to the resin life cycle studies performed at small scale, the applicant evaluates the lifetime of the resins at manufacturing scale. Data for output parameters will be collected according to a protocol until the maximum number of cycles is reached. These protocols for evaluation of the resin lifetimes at manufacturing scale have been submitted and are satisfactory.

Appropriate hold time stability studies in order to qualify that process intermediates are stable for their maximum allowable holding times have been conducted. Intermediate hold times for commercial manufacturing have been established based on the validated hold times and can be agreed on.

By shipping qualification studies, the shipping system was validated to assure the quality of the product.

Manufacturing process development
In the section Manufacturing Process Development the outcome of a quality attribute risk assessment in order to categorise individual product quality attributes either critical or non-critical was presented. The methodology employed for quality attribute risk assessment of SB12 was a modified risk ranking and filtering, in which the potential impact on efficacy (potency), immunogenicity, pharmacokinetics (PK)/pharmacodynamics (PD), safety of the product, and the uncertainty were factored into determining the degree of risk. Numerical scoring systems for the 'impact factor' and 'uncertainty factor' were used to determine the overall risk score, defined as the 'risk priority number (RPN)'.The methodology as well as the proposed classification of quality attributes in critical and non-critical attributes can be agreed.

The development history of the AS manufacturing process was summarised including a process description from the pilot-scale to the commercial scale process. The pilot manufacturing process was developed based on the laboratory scale experiments to support the development for a clinical manufacturing process. The clinical manufacturing process was further developed to the PPQ manufacturing process, only minor changes were introduced from the clinical to the process validation manufacturing. The development of the manufacturing process was done on several process risk assessments as well as on process characterisation studies conducted on appropriately qualified scale down models. Finally, the applicant introduced some changes post-PPQ activities in the input and output parameters which were revised. The revision took place by the process knowledge gained from the validation campaign, manufacturing experience, additional process characterisation results, risk assessments, and overall process capabilities taken into account. Following the post PPQ activities the applicant indicated that an in-process test was removed. The applicant will continue to monitor this parameter during 30 batches or more. The control strategy will be re-classified after 30 batches or more based on the monitored results.

In order to ensure that the batches used at each stage of SB12 development are representative of subsequent development stages, and that changes in the manufacturing process at each stage of development do not affect product quality, two comparability studies were conducted. Comparability assessment was performed based on the quality attributes for release test items and extended characterisation studies. The extended characterisation included physicochemical and biological assays. In addition, comparative stability studies were performed to evaluate the degradation patterns among SB12 batches (pilot, clinical, and PPQ active substance batches).

The first study evaluated the comparability between SB12 clinical and PPQ batches, and the second study the comparability between SB12 pilot and clinical batches. Comparability between active substance materials derived from the different process version has been demonstrated, some issues identified in the first assessment round could be solved with the responses. These issues were related to the calculation of comparability range. The applicant re-calculated comparability range with more appropriate narrow range and re-assessed batches with re-calculated range in the responses. Some of the results were slightly outside the re-calculated comparability range. But the applicant`s justification for these outliers can be followed and the conclusion that these slight differences observed are not considered significant can be accepted.

As requested the data from the individual batches used for the initial calculation of the comparability ranges are provided. These data also confirm a comparable quality profile of the different process version.

An extensive and sound discussion on the applied statistics has been provided which is considered appropriate.

In addition comparability between pilot and clinical batches has been sufficiently established. Batch release results of several produced pilot AS, clinical AS, and clinical FP batches are shown and do not indicate any significant differences between pilot and clinical batches. Together with the data from the comparative in-depth characterisation showing comparability of primary and higher order structure comparability between pilot and clinical batches is confirmed.

Characterisation
SB12 was characterised by a comprehensive battery of physicochemical and biological tests using sensitive and orthogonal state-of-the art qualified analytical methods in accordance with ICH Guideline Q6B. For the majority of quality attributes characterisation was conducted with PPQ active substance as well as with PPQ drug product batches. The selection of AS and FP batches included into the in-depth characterisation of SB12 is appropriate and agreed.

Primary structure and post-translational modifications included characterisation of molecular weights, amino acid sequencing, peptide mapping, N- and C-terminal sequencing, determination of the extinction coefficient, and characterisation of oxidation and deamidation variants. Glycan profiles were studied via identification of N-linked glycosylation sites, N-glycan identification, and N-glycan profiling. One glycosylation site (N-linked) has been identified. The purity/impurity profile and charged variants were investigated by orthogonal method. Hydrophobic heterogeneities were also analysed. In-depth characterisation of higher order structures was comprised of combination of methods to find out specific structural charcter of the protein.,Protein concentration and subvisible particles were also analysed in characterisation..

In summary an extensive in-depth characterisation of the relevant physicochemical has been performed and the relevant discussion has been presented satisfactorily.

Biological characterisation was performed by an cell-based C5 inhibition assay, an anti-hemolytic assay, a C5 binding assay via ELISA and an FcRn binding assay via SPR. These assays aim mostly on high criticality attributes of SB12 and precisely reflect the mode of action of eculizumab. Additional biological characterisation included an orthogonal C5 binding assay by SPR, binding to Fcγ receptors by SPR, and binding to C1q by an ELISA. These assays that are not expected to be relevant for safety and efficacy of the molecule since eculizumab has hybrid human IgG2-IgG4 heavy-chain constant regions, which have been reported to be unable to activate CDC or bind to the Fc-γ receptor of effector cells. Functional activities related to the Fc domain Fc effector functions are not significantly involved in the MoA; this is agreeable. Finally, binding to C5 polymorphic variants was studied by an ELISA. In conclusion, the set of binding and cell-based assays is considered sufficient for biological characterisation of SB12.

Impurities
A brief discussion of the potential product- and process-related impurities in SB12 active substance has been provided. Process-related impurities include HCP and host cell DNA, protein A, leachate. During active substance manufacturing process development, process-related impurities in the "in-process samples" of clinical and PPQ batches were monitored as IPT or in-process measurement (IPM). The test results were reported along with their action range for IPTs, or simply reported to evaluate process consistency for IPMs.

Product-related impurities include high-molecular and low-molecular species. The levels of product-related impurities were determined using two orthogonal methods. In addition to the size-related impurities, charge variants can also be thought as impurities. Although the relative contents of the charge variants have been included in the SB12 AS release specification, the applicant showed that charge variants have no impact on the biological activities.

Container closure system
The container closure comprises the multi-layered film structure bags The bags are sterilised by gamma irradiation and are certified BSE/TSE free in compliance with the EMA guideline "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMEA/410/01 Rev.3) and Ph. Eur. 5.2.8. "Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medical Products". As secondary packaging, the bag is covered by a protective shell.

Extractable studies have been conducted in order to determine the extractable amount of chemical compounds which may migrate from the AS container closure system into model solvents of interest. Organic compounds observed from these analyses went through a toxicological risk assessment. The calculated tolerable exposure threshold (TE) and safety margins for each of these extractables, detected in all solvent extracts of the SB12 AS storage bag, were provided.

The toxicological risk assessment conducted in the extracts showed that the organic compounds detected and identified were present at levels not expected to pose a risk of adverse effects. A safety margin for a single unit was calculated assuming the worst-case scenario. Summarising, the assumption of the applicant, that the risk of detecting any of the listed extractables in the final product is extremely low, can be followed.

Based on the results of the of the extractables study, which demonstrated a safety margin high enough to conclude on a very low toxicological risk to the finished product, the applicant considered leachable studies not necessary. Furthermore, the applicant outlined the long-term storage conditions where release of leachables from the container closure system into the AS is unlikely to occur. Taking these considerations into account, the omission of leachable studies is acceptable.

2.4.2.3. Specification

The AS release and shelf life specifications include tests for general tests (appearance, osmolality, pH), identity (icIEF), quantity (protein concentration), biological activity (bioassay), purity and impurities (SE-HPLC, CE-SDS, icIEF), and safety (endotoxins, microbial enumeration).

The proposed specifications address relevant quality attributes; however, no routine release tests for any of the potential process-related impurities is included in the specifications. The proposed limits and control strategy for controlling impurity were sufficiently justified and are acceptable.

The applicant has proven that the clearance of HC DNA, Protein A as well as HCPs impurities is sufficient.

AS (and FP) endotoxin release acceptance criteria has been tightened, in order to allow Epysqli a sufficient safety margin that has been validated over years of clinical practice in patients being treated with Soliris.

Analytical procedures

An overview of the analytical procedures used for release and stability testing was presented. Either Ph. Eur. methods are used or brief descriptions of the non-Ph. Eur. methods are provided. Validation reports for the non-Ph. Eur. methods have been included whereas the safety relevant methods

(endotoxin and microbial enumeration) have been verified to be suitable for their use. The methods have been appropriately validated and are considered suitable as release and stability test for SB12.

The AS biological activity is controlled by:
- a C5 ELISA-based binding assay was designed to measure the relative binding activity of eculizumab AS and FP to Reference Standard.

- a C5 inhibition assay to determine the relative potency of eculizumab AS and FP to Reference Standard. C1q interacts with the Fc region of anti-CD20 antibody after binding to CD20 on the B-cell surface, thus activating the classical complement cascade and a membrane attack complex (MAC) is inserted into the cell membrane, with multiple MACs leading to cytolysis.. The relative potency of eculizumab can be determined by measuring the inhibition of cytotoxicity.

A description of the used HCP assay was also given. The method is an SB12 process-specific assay based on sandwich immunoassay using polyclonal antibodies produced against HCPs, which is the cell line used to produce SB12. The HCP assay has been validated according to ICH Guideline Q2 (R1).

Certain tests used for release testing are not included in the stability testing. The provided justification for omission of these tests is agreed.

Reference standards

The applicant has described its reference standards used throughout the development of SB12. Different classes of reference standards including the Research Reference Standards, the Interim Reference Standard, the Clinical Reference Standard, the Primary Reference Standard and the Working Reference Standard were defined.

An appropriately characterised in-house primary reference standard (PRS) has been prepared from appropriate AS batch considered representative of production. Primary reference standard was qualified against previous reference standard by using validated or qualified analytical methods. This strategy of potency assignment used for the primary reference standard is acceptable and will also be used for qualification of future primary reference standards.

The stability program in place for the primary reference standard has been sufficiently described. The currently available stability data do not indicate any trends or abnormalities. Consequently, an expiry date is agreed.

The ICH guidance Q6B states that an in-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. The applicant indicated that a working reference standard (WRS) will be prepared in 2nd quarter (Q2) of 2023, and will be implemented via post-approval variation procedure. Currently, the PRS is used for QC release and stability testing of SB12 AS and FP batches until the WRS is established and qualified for routine use. The current reference standard system comprised of the primary reference standard is well managed until the WRS is established. Based on this justification the implementation of the WRS post-approval can be accepted (REC).

Batch analyses

Batch release data from AS batches produced so far have been presented. The AS batches complied with the specifications valid at the time of testing. In general, the batch analyses data confirm that the drug substance manufacturing process is able produce consistently material meeting predefined quality criteria.

The specifications and their acceptance criteria have been justified and are agreed. In order to establish the commercial acceptance criteria from batch analysis data, the historical AS and/or FP batches were evaluated.

2.4.2.4. Stability

The applicant provided the stability data of eculizumab AS for supporting the proposed shelf-life.

Real time stability data at long-term storage condition was provided for a pilot, clinical, PPQ batches. For the same batches, also stability data from the completed stability studies under accelerated storage condition was provided.

The applicant claims that the above batches can be used for establishing the shelf life claim as representativeness for the commercial product is shown. Since any uncertainties identified in the comparability studies in the dossier have been appropriately addressed, this conclusion can be followed.

Regarding available stability data, no out-of-specification results and no significant trends have been observed when stored at long-term storage condition and thus indicate that the AS is stable under long-term storage conditions.

In summary there is a sufficient stability data available which confirms that eculizumab AS is stable for proposed shelf-life. Consequently, the proposed shelf-life for eculizumab AS can be accepted.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Epysqli finished product is a sterile, clear, colourless, preservative-free solution and presented as a single-use vial containing 300 mg of eculizumab for concentrate for solution for infusion intravenously. Epysqli has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Soliris.

The formulation of the FP contains 10 mg/mL eculizumab, trehalose dihydrate, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, and polysorbate 80. The formulation is similar to the reference product Soliris but buffering agents are in different concentrations and the stabiliser is trehalose dihydrate and not sodium chloride. Formulation studies with different stabiliser and the stability under various conditions were performed. As a result, trehalose dihydrate was found better to stabilise Epysqli. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

All physicochemical and biological properties of the FP are closely correlated with the characteristics of the AS.

Epysqli FP is intended for intravenous infusion. The total amount of Epysqli FP from the vial is withdrawn using a sterile syringe and the recommended dose is transferred to an infusion bag. In the infusion bag, Epysqli FP is diluted to required concentration with 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. The suitability of the formulation has been assessed in in-use stability studies. Therefore, no dedicated compatibility studies have been conducted.

Epysqli clinical FP batches and PPQ batches were manufactured at the same FP manufacturer. Epysqli PPQ FP manufacturing process is similar to that of Epysqli clinical FP but many minor process changes proposed for process optimisation.

The applicant presented a risk assessment where these changes in the manufacturing of the clinical batches and the PPQ batches are estimated as low risk. Comparability data of the clinical batches with the PPQ batches at FP level have been presented in the dossier.

Further a comparison of process controls between Epysqli PPQ and post PPQ batches was performed. The rationale to every process parameter of the manufacturing steps was given and classification changes were sufficiently justified. Process characterisation studies were performed.

An engineering batch has been manufactured in order to verify manufacturing process parameters and process consistency like mixing, sterile filtration steps, different filling studies and visual inspection. Satisfactory results were obtained.

The FP primary packaging material consists of a Type I glass vial and a rubber stopper. Container closure integrity has been studied during development of Epysqli FP and this test is included in the on-going stability studies.

In order to assess the suitability of the container closure system, extractables and leachables studies were conducted. Experimental design and description of the analytical methods (GC/MS and LC/MS) for "extractables and leachables" are well presented. In the "extractables" study a number of volatile organic compounds (VOC) and semi-volatile organic compounds (SVOC) and non-volatile organic compounds (NVOC) were detected which were at or above the reporting level and they might be found in the FP in extreme conditions. The extractable compounds that are expected to be at or above the AET (analytical evaluation threshold) level will be monitored by the applicant during the ongoing leachables study, regardless of their volatility. The compounds will be continuously monitored at further time points in this study and subject to toxicological assessment if necessary. The applicant commits to submit the results for the remaining time points of the leachable study under long-term and accelerated storage conditions when these data become available (REC).

2.4.3.1. Manufacture of the product and process controls

Epysqli FP manufacturing process was validated at the proposed commercial manufacturing site. This facility could provide GMP certificates upon the request of the CHMP (Major Objection) and addresses any inquiry on the manufacturing activities of Epysqli product.

FP testing site is the same as for the. Its valid GMP certificate is available. EU batch release is conducted by Samsung Bioepis in Delft, Netherlands. The submitted GMP certificate is older than three years (issued in May 2019) but this extension can be accepted based on the QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE DURING THE COVID-19 PANDEMIC stating that "The validity of GMP certificates for manufacturing/importing sites of active substances and/or finished products in the EEA should be extended until the end of 2023 without the need for further action from the holder of the certificate".

The manufacturing process is sufficiently described and a flowchart was presented. The process is divided into 7 steps starting from AS thawing and ending to storage. Homogeneity of pooled AS and product quality is ensured by validated manufacturing process and in-process testing. The main procedures are filtration to reduce bioburden into the pooling vessel, mixing, sterile filtration and aseptic filling, stoppering/capping into vials.

In-process tests and controls are clearly presented and are adequately defined to each step where it is applicable. Furthermore, critical and key controlled parameters are defined to all steps applicable.

The control strategy in place for the FP manufacturing process is adequate.

Process validation of the SB12 FP manufacturing process has been carried out in the production facility of FP manufacturer. The manufacturing process has been validated on several consecutive PPQ batches according to the commercial process. Critical process parameters and critical quality attributes are taken into account and validated in each step applicable.

Filter sterility for Epysqli FP manufacturing was successfully validated by the manufacturer of the filter.

Media fill qualification was successfully conducted at the Epysqli FP manufacturing site, applying a bracketing approach. The data of this media fills are acceptable. Validation of the aseptic process was performed with several media fill runs.

Shipping qualification is performed for the Epysqli FP in bulk packaging and final packaging to ensure shipping stability.

2.4.3.2. Product specification

The finished product release and shelf-life specifications includes tests for general tests (appearance (clarity, colour, visible particles), osmolality, pH), identity (icIEF), quantity (protein concentration, extractable volume), biological activity (bioassay), purity and impurities (SE-HPLC, CE-SDS, icIEF), and safety (sterility, endotoxins, container closure integrity, particulates).

The panel of analytical procedures is adequate to monitor and control SB12 FP quality at release and during shelf life. The current control strategy for Polysorbate 80 content in AS and FP is sufficiently described and the justification acceptable.

The acceptance criteria of shelf-life specifications for some tests were questioned and tightened during the procedure considering also clinically qualified purity profile for the reference product Soliris.

Nitrosamine impurity risk assessment has been conducted in accordance with the EMA principles outlined in the "Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004" (EMA/369136/2020)". In conclusion, no risk of nitrosamine contamination in Epysqli AS manufacturing process was concluded for Epysqli finished product and therefore, no additional control measures are deemed necessary.

A risk assessment on the potential presence of elemental impurities in the FP has been performed. As a result of the assessment, potential risks associated to the elemental impurities were shown to be almost low in all aspects. No elemental impurity was identified to be above the PDE level for parenteral products according to ICH Q3D. No further controls for elemental impurities seem required.

An overview of the analytical procedures used for release and stability testing of FP was presented. The panel of analytical procedures is adequate to monitor and control Epysqli drug substance quality at release and during shelf life. The analytical methods specific for the FP only are particulate matter, sterility and container closure integrity. The validation reports of the analytical procedures used for Epysqli FP release and stability testing were presented.

The reference standards used in the release and stability testing of the FP are the same as those used for the release and stability testing of the AS (discussed previously).

Batch analysis

Batch analysis data are presented for FP lots used for small scale pilot, clinical trials, stability and process validation. All lots met the acceptance criteria in place at the time of release. The results demonstrate consistency of the manufacturing process capabilities. All lots comply with the commercial acceptance criteria.

2.4.3.3. Stability of the product

The proposed shelf life of Epysqli FP is 36 months when stored at the recommended temperature of 5 ± 3 °C.

Stability studies were conducted in accordance with ICH Guidelines Q1A (R2). The container closure material used for stability studies is identical to that used for the commercial product.

The applicant provided the stability data of Epysqli FP for supporting the proposed shelf-life.

Long-term stability studies for several batches were presented. All submitted results in the long-term stability studies come from these batches which are considered to be representative of the commercial batch since comparability has been successfully demonstrated. All quality attributes of the long-term stability study met the acceptance criteria after 36 months. Accelerated and stress data are also available and acceptable.

To investigate the impact of temperature excursion during handling and transport to product quality, two temperature cycling studies were conducted; a short-term temperature cycling study and a supply chain cycling study. The results support Epysqli FP stability in the immediate pack when exposed to either repeated short-term excursions at extreme temperature conditions or to temperature cycles in the supply chain.

A photostability study was designed and conducted according to ICH Guideline Q1B Stability Testing. All observed changes were within acceptance criteria. The results confirm that the commercial pack sufficiently protects the FP since there were no significant differences in all quality attributes between the dark control and the exposed sample.

An in-use study was conducted for Epysqli DP diluted in 5% dextrose in water and 0.9% and 0.45% NaCl solution diluent. In accordance with the results of this study the in-use storage condition in the SmPC section 6.3 has been set after dilution.

Finally a room temperature stability study monitored the stability profile of unopened Epysqli FP during exposure at room temperature. This study was performed using FP aged to the shelf-life. Results from the study support the storage condition and duration described in the Product Information SmPC (section 6.3 and 6.4).

Based on available stability data, the proposed shelf-life of 3 years with the storage conditions *"2°C – 8 °C"* as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.4. Biosimilarity

In general, a comprehensive and well-established biosimilarity exercise has been conducted. EU Soliris was used as the reference medicinal product (RMP) in quality exercises and clinical studies while US Soliris was used in clinical phase III study. As US-sourced comparator product was also used in the pivotal phase III study the applicant has conducted a three-way comparison between Epysqli, EU and US Soliris. EU-sourced RMP lots and US-sourced comparators lots have been included into the similarity exercise and compare against several produced batches of Epysqli. These Epysqli batches were comprised of PPQ FP, clinical FP and PPQ AS batch. FP batches included into the biosimilarity exercise were manufactured from independent AS batches. The number of RMP lots (and comparator lots for the 3-way comparison) is agreed as it forms a solid basis for evaluation of the variability in quality attributes of RMP. Regarding the proposed biosimilar the inclusion of clinical and process validation drug product lots is acknowledged.

Based on a risk assessment, which evaluated the potential impact on efficacy (potency), immunogenicity, pharmacokinetics (PK)/pharmacodynamics (PD), and safety of the product, quality attributes were categorised into three different tiers (high, moderate and low criticality tiers). The details of the performed risk assessment have been provided in the dossier.

Quality attributes reflecting the mode of action, have been assigned to the high-risk tier. A limited number of further quality attributes mainly related to the purity/impurity profile, the charged variant profile, quantity and certain further biological assays have been classified as moderate risk attributes whereas the remaining quality attributes have been classified as low criticality attributes. Depending on this classification different statistical tools for establishment of biosimilarity ranges and different numbers of RMP (and comparator) lots have been used for similarity evaluation of the quality attributes.

A broad panel of standard and state-of-the-art methods has been applied for similarity evaluation and addresses all relevant physicochemical and biological characteristics of the eculizumab molecule. Qualification information on methods and assays used for comparative characterization of the molecules is included now. It was stated that analytical methods to evaluate physicochemical properties were calibrated and qualified in accordance with ICH Q2 (R1), which is endorsed. Method suitability was ensured by periodical calibration when appropriate or with internal known standard or control testing. Method qualification characteristics to evaluate quality-related properties included specificity, linearity, accuracy, precision, ranges, limits of detection and robustness. For biological assays the applicant used known controls and standards ensuring method suitability for biological assays. The applicant presented tables with tests and analytical methods for similarity attributes as an overview and further goes into more detail with each method suitable for each quality attribute investigated during comparability assessment. Performance characteristics and results are tabularly outlined. A tabulated summary of the tests and analytical methods used in similarity assessment is presented in Table 1.

Table 1. Tests and Analytical Methods Used in Similarity Assessment

Molecular parameter	**Attribute**	**Methods**	**Key findings, conclusions**
Primary structure and post translational modification	Molecular weight	LC-ESI-MS	Similar
	Amino acid sequence	LC-ESI-MS	Identical primary sequence
	Peptide mapping	LC-ESI-MS	Similar
	N-terminal sequence	LC-ESI-MS	Similar
	C-terminal sequence	LC-ESI-MS	SB12 and Soliris contain the same C-terminal sequences but with minor quantitative difference. A slight difference was observed in the relative contents of C-terminal forms of heavy chain between SB12 and Soliris. However, the detected difference is considered unlikely to be clinically significant.
	Extinction coefficient	SEC-MALS	Similar
	Oxidation	LC-ESI-MS	A slight difference was observed in levels of oxidation between SB12 and Soliris. However, the detected difference is considered unlikely to be clinically significant.
	Deamidation	LC-ESI-MS	A slight difference was observed in levels of deamidation between SB12 and Soliris. However, the levels of deamidation in SB12 and Soliris were low and the detected difference is considered unlikely to be clinically significant.
Glycan profiles	N-linked glycosylation site	LC-ESI-MS	Similar

Molecular parameter	Attribute	Methods	Key findings, conclusions
	N-glycan identification	LC-ESI-MS	Minor differences were observed in the detected N-glycan species between SB12 and Soliris derived from cell line differences. The difference N-glycan form is not considered to have an adverse impact on immunogenicity and PK profile.
	N-glycan profile (afucosylation, high mannose variants, galactosylation)	HILIC-UPLC	Minor differences were observed in the detected N-glycan species between SB12 and Soliris. However, the slight difference is considered unlikely to be clinically significant.
Purity and impurities	Monomers, HMW (multimers), and fragments	SE-HPLC	Similar
		CE-SDS (Non-reducing)	Similar
		CE-SDS (Reducing)	Similar
Charge variants	Main, acidic and basic variants	icIEF	All batches of SB12, EU and US Soliris had the same pI of main peak. The relative contents of acidic and basic variants for all SB12 batches were within both EU and US similarity ranges. For the relative contents of main, one batch of SB12 was slightly higher than EU and US similarity ranges, but the detected difference was considered unlikely to be clinically significant.
		AEX-HPLC	Similar
Hydrophobicity	Main and post-main	RP-UPLC	Similar
Higher order structure	Disulfide bond	LC-ESI-MS	Similar
	Free sulfhydryl group quantification	Thiol-assay	Similar
	Secondary and tertiary structure	CD spectroscopy (far-UV, near-UV), ITF, FTIR, DSC, H/DX-MS	Similar
	Aggregate	SEC-MALS, SV-AUC, DLS, MFI	Similar
Quantity	Protein concentration	UV/Vis at A_{280}	Protein concentrations of all SB12 batches were within the EU similarity range while two batches of SB12 were out of the US similarity range. However, the slight difference in protein concentration was not considered significant as the results met the CoA requirement of Soliris.
Biological properties	Potency	C5 inhibition assay, C5 binding assay, anti-hemolytic assay	Similar
	Additional biological properties	FcRn, Fcy receptors and C1q binding assays, C5 polymorhic variants binding assay	Similar

Comparative characterisation of primary structure and post-translational modifications included molecular weight determination by LC-ESI-MS, amino acid sequencing by LC-ESI-MS, peptide mapping

by LC-ESI-MS, N- and C-terminal sequencing by LC-ESI-MS, extinction coefficient analysis by SEC-MALS, oxidation by LC-ESI-MS, and deamidation by LC-ESI-MS.

Comparison of glycan profiles included the identification of N-linked glycosylation site using LC-ESI-MS, N-glycan identification by LC-ESI-MS, and determination of the relative contents of the identified N-glycans by using HILIC-UPLC.

Purity and product-related impurities were investigated by SE-HPLC to evaluate the relative contents of high molecular weight species and monomer. In addition, CE-SDS under reducing & non-reducing conditions was applied to measure the relative contents of LC and HC as well as the level of various types of mis-assembled species such as single LC, HC, two heavy chain and one light chain (2H1L), and other fragmented species.

In order to evaluate the charge variants (%Acidic, %Main, and %Basic), icIEF is used, as well as, anion exchange-high performance liquid chromatography (AEX-HPLC) is also used as supportive orthogonal method of icIEF whereas hydrophobic heterogeneities were analysed by reverse phase-ultra performance liquid chromatography (RP-UPLC).

Comparative characterisation of higher order structures included disulfide bond analysis performed by LC-ESI-MS, far-UV and near-UV CD characterisation of secondary and tertiary structure, intrinsic tryptophan fluorescence (ITF) to evaluate the protein folding, and fourier transform infrared (FTIR) spectroscopy as one of the methods for comparative evaluation of the secondary structure. In addition differential scanning calorimetry (DSC) was used to determine the heat-induced protein denaturation pattern, hydrogen/deuterium exchange with mass spectrometry (H/DX-MS) to determine the conformation and conformational dynamics, SEC-MALS in order to determine the molecular weights of the monomer and sedimentation velocity analytical ultracentrifugation (SV-AUC) employed as a method orthogonal to SEC-MALS. Finally, dynamic light scattering (DLS) and micro-flow imaging (MFI) were used for particle assessment.

The results support the applicant`s conclusion that similarity for the relevant physicochemical quality attributes has been demonstrated. No significant differences were observed, for the majority of the compared quality attributes the data for SB12 were within the pre-established similarity ranges. Nevertheless, for certain physicochemical attributes differences were observed discussed below.

Slight difference of oxidation and deamidation levels was sufficiently justified to have no impact.

A slightly different qualitative profile of N-glycans by LC-ESI-MS has been reported. These differences were explained by the different expression systems (CHO cells for SB12 whereas Soliris is produced in NS0 murine cells). Minor glycan species were varied in SB12 and Soliris but the applicant provide a discussion and sufficiently justified that these differences have no impact on efficacy, PK and immunogenicity. Reference is made to the EMA guideline EMA/CHMP/BWP/247713/2012 which states that "Differences that may confer a safety advantage (e.g. lower levels of impurities) should be explained but are unlikely to preclude biosimilarity".

In summary, it is not expected that the differences in N-glycan pattern would affect safety and efficacy of SB12 in future patient applications; thus, these slight differences can be accepted and do not jeopardize the biosimilarity claim.

Concerning the charged variants by imaged capillary isoelectric focusing, one batch of SB12 had a higher %main form than EU and US similarity ranges. Taking into account that this batch is only marginally outside the similarity ranges, this outlier is not seen as a concern for the biosimilarity claim.

Size exclusion chromatography with multi angle light scattering (SEC-MALS) was used to determine the molecular weights of the monomer.

Similarity between SB12 and Soliris in terms of biological activity was studied by a C5 inhibition assay to measure the inhibitory activity for C5-dependent CDC of SB12 and Soliris and a C5 binding assay using an enzyme linked immunosorbent assay (ELISA). Further assays include an anti-heamolytic assay to measure inhibitory effect of SB12 and Soliris on C5-induced heamolysis as well as binding to FcRn determined based on surface plasmon resonance (SPR). For binding to FcRn, the results are given %Relative Binding Activity, in addition the data for binding kinetics and affinity (e.g. ka, kd KD values) derived from the SPR analysis are included.

Further to the above-mentioned assays, the applicant has investigated a number of additional biological properties. The assays used for determination of these attributes are either orthogonal to methods used for high-risk attributes or these additional attributes are unlikely to have any impact on the clinical behaviour. Thus, these additional biological attributes were classified as low critical and the similarity evaluation was conducted with a limited number of batches in a side-by-side manner (without any pre-established similarity criteria). These properties included C5 binding additionally determined using an orthogonal method SPR, Fcy receptors by SPR, binding to C1q using ELISA and binding to C5 polymorphic variants using ELISA. The side-by-side evaluation of these additional, low criticality attributes with a limited number of batches can be accepted.

It is agreed that a broad panel of binding and *in-vitro* assays have been applied in order to demonstrate similarity for biological properties between SB12 and Soliris. Eculizumab has hybrid human IgG2-IgG4 heavy-chain constant regions, which have been reported to be unable to activate CDC or bind to the Fc-γ receptor of effector cells. Thus, functional activities related to the Fc domain such as ADCC, ADCP and CDC have not been evaluated in the biosimilarity exercise, this strategy is acceptable.

Overall, a thorough and extensive biological function description was carried out by the applicant. The assays aim mostly on high criticality attributes of SB12 and precisely reflect the mode of action of eculizumab. The applicant likewise showed assays for low criticality attributes that are not expected to have an influence on safety and efficacy of the molecule. As there are no known Fc effector functions it is acceptable to omit ADCC, ADCP and CDC characterisation. A few minor concerns raised during the initial assessment have been sufficiently addressed.

To further support the biosimilarity claim a number of comparative stress stability studies have been conducted for Epysqli FP and Soliris. The results demonstrated that the stability profile of Epysqli was similar to that of Soliris.

In addition to the similarity assessment of SB12 versus EU Soliris, comparability of EU Soliris versus US Soliris has been investigated. A comparable quality profile between both products was demonstrated.

Overall, a well-established biosimilarity exercise has been conducted, which confirms biosimilarity of SB12 with its reference product EU Soliris.

2.4.3.5. Adventitious agents

The microbial and virus testing of MCB and WCB was performed as part of cell bank characterisation, results confirmed no contamination and therefore from adventitious safety perspective the MCB is considered suitable for routine production. The routine control strategy for unprocessed bulk harvest concerning microbial and virus contamination is considered adequate and the results for clinical and PPQ batches confirming no contamination were provided Overall, the testing for cell banks and unprocessed bulk harvest is considered in compliance with ICH Q5A.

No raw materials of animal origin were used in MCB/WCB generation and routine production. Adequate information and supportive documentation for the materials of animal origin were provided and the TSE relevant materials are considered compliant with NfG EMA/410/01 rev.3. For the raw material used in the SB12 host cell line production a reference to previous (obsolete) version of the TSE CEP was provided. This is however considered acceptable, as the raw material was used in the past and the certificate of suitability was valid at that time. Related TSE-risk for the final product is considered negligible (age of animals, country of origin, category of material, stage in process).

Virus validation claim is based on the following steps: low pH inactivation, viral filtration (single-use), and chromatography steps including protein A affinity. Four relevant model viruses (Table 2) were selected for these studies.

Table 2. Model Virus List for Viral Clearance Studies

Virus	Virus Family	Envelope	Genome	Approx. Size (nm)
MVM	*Parvoviridae*	No	DNA	18-24
PRV	*Herpesviridae*	Yes	DNA	120-200
Reo-3	*Reoviridae*	No	RNA	60-80
X-MuLV	*Retroviridae*	Yes	RNA	80-110

MVM: Minute virus of mice, PRV: pseudorabies virus, Reo-3: reovirus type 3, XMuLV: xenotropic murine leukemia virus

The scale-down conditions relevant for the virus validation studies are listed and scale-down models for chromatography and viral filtration are described in detail including results of performance parameters. Resin lifetime evaluation was performed, naive and aged resins were used for virus validation. Calculation of the virus particles per dose and estimated safety margin is considered acceptable. Retrovirus risk assessment is based on TEM in unprocessed bulk, calculation was provided and is considered sufficiently in line with ICH Q5A (R1). Resulting safety margin is acceptable. The respective validation report was submitted.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Epysqli was developed as a biosimilar to Soliris. A well-established Module 3 has been provided. The AS as well as FP manufacturing with their process controls have been sufficiently described. GMP compliance of the manufacturing, testing and storage sites has been confirmed. A Major Objection raised concerning the GMP status of the FP manufacturing site has been resolved by provision of a valid GMP certificate.

Process validation has been performed and confirms that both, the AS and FP manufacturing process, are capable to produce material which meets its predefined quality requirements. Control of critical steps have been clearly presented, an appropriate process control strategy is in place which together with the release specifications ensures that only product confirming to predefined quality standards will enter the market. Raw and starting materials used in the active substance manufacturing as well as the well-known and compendial excipients used for formulation of SB12 have been appropriately addressed. The manufacturing history of the AS and FP manufacturing process from pilot to clinical and further to the intended commercial process has been presented. To address the changes implemented in the process after conduct of the clinical trials a comparability exercise has been performed. This evaluation confirmed comparability of clinical with PPQ material. The specifications for AS and FP include tests for relevant quality attributes. The container closure systems for AS and FP are sufficiently addressed. Finally the stability data have been presented and support the proposed shelf-life claims for AS and FP.

An extensive and well-suited biosimilarity exercise has been conducted. A three-way comparison was performed between SB12, EU and US Soliris. A broad panel of state-of the art methods has been used

to evaluate similarity at quality level; suitability of these methods has been confirmed. In summary similarity was demonstrated, a few minor differences in certain attributes (N-glycosylation, oxidation and deamidation, and charged variants) were justified to have no impact on efficacy, PK and safety. Regarding the differences in N-glycosylation it should be noted that Fc effector functions (which could be impacted by different N-glycan profiles) do not play a role in the mode of action of eculizumab. A thorough discussion of potential clinical impact on efficacy, pharmacokinetics (PK), and safety/immunogenicity derived from the difference in N- glycans has been provided by the applicant. It is concluded that the different N-glycan profiles would not have an impact on efficacy, PK, and safety/immunogenicity which can be supported. No atypical N-glycan structures which may raise any safety concern were identified. Finally, it is not expected that these differences have any biological relevance which was confirmed by a broad panel of binding and in-vitro assays applied in order to demonstrate similarity for biological properties between SB12 and Soliris.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the implementation of the working reference standard and the submission of the results of the leachable study. These points are put forward and agreed as CHMP Recommendations for future quality development.

In summary, all raised concerns have been solved. No quality issues negatively impacting on the Benefit-Risk balance have been identified for SB12. Consequently, from a quality perspective the MAA for Epysqli is approvable.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Satisfactory information has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to implement the working reference standard until Q2/2023.
- The applicant is recommended to submit the results from the leachable study for the container closure system of Epysqli finished product under long-term and accelerated storage conditions should be submitted when these data become available.

2.5. Non-clinical aspects

2.5.1. Introduction

The pharmacology program was focused on primary PD. A series of *in vitro* PD studies was performed to assess any potential differences in biological activity between SB12 and EU or US Soliris. Given that SB12 is developed as a proposed biosimilar, secondary PD, safety pharmacology and PD drug interaction studies were not deemed necessary in accordance with EMA guideline [EMA/CHMP/BMWP/403543/2010].

As there were no underlying uncertainties after quality and *in vitro* studies, *in vivo* studies were not performed, which had been agreed by the EMA SA [EMA/CHMP/SAWP/634958/2017]. Thus, the similarity data with respect to pharmacokinetic (PK) profiles of SB12 and Soliris in non-clinical animal studies are not available.

Toxicological *in vivo* studies were not performed. Animal studies are less sensitive to detect differences between biosimilar and reference products and species differences between animals and humans limit the suitability of this approach to evaluate biosimilarity [Van Aerts *et al.,* 2014]. Thus, no *in vivo* animal studies for SB12 were conducted which was agreed by the European Medicine Agency (EMA) [EMA/CHMP/SAWP/634958/2017].

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Comparative *in vitro* studies to evaluate similarity between SB12 and EU/US Soliris with regard to biological properties were conducted and generally showed similar biological properties between both products. Additional biological properties of SB12 (e.g. C5 binding by SPR (surface plasmon resonance), Fcγ receptors , C1q binding, C5 polymorphic variants binding) were also compared to EU/US Soliris in side-by-side analyses. Study reports of those studies were submitted in Module 3 of the dossier and were thus assessed and discussed in detail in the Quality section of the assessment report. Please refer to the Quality AR.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed.

2.5.2.3. Safety pharmacology programme

No safety pharmacology studies were conducted given no residual uncertainties in the comparative analytical similarity assessment (inclusive of comprehensive *in vitro* functional evaluation, and supplementary comparative *ex vivo* pharmacology studies).

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic interaction studies were not conducted given Soliris (eculizumab) has been administered to patients treated concomitantly with a broad range of commonly used medications and no safety issues have arisen.

2.5.3. Pharmacokinetics

Comparative *in vivo* pharmacokinetic (PK)/toxicokinetic studies with SB12 and Soliris were not conducted and are not required. The lack of these types of studies is justified, and is in line with relevant guidelines for biosimilars, on basis that studies in animals for demonstrating biosimilarity are generally more insensitive than *in vitro* studies, and no differences indicating potential effects on PK was noted in *in vitro* binding analyses to FcRn. Moreover, eculizumab is specific to human C5 and does not inhibit C5 in species commonly used in nonclinical studies.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single-dose toxicity studies were not conducted given the lack of a pharmacologically relevant species and is also in accordance with the EMA guideline (EMA/CHMP/BMWP/403543/2010), and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017].

2.5.4.2. Repeat dose toxicity

No pivotal nor non-pivotal repeat-dose toxicity studies have been performed in accordance with the EMA guideline (EMA/CHMP/BMWP/403543/2010), and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017].

2.5.4.3. Genotoxicity

No *in vitro* nor *in vivo* genotoxicity studies have been performed in line with the EMA guideline (EMA/CHMP/BMWP/403543/2010), and the FDA guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Guidance for Industry".

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been performed in line with the EMA guideline (EMA/CHMP/BMWP/403543/2010), and the FDA guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Guidance for Industry".

2.5.4.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies (fertility and early embryonic developmental, embryo-fetal development, pre- and postnatal development including maternal functions, offspring studies) have been performed, which is in line with the EMA guideline (EMA/CHMP/BMWP/403543/2010) and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017].

2.5.4.6. Toxicokinetic data

Not Applicable.

2.5.4.7. Local Tolerance

Not Applicable.

2.5.4.8. Other toxicity studies

No other toxicity studies (antigenicity, immunotoxicity, dependence, metabolites, studies on impurities) have been performed in line with the EMA guideline (EMA/CHMP/BMWP/403543/2010) and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017].

2.5.5. Ecotoxicity/environmental risk assessment

The active substance (eculizumab) is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, SB12 is not expected to pose a risk to the environment. The EMA guideline "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 2*) makes specific reference to certain types of products including proteins (such as SB12), indicating that these products are due to their nature unlikely to result in a significant risk to the environment.

2.5.6. Discussion on non-clinical aspects

Study reports of the conducted PD studies were submitted in Module 3 of the dossier and were thus assessed and discussed in detail in the Quality section of the assessment report. Please refer to the Quality AR.

Dedicated studies on Secondary pharmacodynamics, Safety pharmacology and PD drug interactions were not conducted. This is in line with recent guidance and recommendations.

In accordance with the EMA's "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" [EMA/CHMP/BMWP/42832/2005 Rev 01] and FDA's "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", independent toxicity studies to evaluate non-clinical safety, genotoxicity, reproductive and developmental toxicity, and carcinogenicity were not performed. Animal studies are less sensitive to detect differences between biosimilar and reference products and species differences between animals and humans limit the suitability of this approach to evaluate biosimilarity [Van Aerts et al., 2014]. Thus, not performing *in vivo* animal studies for SB12 development was endorsed by the EMA [EMA/CHMP/SAWP/634958/2017].

Furthermore, the non-clinical development program for SB12 is in accordance with the European Medicines Agency (EMA) guideline "Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" [EMA/CHMP/BMWP/403543/2010] and the US Food and Drug Administration (FDA) guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Guidance for Industry". This development program for SB12 was endorsed by the EMA [EMA/CHMP/SAWP/634958/2017].

Considering the expected exposure, the nature of the product and the concessions of the current guidelines, the absence of studies in the context of a formal environmental risk assessment (ERA) for SB12 is considered justified. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, eculizumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The nonclinical data support the biosimilarity of SB12 versus the Soliris-EU (and Soliris-US).

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 3: overview of the clinical development plan

Study ID (Country)	Study Objective	Study Design/Duration	Study Population	Primary Endpoint
SB12-1001 **Phase I** (Germany)	Comparative PK, safety, tolerability, immunogenicity, PD Primary Objective: To demonstrate PK similarity of SB12 to EU Soliris® and US Soliris®, and EU Soliris® to US Soliris® in healthy subjects	Randomized, double-blind, three-arm, parallel group, single-dose study Total duration of approximately 92 days including 28-days screening period	Healthy subjects	PK • Area under the concentration-time curve from time zero to infinity (AUC_{inf})
SB12-3003 **Phase III** (India, Republic of Korea, Malaysia, Mexico, Romania, Taiwan, Thailand, Ukraine)	Comparative efficacy, safety, PK, and immunogenicity Primary Objective: To demonstrate comparable clinical efficacy of SB12 and Soliris® by evaluating LDH in patients with PNH	Randomized, double-blind, multicenter study Total duration of treatment of 50 weeks. Depending on the applicable version of the study protocol for each patient, the last assessment was performed either at Week 52 or Week 58 or 8 weeks after the last dose of SB12 or Soliris® in case of early termination.	Patients with PNH	For EMA: • LDH level (U/L) at Week 26 For FDA: • Time-adjusted AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52

AUC_{inf} = Area under the concentration-time curve from time zero to infinity; AUEC = area under the effect curve; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal hemoglobinuria; PD = pharmacodynamic(s); PK = pharmacokinetic(s)

2.6.2. Clinical pharmacology

The pharmacology of SB12 has been investigated in two clinical studies:

Phase I study (SB12-1001): A randomized, double-blind, three-arm, parallel group, single dose study in healthy subjects to demonstrate similarity in PK, safety, tolerability, immunogenicity and PD between SB12 and Soliris.

Phase III study (SB12-3003): A randomized, double-blinded, multicentre study to compare the efficacy, safety, PK, and immunogenicity in patients with PNH between SB12 and Soliris.

2.6.2.1. Pharmacokinetics

Bioanalytical Method – Pharmacokinetic Assay

A quantitative assay developed for the determination of SB12 and Soliris in human serum using an electrochemiluminescence (ECL) assay of Meso Scale Discovery (MSD) platform was successfully validated. In this assay, SB12 is used to prepare standard samples and SB12 or EU/US Soliris is used to prepare Quality Control samples. All samples undergo acid dissociation (acetic acid, 300 mM) to release any endogenous C5 protein bound with drug (SB12, or EU/US Soliris). Samples are then neutralised and incubated with capture solution to allow drug to bind to excess biotinylated C5. After incubation with excess biotinylated C5, samples are added to the streptavidin-coated MSD plate, following incubation with sulfo-TAG labelled anti-human IgG4-peroxidase antibody. Then, the assay produces chemiluminescence signal following the addition of read buffer containing tripropylamine when an electrical voltage is applied. The resulting chemiluminescence is measured in relative light units (RLU) using the MESO Quickplex SQ120 plate reader.

Table 4: Validation parameters

Validation Parameter	Results	
Analytical procedure number	10010718-HAR-IC18-069	
This analytical method was used in the following study:	SB12-1001	SB12-3003
Analyte	Eculizumab in normal healthy human serum	Eculizumab in PNH patient serum
Method of detection	Electrochemiluminescence (Meso Scale Discovery)	
Calibration model	4 Parameter Logistic curve	

Weighting factor	$1/Y^2$	
Quantifiable working range	0.80 µg/mL to 12.50 µg/mL (neat serum)	
Quality control (QC) levels	LLOQ: 0.80 µg/mL LQC: 2.40 µg/mL MQC: 3.20 µg/mL HQC: 9.40 µg/mL ULOQ: 12.50 µg/mL UHQC: 500.00 µg/mL only using stability test (diluted 1 in 150)	
Minimum Required Dilution (MRD)	1 in 150	
MRD solution	Low Cross Buffer	
Precision and accuracy (≤ 20% at LQC, HQC, MQC and ≤ 25% at LLOQ and ULOQ)	Requirements fulfilled	
Selectivity (matrix)	Requirements fulfilled using serum from normal healthy individuals	Requirements fulfilled using serum from PNH patient individuals
Hemolyzed serum interference	Up to 5% hemolysis	
Lipemic serum interference (Approximately 300 mg/dL)	Requirements fulfilled	
Dilution linearity/hook effect	1 in 500 dilution (in addition to 1 in 150 MRD)	
Specificity/Interference (C5 protein)	No interference detected with C5 up to 400.00 µg/mL, at 0.80 µg/mL and 12.50 µg/mL of SB12, EU Soliris® and US Soliris®.	
Specificity/Interference (Bilirubin)	No interference detected with Bilirubin up to 10.00 mg/dL, at 0.80 µg/mL and 12.50 µg/mL of SB12 and EU Soliris®. No interference detected with Bilirubin up to 10.00 mg/dL, at 0.80 µg/mL US Soliris®. Interference observed at 10.00 mg/dL Bilirubin at 12.50 µg/mL of US Soliris®. No interference detected with Bilirubin up to 5.00 mg/dL, at 0.80 µg/mL and 12.50 µg/mL of US Soliris®.	
Specificity/Interference (Rifampicin)	No interference detected with Rifampicin up to 100.00 µg/mL, at 0.80 µg/mL and 12.50 µg/mL of SB12 and EU Soliris®. Interference observed at 100.00 µg/mL of Rifampicin at 0.80 µg/mL US Soliris®. No interference detected with Rifampicin up to 50.00 µg/mL, at 0.80 µg/mL and 12.50 µg/mL of US Soliris®.	
Bench top stability	SB12 and EU Soliris®: 72 hours at room temperature. US Soliris®: 24 hours at room temperature	
Freeze-thaw matrix stability	SB12 and EU Soliris®: 8 cycles at < −50°C (−80°C nominal) US Soliris®: 6 cycles at < −50°C (−80°C nominal)	
Frozen matrix stability at <−50°C (−80°C nominal)	SB12: 744 days EU Soliris®: 744 days US Soliris®: 448 days	
Frozen matrix stability at <−10°C (−20°C nominal)	SB12: 70 days[a] EU Soliris®: 455 days US Soliris®: 231 days	

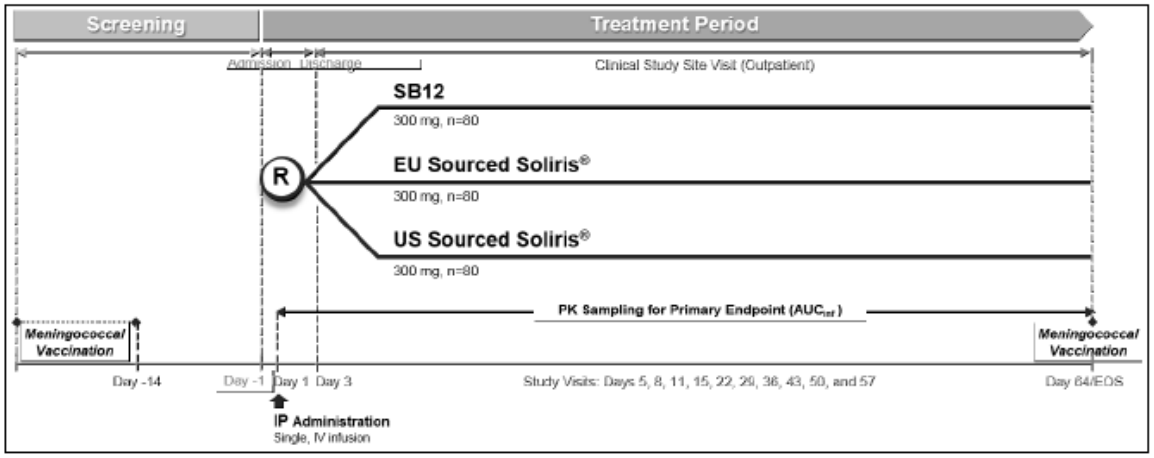
HQC =high quality control; LLOQ = lower limit of quantification; LQC = low quality control; MQC = medium quality control; MRD = minimum required dilution; PL = parameter logistic; QC = quality control; UHQC = ultra high quality control; ULOQ = Upper limit of quantification

[a] No clinical samples were stored at −20°C more than 70 days

Phase I study SB12-1001

Study Design

The Phase I study SB12-1001 was a double-blind, three-arm, parallel group, and single-dose study. A total of 240 healthy subjects aged 18-55 years were enrolled and randomised in a ratio of 1:1:1 to receive a single dose of either SB12, EU sourced Soliris, or US sourced Soliris via IV infusion for 35 minutes. The study design is depicted in the figure 1 below.



AUC_{inf} = area under the concentration-time curve from time zero to infinity; EOS = end of study; IP = investigational product; IV = intravenous; PK = pharmacokinetic; R = randomisation

Figure 1: Graphical study design

Treatments

SB12, EU sourced Soliris, and US sourced Soliris were administered by IV infusion at a dose of 300 mg (concentration of 5 mg/mL) on Day 1.

Outcomes/endpoints

Primary PK Endpoint:

Area under the concentration-time curve (AUC) from time zero to infinity (AUC_{inf})

Secondary PK Endpoints:

AUC from time zero to the last quantifiable concentration (AUC_{last}); Maximum serum concentration (C_{max}); Time to reach Cmax (T_{max}); Volume of distribution during terminal phase (V_z); Terminal rate constant (λ_z) calculated by linear least squares regression analysis using the last three (or more) non-zero concentrations; Terminal half-life ($t_{1/2}$) calculated by $\ln(2)/\lambda_z$; Total body clearance (CL); Percentage of AUC_{inf} due to extrapolation from time of last measurable concentration (T_{last}) to infinity ($\%AUC_{extrap}$)

PD Endpoint:

Change in terminal complement activity over time.

Safety Endpoints:

Adverse events (AEs) and serious AEs (SAEs); Clinical laboratory values including haematology, biochemistry, and urinalysis; 12-lead ECG; Vital signs; Physical examination

Immunogenicity Endpoints:

Incidence of anti-drug antibodies (ADAs) to eculizumab; Incidence of neutralising antibodies (NAbs) to eculizumab

Randomisation

Screening numbers were assigned to subjects sequentially after signing the informed consent form and prior to any screening procedure. Each screening number was assigned to only one subject and was not re-used.

Blinding (masking)

A double-blind technique was used. The IPs were prepared and dispensed by unblinded pharmacists or properly trained pharmacy delegate(s). The unblinded pharmacist provided the site staff with ready-to-use blinded IP infusion solutions, packaged identically in order to maintain the blinding for IP administration. The subject, the Investigator, the site staff, the Sponsor, and other study personnel who were involved in the treatment or clinical evaluation of subjects were unaware of the treatment group assignments.

Participant flow

A total of 240 subjects were planned to be randomised. 479 subjects were screened of whom 240 subjects were randomised. The most common reason for screening failure was failure to meet the randomisation criteria. Of the subjects who were randomised, 239 completed the study and 1 subject discontinued the study (i.e., EU sourced Soliris treatment group, who withdrew consent for further participation on Day 9). None of the subjects discontinued the study due to an AE.

Conduct of the study

One non-substantial amendment was made to the original protocol (version 1.0 dated Jun 04, 2018) prior to study initiation, to correct minor administrative errors. The study was conducted in accordance with the study protocol version 2.0 dated Jul 05, 2018.

Baseline data

The demographic characteristics for the RAN are summarised in the Table 5 below

Table 5: Demographic characteristics (randomised set)

Characteristics	SB12 N=80	EU sourced Soliris® N=80	US sourced Soliris® N=80	Total N=240
Age (years)				
Mean	39.6	40.9	40.2	40.2
SD	10.73	9.29	9.15	9.72
Median	40.5	41.0	39.0	40.0
Min	20	19	23	19
Max	55	55	55	55
Gender, n (%)				
Male	78 (97.5)	76 (95.0)	76 (95.0)	230 (95.8)
Female	2 (2.5)	4 (5.0)	4 (5.0)	10 (4.2)
Race, n (%)				
White	79 (98.8)	75 (93.8)	76 (95.0)	230 (95.8)
Black or African American	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.4)
Asian	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.4)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.3)	3 (3.8)	3 (3.8)	7 (2.9)
Ethnicity, n (%)				
Hispanic or Latino	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.8)
Not Hispanic or Latino	80 (100.0)	78 (97.5)	78 (97.5)	236 (98.3)
Unknown	0 (0.0)	2 (2.5)	0 (0.0)	2 (0.8)
Height (cm)				
Mean	179.9	180.6	180.5	180.3
SD	5.95	6.88	6.48	6.43
Median	180.0	180.5	181.0	181.0
Min	166	162	164	162
Max	196	195	198	198
Weight (kg)				
Mean	82.33	81.26	83.52	82.37
SD	6.544	6.697	6.767	6.706
Median	83.35	80.35	82.60	82.40
Min	70.0	70.0	70.1	70.0
Max	94.3	94.2	94.3	94.3
BMI (kg/m^2)				
Mean	25.49	24.98	25.67	25.38
SD	2.231	2.290	1.993	2.186
Median	25.55	24.80	25.75	25.50
Min	20.2	20.0	21.8	20.0
Max	29.9	29.6	29.9	29.9

BMI = body mass index; N = number of subjects in the Randomised Set; n = number of subjects within the category; SD = standard deviation
Percentages were based on the number of subjects in the Randomised Set.

Numbers analysed

The number of subjects in each of the analysis sets are summarised by treatment group in the table 6 below.

Table 6: Data Sets Analysed (randomised set)

Treatment	SB12	EU sourced Soliris®	US sourced Soliris®	Total
Number (%) of subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Randomised Set	80 (100.0)	80 (100.0)	80 (100.0)	240 (100.0)
Safety Set	80 (100.0)	80 (100.0)	80 (100.0)	240 (100.0)
PK Analysis Set	80 (100.0)	80 (100.0)	80 (100.0)	240 (100.0)

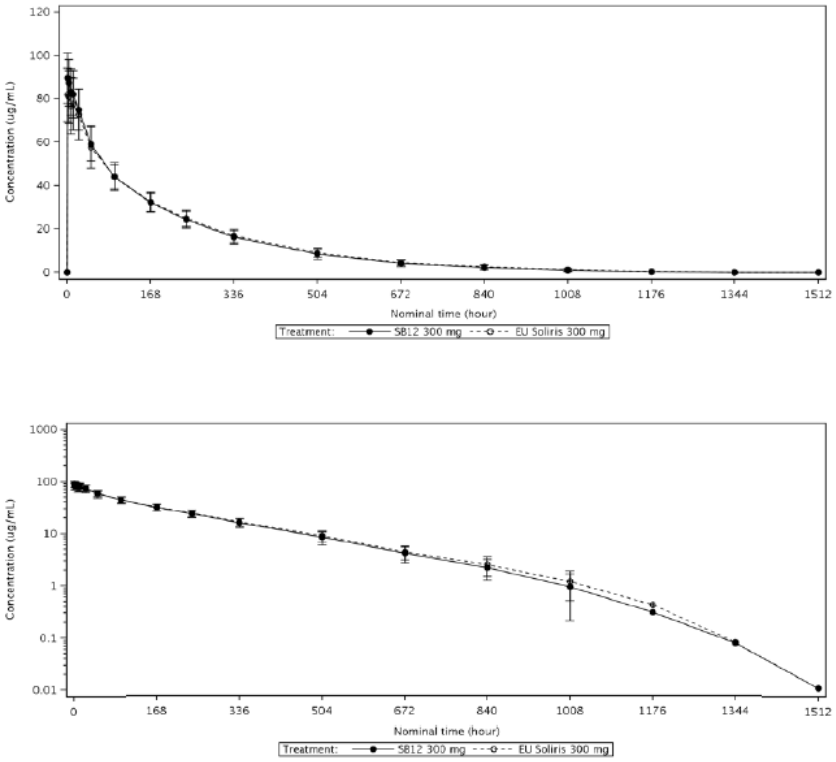
n = number of subjects within the category; PK = pharmacokinetics
Percentages were based on the number of subjects in the Randomised Set.

PK Results Study SB12-1001

Serum Concentrations

The mean serum concentration versus nominal time curves on linear and semi-logarithmic scale for the PKS are presented for pairwise comparisons of all study treatment groups. The comparison of SB12 and EU sourced Soliris is shown in the Figure 2 below.

Figure 2: Mean serum concentrations versus nominal times on linear (top graph) and semi-Logarithmic (bottom graph) of SB12 and EU sourced Soliris



Summary Statistics of Pharmacokinetic Parameters

The summary statistics of the PK parameters are presented for the PKS in the Table 7 below.

Table 7: Summary of pharmacokinetic endpoints by treatment group (PK analysis set)

PK Parameter	Statistics	SB12 N=80	EU sourced Soliris® N=80	US sourced Soliris® N=80
AUC_{inf}	n	80	79	80
(µg·h/mL)	Mean	16834.3	17008.9	17773.1
	SD	2426.80	2449.89	3138.67
	Median	16339.7	16759.5	17513.4
	Min	12046	10801	11538
	Max	23813	22665	30742
AUC_{last}	n	80	79	80
(µg·h/mL)	Mean	16498.8	16709.1	17482.1
	SD	2373.26	2435.32	3128.54
	Median	16044.2	16493.3	17137.7
	Min	11835	10622	11325
	Max	23515	22382	30493
C_{max}	n	80	80	80
(µg/mL)	Mean	91.609	84.327	88.832
	SD	11.6870	12.5412	12.9380
	Median	89.205	83.435	87.750
	Min	69.01	61.75	62.07
	Max	120.59	120.81	124.69
T_{max}	n	80	80	80
(h)	Median	0.708	3.967	2.317
	Min	0.60	0.60	0.60
	Max	24.18	24.03	24.15
V_z	n	80	79	80
(mL)	Mean	4705.7	4656.7	4381.8
	SD	2030.73	718.33	658.27
	Median	4625.4	4514.7	4329.5
	Min	3042	2799	2722
	Max	21832	6337	6220
CL	n	80	79	80
(mL/h)	Mean	18.162	18.021	17.352
	SD	2.4399	2.7446	2.8219
	Median	18.360	17.900	17.130
	Min	12.60	13.24	9.76
	Max	24.91	27.77	26.00
$t_{1/2}$	n	80	79	80
(h)	Mean	183.88	180.78	176.67
	SD	101.665	25.122	20.879
	Median	171.93	179.13	177.12
	Min	100.7	97.0	97.8
	Max	1051.5	232.3	247.0

N = number of subjects in the PK Analysis Set; n = number of subjects with an available assessment; SD = standard deviation
Source: Table 14.2-1.2

As shown in the Table 8 below, the mean (SD) of Tmax in the SB12, EU Soliris and US Soliris treatment groups were 3.173 (3.8709) h, 4.286 (5.3312) h, and 4.560 (5.3275) h, respectively.

Table 8: Summary statistics of T_{max} by treatment group (pharmacokinetic analysis set, study SB12-1001) (*ad hoc* analysis)

Pharmacokinetic Parameter	Statistics	SB12 N=80	EU Soliris N=80	US Soliris N=80
T_{max} (h)	n	80	80	80
	Median	0.708	3.967	2.317
	Min	0.60	0.60	0.60
	Max	24.18	24.03	24.15
	Mean	3.173	4.286	4.560
	SD	3.8709	5.3312	5.3275
	Geo. Mean	1.741	2.134	2.128
	Geo. SD	3.0103	3.3710	3.6553

Geo. Mean = geometric mean; Geo. SD = geometric standard deviation; Max = maximum; Min = minimum; n = number of subjects with available assessments; N = number of subjects in the Pharmacokinetic Analysis Set; SD = standard deviation; T_{max} = time to reach maximum serum concentration (C_{max})

Comparison between SB12 and EU sourced Soliris

The geometric LSMean ratio (90% CI) for SB12 and EU sourced Soliris in AUC_{inf} was 0.991 (0.9541 to 1.0285), which was within the pre-defined equivalence margin of 0.8 to 1.25.

Comparison between SB12 and US sourced Soliris

The geometric LSMean ratio (90% CI) for SB12 and US sourced Soliris in AUC_{inf} was 0.951 (0.9140 to 0.9904), which was within the pre-defined equivalence margin of 0.8 to 1.25.

Comparison between EU sourced Soliris and US sourced Soliris

The geometric LSMean ratio (90% CI) for EU sourced Soliris and US sourced Soliris in AUC_{inf} was 0.960 (0.9216 to 1.0010), which was within the pre-defined equivalence margin of 0.8 to 1.25.

PK in target population

Phase III study SB12-3003

Analysis of Pharmacokinetics in Study SB12-3003

Eculizumab C_{trough} by visit and actual treatment sequence within period for the PKS are presented in Table 11-15. The mean (SD) of eculizumab C_{trough} versus nominal time plot is presented in Figure 3 below.

The PK Analysis Set of Phase III study SB12-3003 included 49 subjects with PHN in total, randomized 1:1 to receive Soliris or SB12 during Period 1 until Week 26. Hence, 25 subjects received Soliris and 24 subjects received SB12 during this period. Steady-state concentrations for SB12 and Soliris were achieved by Week 4, which is in line with Soliris SmPC using PNH adult dosing regimen. For PK assessment in PNH subjects, no equivalence range has been pre-defined, and results are summarized descriptively. The mean (SD) eculizumab C_{trough} at Week 26 was 150.041 (62.6232) µg/mL in the Soliris group and 133.807 (71.6412) µg/mL in the SB12 group. Hence, eculizumab levels appeared similar with overlapping SD bars, albeit C_{trough} concentrations were consistently lower in the SB12 group compared to Soliris throughout Period 1.

At the beginning of Period 2, subjects were switched to receive the respective other treatment. Since the issue of a shortage of the comparator (Soliris) led to unplanned IP switch in Period 2 in 8 subjects, a total of 16 subjects were included in the actual Soliris treatment sequence during Period 2. Although at Week 52 mean (SD) eculizumab C_{trough} levels are highly similar between treatment groups [SB12:

129.084 (52.5487) µg/mL, Soliris: 127.102 (60.2749)], the plot showing eculizumab levels over time suggests that again SB12 levels appear lower at most time points during Period 2 compared to Soliris. Furthermore, 8 subjects with unplanned IP switch (back to SB12) had even lower eculizumab levels, compared to mean levels of other study participants receiving either SB12 or Soliris.

All subjects were ADA negative; hence, no comparison between ADA positive and ADA negative subjects was possible.

Table 9: Summary statistics for eculizumab C_{trough} (µg/mL) by visit (baseline, week 26 and week 52) and actual treatment sequence within period (pharmacokinetic analysis set)

Visit	Soliris® to SB12 N = 25	SB12 to All N = 24	SB12 to Soliris® N = 16	Unplanned IP Switch N = 8	Total N = 49
Baseline					
n	25	24	-	-	49
Mean	0.000	0.130	-	-	0.063
SD	0.0000	0.6348	-	-	0.4443
Median	0.000	0.000	-	-	0.000
Min, Max	0.00,0.00	0.00,3.11	-	-	0.00,3.11
%CV	N/A	489.9	-	-	700.0
Geo.Mean	N/A	3.110	-	-	3.110
Geo.SD	N/A	N/A	-	-	N/A
Geo.%CV	N/A	N/A	-	-	N/A
Week 26					
n	23	23	-	-	46
Mean	150.041	133.807	-	-	141.924
SD	62.6232	71.6412	-	-	67.0359
Median	148.470	100.750	-	-	135.445
Min, Max	45.28,282.86	50.57,298.82	-	-	45.28,298.82
%CV	41.7	53.5	-	-	47.2
Geo.Mean	135.832	117.475	-	-	126.321
Geo.SD	1.6255	1.6784	-	-	1.6518
Geo.%CV	51.6	55.5	-	-	53.5
Week 52					
n	21	22	14	8	43
Mean	129.084	116.563	127.102	98.120	122.678
SD	52.5487	53.8062	60.2749	36.4326	52.9396
Median	121.870	106.545	106.545	90.675	107.410
Min, Max	45.24,240.88	52.80,281.81	60.24,281.81	52.80,156.01	45.24,281.81
%CV	40.7	46.2	47.4	37.1	43.2
Geo.Mean	118.622	106.608	115.817	92.218	112.315
Geo.SD	1.5425	1.5293	1.5526	1.4618	1.5331
Geo.%CV	45.5	44.5	46.2	39.4	44.8

BLQ = below the limit of quantification; CV = coefficient of variation; Geo.Mean = geometric mean; Geo.SD = geometric mean standard deviation; Geo.%CV = geometric percent coefficient of variation; IP = investigational product; Max = maximum; Min = minimum n = number of subjects with non-missing values or without protocol deviation for pharmacokinetic (PK) blood sampling at the timepoint; N = total number of subjects in PK Analysis Set; N/A = not applicable; SD = standard deviation

- BLQ values were set to missing for the calculation of geometric summary statistics and were set to zero for the calculation of all other summary statistics.
- Geo CV% = SQRT ($e^{s^2} - 1$) × 100; where s is the standard deviation of the log-transformed values

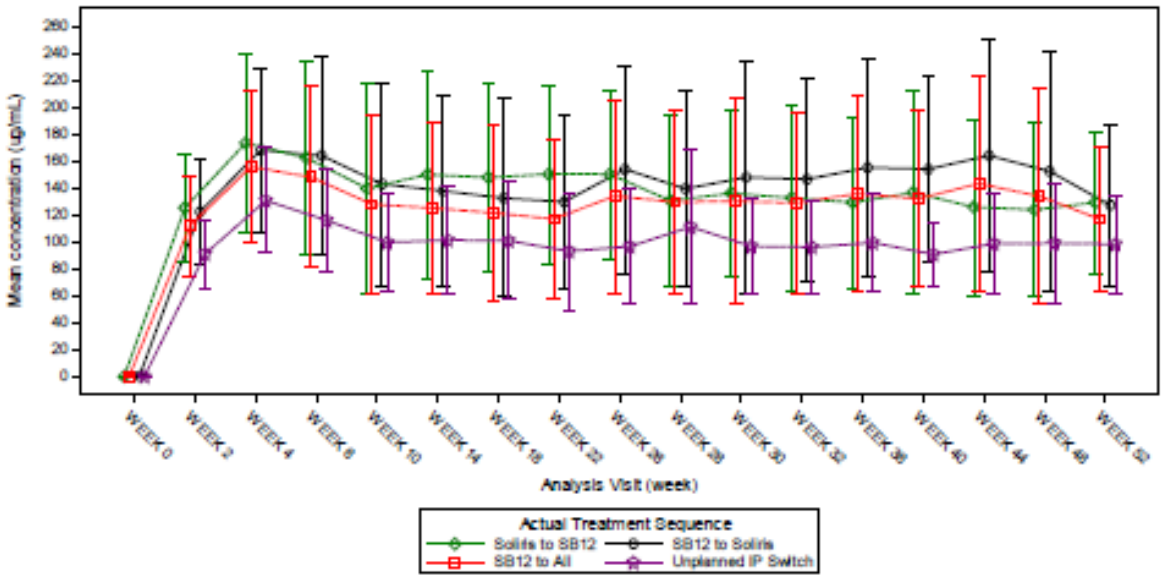


Figure 3: Plot of mean (±SD) eculizumab C_{trough} (µg/mL) by actual treatment sequence (pharmacokinetic analysis set, study SB12-3003) (ad hoc analysis)

2.6.2.2. Pharmacodynamics

Mechanism of action

The mode of action of eculizumab has been established. Eculizumab is a humanised monoclonal antibody that binds to the human C5 complement protein (C5). C5 is a soluble protein and is central to all pathways of complement activation. C5 is cleaved by C5 convertase, producing C5a, which is a ligand for the inflammatory receptor C5aR, and C5b, which is a necessary component in the formation of the membrane attack complex, which mediates cell lysis. Eculizumab binds to human C5 in the region of the protein that becomes C5b, and blocks cleavage, thereby inhibiting the complement cascade and ultimately blocking terminal complement mediated intravascular haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) patients.

Bioanalytical Methods – Pharmacodynamic Assay

A PD assay for measurement of the terminal complement complex in human serum has been set up. A commercial ELISA kit (Wieslab Enzyme-linked Immunosorbent Assay from Svar Life Science) was used and validated according to the EMA Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr.

Table 10: Validated Parameters for the Quantitative ELISA for Determination of Terminal Complement Activity

Validation Parameter	Results	
Analytical Procedure Number	10010718-HAR-IC18-040	
This analytical method was used in the following study:	SB12-1001	SB12-3003
Analyte	Terminal complement activity in normal healthy human serum	Terminal complement activity in PNH patient serum
Method of detection	Enzyme-linked Immunosorbent Assay (ELISA)	
Calibration model	4 Parameter Logistic curve	
Weighting factor	$1/Y^2$	
Quantifiable working range	10.0 to 125.0%	
Quality control (QC) levels	LLOQ: 10.0% LQC: 37.5% MQC: 60.0% HQC: 95% ULOQ: 125%	
Minimum Required Dilution (MRD)	1 in 101	
MRD solution	Assay buffer (CP diluent)	
Precision and accuracy (≤ 20% at LQC, HQC, MQC and ≤ 25% at LLOQ and ULOQ)	Requirements fulfilled	
Hemolyzed serum interference	Up to 10% hemolysis	
Lipemic serum interference	300 mg/dL Triglyceride	
Specificity	SB12, EU and US Soliris®, inhibition observed > 10 µg/mL (lowest concentration of drug tested) No interference of Bilirubin at up to 10.00 mg/dL compared to baseline No interference of Rifampicin at up to 100.00 µg/mL compared to baseline	SB12 and EU Soliris®, inhibition observed > 10 µg/mL (lowest concentration of drug tested).
Parallelism	Requirements fulfilled using serum from normal healthy pooled and normal healthy individuals	Requirements fulfilled using serum from PNH patient individuals
Wet Ice stability	6 hours 14 minutes	
Refrigerated stability	48 hours 15 minutes	
Room Temperature stability	24 hours 50 minutes	
Freeze/Thaw matrix stability	3 cycles at <−50°C, although first time analysis should be used initially and F/T only used in cases of sample volume issue	
Freeze stability	95 days at <−10°C 624 days at <−50°C	

F/T = Freeze/Thaw; HQC = high quality control; LLOQ = lower limit of quantification; LQC = low quality control; MQC = medium quality control; MRD = minimum required dilution; QC = quality control; UHQC = ultra high quality control; ULOQ = Upper limit of quantification

Primary and Secondary pharmacology

Study SB12-1001

PD endpoint

• Change in terminal complement activity over time

PD sampling time points

Blood samples for PD analysis were collected at 0 (pre-dose), 0.58 (35 minutes; immediately after the end of infusion), 4, 24, 48, 96, 168, 240, 336, and 1512 hours after the start of infusion.

Analysis of Pharmacodynamic Data

The mean terminal complement activity and mean change from baseline of complement activity over nominal time for the PKS are presented for pairwise comparisons of all study treatment groups in Figure 4 (for comparison of SB12 and EU sourced Soliris), Figure 5 (for comparison of SB12 and US sourced Soliris), and Figure 6 (for comparison of EU sourced Soliris and US sourced Soliris).

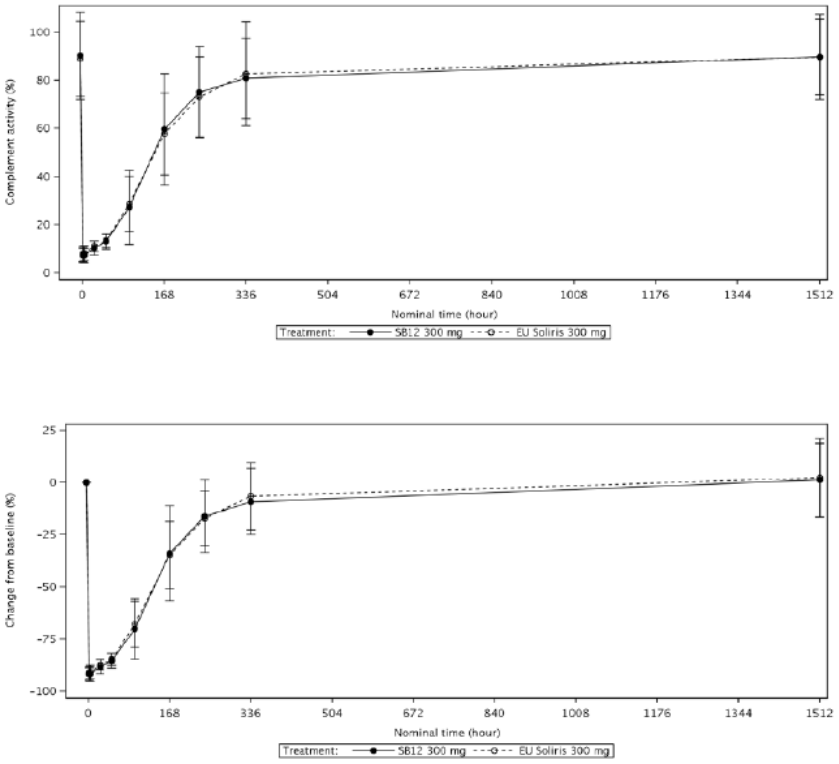


Figure 4: Mean complement activity (top graph) and change from baseline in terminal complement activity (bottom graph) over nominal time of SB12 and EU sourced Soliris

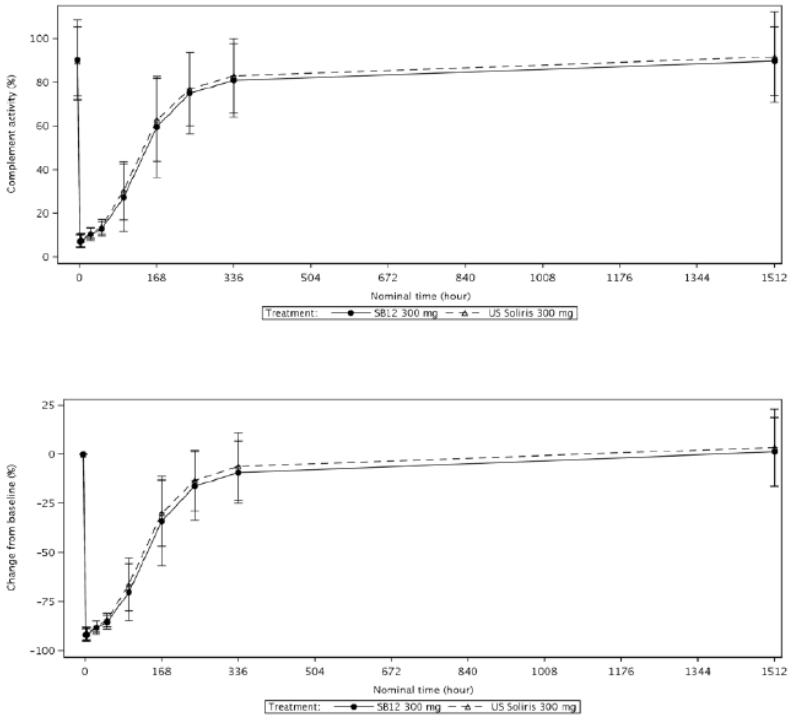


Figure 5: Mean complement activity (top graph) and change from baseline in terminal complement activity (bottom graph) over nominal time of SB12 and US sourced Soliris

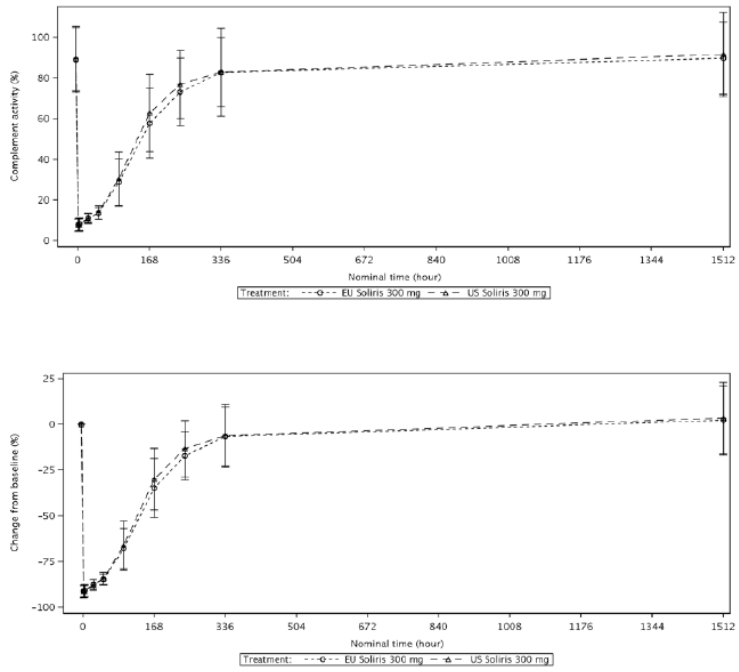


Figure 6: Mean complement activity (top graph) and change from baseline in terminal complement activity (bottom graph) over nominal time of EU sourced Soliris and US sourced Soliris

Study SB12-3003

Terminal complement activity was assessed as PD marker in Phase III study SB12-3003. The same set of subjects was assessed for PK and PD evaluation in this study. The same assay as in Phase I study SB12-1001 was used for PD evaluation. The absolute value and percent change from baseline in terminal complement activities are presented in the Table below. The mean (SD) of absolute value and percentage change from baseline in terminal complement activities versus nominal time plot are presented in Figure 7 and Figure 8.

At Week 26 (end of Period 1), before IP switch, the mean (SD) change from baseline of terminal complement activity was -84.23 (11.970) % in the Soliris group and -80.06 (14.534) % in the SB12 group. At Week 52 mean (SD) change from baseline of terminal complement activity was -84.68 (15.066) % in the actual SB12 treatment group and -86.51 (11.766) % among the 14 subjects who received Soliris during Period 2 and were included in PD assessment. The 8 subjects with unplanned IP switch (back to SB12) during Period 2 had a lower mean (SD) reduction of terminal complement activity [-76.08 (21.998) %] compared to other subjects receiving either SB12 or Soliris.

No ADA were reported throughout the study, hence no possible impact of ADA on terminal complement activity could be assessed.

Table 11: Summary statistics for terminal complement activities by visit (baseline, week 26 and week 52) and actual treatment sequence within period (pharmacodynamic)

Visit Statistics	Soliris® to SB12 N = 25 Value	Change (%)	SB12 to All N = 24 Value	Change (%)	SB12 to Soliris® N = 16 Value	Change (%)	Unplanned IP Switch N = 8 Value	Change (%)	Total N = 49 Value	Change (%)
Baseline										
n	25	-	24	-	-	-	-	-	49	-
Mean	98.64	-	98.85	-	-	-	-	-	98.74	-
SD	24.437	-	17.531	-	-	-	-	-	21.116	-
Median	97.10	-	104.45	-	-	-	-	-	97.40	-
Min,	50.6	-	62.0	-	-	-	-	-	50.6	-
Max	146.9		128.4						146.9	
%CV	24.8	-	17.7	-	-	-	-	-	21.4	-
G.Mean	95.64	-	97.21	-	-	-	-	-	96.41	-
G.SD	1.294	-	1.212	-	-	-	-	-	1.253	-
G.%CV	26.2	-	19.4	-	-	-	-	-	22.9	-
Week 26										
n	23	23	23	23	-	-	-	-	46	46
Mean	14.91	−84.23	20.24	−80.06	-	-	-	-	17.58	−82.14
SD	11.234	11.970	16.631	14.534	-	-	-	-	14.290	13.333
Median	12.20	−87.47	14.30	−86.34	-	-	-	-	12.70	−86.92
Min,	5.0	−95.5	5.0	−95.4	-	-	-	-	5.0	−95.5
Max	59.5	−38.8	57.1	−46.4					59.5	−38.8
%CV	75.4	−14.2	82.2	−18.2	-	-	-	-	81.3	−16.2
G.Mean	12.49	N/A	15.01	N/A	-	-	-	-	13.69	N/A
G.SD	1.786	N/A	2.210	N/A	-	-	-	-	2.000	N/A
G.%CV	63.2	N/A	93.6	N/A	-	-	-	-	78.5	N/A
Week 52										
n	21	21	22	22	14	14	8	8	43	43
Mean	14.87	−84.68	17.50	−82.72	12.40	−86.51	26.43	−76.08	16.22	−83.68
SD	14.641	15.066	20.086	16.534	10.793	11.766	29.172	21.998	17.481	15.677
Median	11.60	−88.56	11.75	−87.44	7.90	−92.23	15.80	−83.63	11.60	−88.40
Min,	5.0	−95.5	5.0	−95.4	5.0	−95.4	5.0	−94.3	5.0	−95.5
Max	75.2	−22.7	94.4	−26.5	35.6	−64.0	94.4	−26.5	94.4	−22.7
%CV	98.5	−17.8	114.8	−20.0	87.0	−13.6	110.4	−28.9	107.8	−18.7
G.Mean	11.75	N/A	11.87	N/A	9.34	N/A	18.05	N/A	11.81	N/A
G.SD	1.896	N/A	2.313	N/A	2.099	N/A	2.409	N/A	2.095	N/A
G.%CV	71.1	N/A	101.0	N/A	85.6	N/A	108.0	N/A	85.3	N/A

CV = coefficient of variation; G.Mean = geometric mean; G.SD = geometric mean standard deviation; G.%CV = geometric percent coefficient of variation; IP = investigational product; N = total number of subjects in PD Analysis Set; N/A = not applicable; PD = pharmacodynamics; SD = standard deviation
- Geo CV% = SQRT (e^s² − 1) × 100; where s is the standard deviation of the log-transformed values
- Change: percent change from baseline, which is = 100 × (value at each visit − baseline value) / baseline value
- PD assessments from subjects with protocol deviations for PD blood sampling at a visit were excluded from the summary of that visit (not included in calculation of n at that visit).
- Geometric statistics were not calculated for change from baseline values.

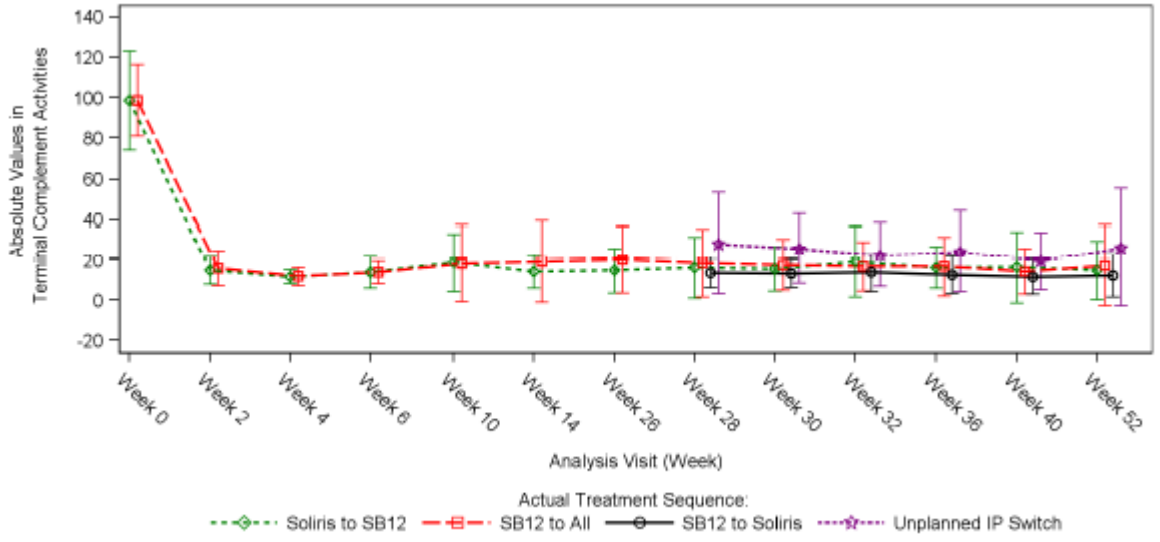


Figure 7: Plot of mean (± SD) terminal complement activities by actual treatment sequence (pharmacodynamic analysis set)

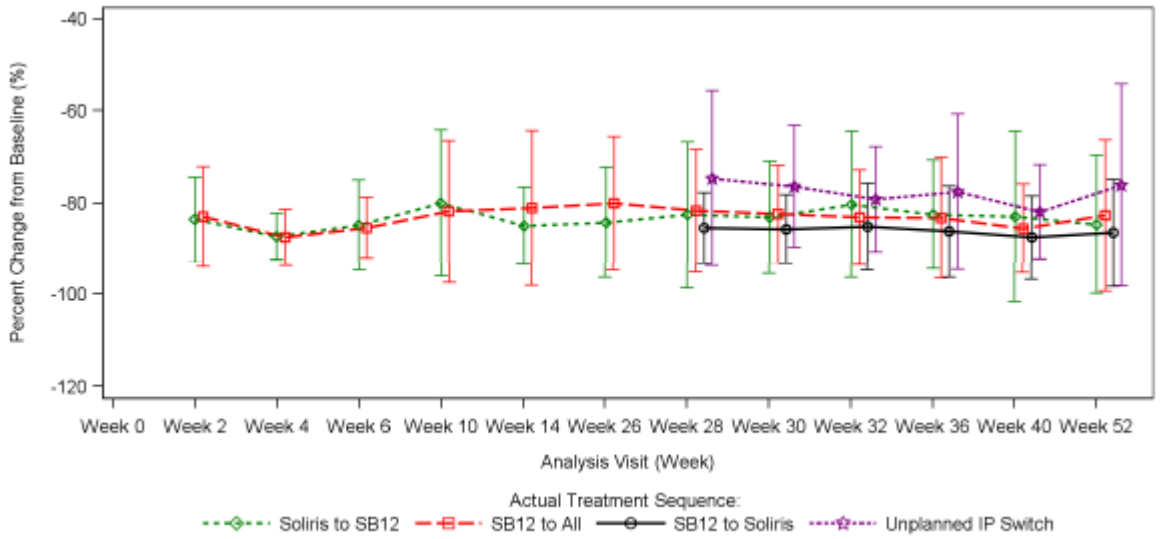


Figure 8: Plot of mean (±SD) percent change from baseline in terminal complement activities by actual treatment sequence (pharmacodynamic analysis set)

2.6.3. Discussion on clinical pharmacology

The pharmacology of SB12 has been investigated in two clinical studies, the Phase I study SB12-1001 and the Phase III study SB12-3003.

The Phase I study SB12-1001 is the pivotal study investigating PK similarity. The study was a randomized, double-blind, three-arm, parallel group, single dose study in healthy subjects to demonstrate similarity in PK, safety, tolerability, immunogenicity, and PD between SB12 and Soliris. Due to the long half-life of the product, the parallel design is considered appropriate. The study consisted of the screening and the treatment period. Subjects were randomized in a 1:1:1 ratio to receive either SB12, EU-sourced Soliris or US-sourced Soliris. The total study duration was approximately 92 days (including the 28-day Screening period). The study was conducted at a single centre in Berlin, Germany. Overall, the design of the Phase I study SB12-1001 is acceptable and is generally in agreement with previous Scientific Advice (EMA/CHMP/SAWP/634958/2017). A parallel study design was chosen due to the long half-life of eculizumab (mean 11.3 days in PNH patients), which is appropriate. Specific design aspects that were not followed or were not conducted as initially planned, will be discussed below.

The study started on 13-Nov-2018 with the first subject signing informed consent and was completed on 08-Apr-2019 with the last subject last visit. The database lock was on 10-Jul-2019. No concerns arise from the provided dates. The protocol of the study was amended once in order to correct minor administrative errors. The amendment happened prior to initiation of the study and the applicant provided both protocol versions.

The main inclusion criteria for the Phase I study were age between 18-55 years, body weight between 70.0 and 95.0 kg and BMI between 20.0 and 29.9 kg/m2. This is appropriate. The applicant performed its Phase I PK study SB12-1001 in healthy male and female volunteers. It would have been preferable to conduct the study only in male subjects, as this would have been considered a more homogenous and sensitive model to demonstrate, or exclude, differences between the treatment arms, if existent. This was also an issue in a previous EMA Scientific Advice (EMA/CHMP/SAWP/634958/2017). Initially, the applicant proposed to include only healthy male subjects to the study and this was regarded acceptable by the CHMP. However, it seems that the applicant changed the inclusion criteria after this advice, as the study was open for male as well as female subjects. Further discussion on implications of this issue on PK similarity will be provided further below when the PK results of the study are discussed. Furthermore, and as was also discussed in the initial Scientific Advice (EMA/CHMP/SAWP/634958/2017), an ethnically homogenous study population would have been preferable as a more homogeneous model to study PK differences in this parallel study design. In the initial Scientific Advice, the applicant proposed stratified randomization by ethnicity to ensure comparable study groups. However, this did not seem to have been implemented in the planning of the study, as it was not defined in the protocol nor in the SAP. Further discussion on implications of this issue on PK similarity are provided below when discussing the PK results of the study are discussed. Overall, apart from the aspects discussed above, the main in- and exclusion criteria are acceptable.

SB12, EU sourced Soliris, and US sourced Soliris were administered by IV infusion at day 1. The applicant chose a dose of 300 mg eculizumab for the Phase I study in healthy volunteers. This is the lowest therapeutic dose of Soliris used for aHUS patients. The dose is considered sensitive to detect differences between the treatment arms and is therefore considered appropriate.

The primary objective of this study was the demonstration of PK similarity of SB12 to the EU- and US-sourced reference products Soliris. The secondary objectives included further PK characteristics and to assess the safety, tolerability, immunogenicity and PD aspects of SB12 and the reference products. This is overall endorsed. The primary PK endpoint of the study was AUC_{inf}. The secondary PK endpoints

comprised AUC_{last}, C_{max}, T_{max}, V_z, lambda_z, $t_{1/2}$, CL and $\%AUC_{extrap}$. The primary and secondary PK endpoints are in line with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)" and are therefore endorsed.

The measurement of free eculizumab concentrations could have provided additive data in support for the demonstration of biosimilarity. However, for the evaluation of PK, the applicant only measured total eculizumab. Although this is not regarded optimal, a request at this point in time would not be regarded fruitful. Therefore, no concern is raised.

The PK assay has been sufficiently described and validated and is considered suitable for its use.

The secondary PD endpoint was defined as the "Change in terminal complement activity over time".

The used PD assay combines principles of the haemolytic assay for complement activation with the use of alkaline phosphatase (APh)-conjugated antibodies specific for the neoantigen produced as a result of complement activation. The assay principle has been appropriately described and the results generated from the validation work confirm that this assay is robust and suitable for measurement of terminal complement complex in human serum. A validation summary as well as the detailed validation results have been provided; certain deviations, which occurred during the validation study, were documented and sufficiently justified to have no impact on the validity of the study. It was also verified that the same method used in the clinical Phase I study (healthy subject) can be employed for sample analysis to determine terminal complement activities in PNH patients in Study SB12-3003.

However, in the Scientific Advice EMA/CHMP/SAWP/634958/2017, provided to the applicant in October 2017, it was recommended to include CH50 at least as a key secondary endpoint for the confirmatory phase III trial as recent literature indicates that CH50 activity might be a more specific and predictive PD marker for clinical efficacy and pharmacological action of eculizumab. A justification why the applicant has not included the recommended functional haemolytic CH50 assay was requested. The applicant provided a justification for using the terminal complement activity ELISA. This included a rationale for the selection, a correlation between functional haemolytic assay and terminal complement activity ELISA and a correlation of terminal complement activity ELISA and lactate dehydrogenase. The applicant states that there were problems with the validation of the functional haemolytic assay. Although validation feasibility and technical issues are rather regarded as weak arguments, the described limitations can be understood. In addition, the applicant provided literature references showing correlation between terminal complement activity ELISA and functional haemolytic CH50 assay both in healthy subjects and patients. This is acceptable. Furthermore, the applicant provided in house data showing that the terminal complement activity ELISA might be more sensitive than the haemolytic assay and that there is reasonable correlation between the two assays. Although it is agreed that the results show a greater sensitivity for the terminal complement activity ELISA and there might be a correlation between the two assays, these results have to be interpreted carefully due to the above described lack of validation of the haemolytic assay. Analysis of correlation between lactate dehydrogenase and terminal complement activities with samples from Study SB12-3003 also showed good correlation between LDH and terminal complement activity. This is accepted.

The secondary safety endpoints included adverse events and serious adverse events, clinically laboratory values, 12-lead ECG, vital signs and physical examinations. This is acceptable. The secondary immunogenicity endpoints were defined as the "Incidence of anti-drug antibodies to eculizumab" and "Incidence of neutralising antibodies to eculizumab". This is acknowledged. Apart from non-inclusion of the PD endpoint CH50 (as discussed above), the secondary endpoints are considered acceptable. In addition, the PK sampling time points (collected at 0, 0.58, 4, 8, 12, 24, 48, 96, 168, 240, 336, 504, 672, 840, 1008, 1176, 1344, and 1512 hours after the start of infusion) are deemed acceptable to reflect the characteristics of eculizumab and to gain respective data for a

comparative evaluation of the critical PK parameters of SB12 and the reference products. The immunogenicity sampling time points (collected at 0, 336, 672, and 1512 hours after the start of infusion) are also appropriate.

Subjects were randomized in a 1:1:1 ratio to one of the three treatments groups. The process of randomization was adequately described and is considered acceptable. The Phase I study SB12-1001 was a subject-, investigator- and sponsor-blinded study. The pharmacists who prepared and dispensed the IPs were unblinded. The process of blinding was adequately described and is considered acceptable.

The PK parameters were calculated based on actual sampling times and non-compartmental analysis methods using Phoenix WinNonlin version 8.0. This is considered acceptable.

Of the 479 screened subjects, 239 were screening failures due to not meeting the randomization criteria, withdrawal by subject or others. For a study conducted in healthy volunteers, the high number of screen failures is remarkable. However, the applicant has provided a detailed listing with the reasons for screen failures. No concerns arise from these data. Of the 240 randomized subjects, 239 completed the study. One subject in the EU-sourced Soliris group withdrew before completion due to personal reasons on day 9.

The number of subjects with any protocol deviation was similar between the groups. 55 % of the subjects in the SB12 group, 57.5 % of the subjects in the EU-sourced Soliris group and 57.5 % of the subjects in the US-sourced Soliris group had a protocol deviation. All of the protocol deviations were minor and none of the subjects had a major protocol deviation. The reasons for protocol deviation included deviations from concomitant medication criteria and study procedure criteria and were well balanced among the groups.

The participant flow is described in sufficient detail and is comprehensible. Furthermore, all of the protocol deviations were minor and do not seem to influence the biosimilarity assessment of SB12 and the reference products. Thus, no concerns arise.

The baseline characteristics were well balanced among the SB12, EU-sourced Soliris and US-sourced Soliris groups. The mean age was 39.6, 40.9 and 40.2 years, respectively. Most of the subjects in the study were male, with 95.8% of the subjects being male and 4.2% of the subjects being female. The majority of the subjects in the study were White (95.8%) and "Not Hispanic or Latino" (98.3%). Gender, race and ethnicity aspects were well balanced among the groups. In addition, the height, weight and BMI of the subjects was comparable among the groups. This is regarded acceptable.

Furthermore, the fact that the majority of subjects were "male", "White" and "Not Hispanic or Latino", puts into perspective the homogeneity issue of the population, that was discussed above in relation to the deviation from the initial Scientific Advice (EMA/CHMP/SAWP/634958/2017). Although the study would have been open for both male and female subjects and an ethnically diverse population, the demographic data show that a very homogenous population was actually recruited, that is considered sensitive enough to elucidate differences between SB12 and the reference products, if existent. Thus, no concerns arise from these issues.

The number of subjects randomized to the study was 240 (80 per treatment group). All subjects were included in the randomized set, the safety set and the PK Analysis Set. For the one subject who discontinued the study on day 9, the PK parameters AUC_{inf}, AUC_{last}, V_z, $t_{1/2}$, λ_z, CL, and $\%AUC_{extrap}$ were excluded from the PK summary statistics and primary PK analysis. This is regarded acceptable. The numbers analysed were well presented by the applicant and are considered appropriate.

The applicant provided the mean serum concentration time-profiles. The profiles were comparable among the SB12, EU-sourced Soliris and US-sourced Soliris groups. The applicant also provided the individual serum concentrations time-profiles for each subject. This is endorsed.

The summary statistics of the PK parameters revealed that most of the PK parameters, such as AUC_{inf}, AUC_{last}, C_{max}, V_z, CL and $t_{1/2}$ were similar among the three treatment groups. However, the median T_{max} was quite different among the treatment groups. For the SB12 group, median T_{max} was 0.708 h, for the EU-sourced Soliris group median T_{max} was 3.967 h and for the US-sourced Soliris group, median T_{max} was 2.317 h. The applicant was asked to provide an explanation for the apparently different Tmax results among the treatment groups. The applicant has provided the requested mean and SD statistics for T_{max}. The mean values for T_{max} are similar among treatment groups and the SD is high. In addition, the applicant has provided a possible explanation for the different median T_{max} levels among the groups, which might be due to a higher number of subjects in the EU and US Soliris groups with an exceptionally high T_{max} value. Excluding these subjects from the analyses leads to similar median T_{max} values among the groups. Although it is not entirely clear why there are more subjects with an exceptionally high T_{max} in the EU and US Soliris groups, the issue is not further pursued due to the similar mean T_{max} among the groups and the fact that the median T_{max} for SB12 described in this study is similar to what had been observed for Soliris in a similar designed study.

The point estimate of the ratio (SB12/EU-sourced Soliris) of the geometric LS means for AUC_{inf} was 0.991 with the corresponding 90% CI being (0.9541; 1.0285). The point estimate of the ratio (SB12/US-sourced Soliris) of the geometric LS means for AUC_{inf} was 0.951 with the corresponding 90% CI being (0.9140; 0.9904). The point estimate of the ratio (EU-sourced Soliris /US-sourced Soliris) of the geometric LS means for AUC_{inf} was 0.960 with the corresponding 90% CI being (0.9216; 1.0010). Thus, the primary endpoint of the Phase I study SB12-1001 was met, as the ratio of the geometric LSMeans was within the pre-defined acceptance criteria of 0.8 to 1.25.

The primary endpoint analyses were supported by analyses on AUC_{inf} in post-dose ADA negative subjects, which led to similar conclusions as the primary analyses. Due to the low number of ADA positive subjects in the study (3 subjects in total), analyses on AUC_{inf} in post-dose ADA positive subjects was not performed. This can be followed.

Phase III study SB12-3003 was a randomized, double-blinded, multicentre, cross-over study to compare the efficacy, safety, PK, and immunogenicity in patients with PNH between SB12 and Soliris. For PK assessment in the target population of PNH subjects, no equivalence range has been pre-defined, and results were summarised descriptively due to the limited number of subjects enrolled. This is acceptable, provided that robust PK results from Phase I study in healthy volunteers are able to demonstrate biosimilarity between SB12 and Soliris.

In Phase III study SB12-3003 C_{trough} levels were assessed in 23 subjects in both treatment groups at Week 26 (Period 1), which was also the timepoint of the primary assessment and before subjects were switched to the other treatment (cross-over design). The mean (SD) eculizumab C_{trough} at Week 26 was 150.041 (62.6232) µg/mL in the Soliris group and 133.807 (71.6412) µg/mL in the SB12 group. Hence, eculizumab levels appeared similar between treatment groups with overlapping SD bars. After the planned IP switch in Period 2, the issue of a shortage of the comparator (Soliris) led to unplanned IP switch in Period 2 in 8 subjects, resulting in C_{trough} level evaluation of 14 patients at Week 52 (of 22 included in PK assessment at Week 52). Of those, mean (SD) eculizumab C_{trough} levels were highly similar between treatment groups [SB12 (n=21): 129.084 (52.5487) µg/mL, Soliris (n=14): 127.102 (60.2749)]. Due to the low number of subjects, high variability and unplanned IP switch, the data are limited, but can be considered supportive for PK equivalence of SB12 and Soliris as demonstrated in Phase I study SB12-1001.

Nevertheless, C_{trough} concentrations were consistently lower in the SB12 group compared to Soliris throughout the study. By far the lowest C_{trough} concentrations were observed in the subgroup of patients with unplanned IP switch (back to SB12) during Period 2 (n=8). Upon request, the applicant provided an overview of the actual treatment by timepoint during period 2 for the 8 patients with the unplanned IP switch, which showed that during period 2, SB12 and Soliris was administered at approximately half of the timepoints, respectively. Thus, it is agreed that it cannot be generally concluded that SB12 treatment leads to lower PK levels in the IP switched patients. In addition, the applicant provided the requested plot of mean eculizumab $C_{through}$ levels for period 1 of the same 8 patients, which clearly shows that the unplanned IP switch sequence is generally lower than the other treatment sequences, independent of actual treatment. Thus, it is agreed that lower levels might be rather due to individual disposition than the product itself. Further analyses of confounding factors revealed that the 8 patients with the unplanned IP switch had similar demographic and baseline characteristics as the remaining 41 patients without IP switch. One striking difference that was not discussed by the applicant is the higher percentage of males in the IP switch group (87.5% in the IP switch group versus 48.8% in the other group). This might to a certain extent explain the lower exposure in this group, as further PK/PD analysis identified body weight as a statistically significant covariate on clearance. The unplanned IP switch subjects have a slightly higher body weight. Indeed, there seems to be also a higher clearance in the unplanned IP switch subjects, which might explain the lower PK observed in these subjects. This is acceptable.

In the Phase I study SB12-1001, the "Change in terminal complement activity over time" was evaluated as a secondary pharmacodynamics endpoint. The sampling time points for this evaluation (at 0, 0.58, 4, 24, 48, 96, 168, 240, 336, and 1512 hours after the start of infusion) are considered appropriate. The profiles for mean complement activity among SB12, EU-sourced Soliris and US-sourced Soliris group were similar. The same holds true for the profiles of the change from baseline in terminal complement activity. These results can be considered as supportive PD results.

Evaluation of terminal complement activity as PD marker in Phase III study SB12-3003 confirmed the trends observed in the PK analysis in PNH patients. The mean reduction of terminal complement activity was lower in the SB12 group (-80.06%) compared to Soliris (-84.23%) at Week 26 and similar trends were observed throughout the study.

2.6.4. Conclusions on clinical pharmacology

Overall, the design of the Phase I study SB12-1001 was appropriate and mostly in line with previous Scientific Advice (EMA/CHMP/SAWP/634958/2017). The primary endpoints were met and the applicant could demonstrate comparable PK among the SB12, EU-sourced Soliris and US-sourced Soliris group. In addition, pharmacokinetic analysis in target population of PNH patients was performed by evaluating C_{trough} levels in the Phase III study SB12-3003, but no acceptance criteria to demonstrate biosimilarity regarding PK were pre-defined in this study.

The evaluation of terminal complement activity in the Phase I and Phase III study can be considered as supportive PD results. Overall, the available PK/PD data from pivotal PK Phase I study SB12-1001 support biosimilarity versus the EU reference product and also versus the US reference product. Supportive PK/PD data is provided from Phase III study SB12-3003.

2.6.5. Clinical efficacy

In order to demonstrate similarity in efficacy between SB12, and Soliris, a randomized, double-blind, multicentre, comparative clinical Phase III study (SB12-3003) in patients with PNH was conducted.

The clinical Phase III study (SB12-3003) is not aimed to demonstrate efficacy *per se*, but to confirm clinical equivalence between SB12 and Soliris in a representative indication evaluating the efficacy, safety, pharmacokinetics and immunogenicity.

In view of obvious shortcomings of Study SB12-3003, related to a limited sample size (n=25 per study arm), and short period for safety evaluation (26 weeks before IP switch), the importance of the Phase I PK study in providing supporting evidence for the overall comparability exercise was emphasised. Therefore, assessment of clinical biosimilarity of SB12 and Soliris will be based mostly on PK/PD results of Phase I study (SB12-1001), and confirmatory clinical efficacy and safety results from Phase III study SB12-3003.

2.6.5.1. Dose response study

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

2.6.5.2. Main study

SB12-3003 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

Methods

The study design is provided in the Figure 9 below.

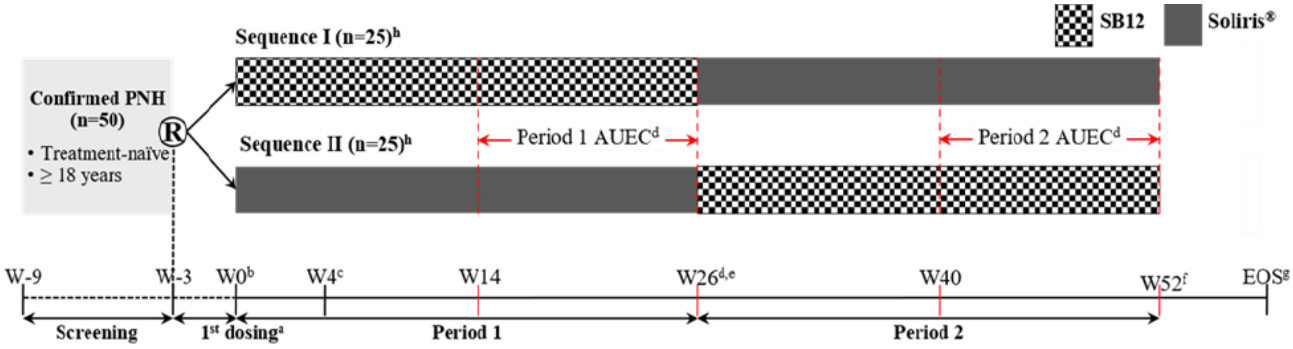


Figure 9: Graphical study design (study SB12-3003)

For Study SB12-3003, eligible patients were randomized in a 1:1 ratio to treatment sequence I (SB12 to Soliris) or treatment sequence II (Soliris to SB12). Patients randomly assigned to treatment with SB12 or Soliris received 600 mg of eculizumab IV every 7 ± 2 days for first 4 weeks (initial phase) and 900 mg for the fifth dose (Week 4) 7 ± 2 day later, then 900 mg every 14 ± 2 days thereafter. Patients who were randomized to initially receive SB12 were switched to receive Soliris and patients who were randomized to initially receive Soliris were switched to receive SB12 at Week 26. SB12 or Soliris was given until Week 50.

- **Study Participants**

Inclusion criteria (shortened)

1. Male or female aged 18 or older at the time of signing the ICF
2. Documented diagnosis of PNH.
3. Presence of the PNH white blood cell (WBC) clone, with a granulocyte or monocyte clone size of $\geq$ 10% by high-sensitivity flow cytometry at Screening.
4. Documented LDH level $\geq$ 1.5 $\times$ 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 had to 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. Subjects and their partners of childbearing potential (female or male) who agreed to use of a highly effective contraceptive method from Screening until 5 months after the last dose of study drug.

Exclusion criteria (shortened)

1. Had previous treatment with a complement pathway inhibitor (including eculizumab).
2. Had a known hypersensitivity to the investigational product (IP) or any of the ingredients or excipients of the IP.
3. Had 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 $< 70 \times 10^3/\mu L$
4. Had a history of meningococcal disease.
5. Had a history of haematopoietic stem cell transplantation.
6. Had a history of serious thrombotic event
7. Known or suspected active bacterial, virus, fungal infection within 30 days prior to initiation of study drug (Day 1).
8. Had a 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 had 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 had not been on a stable dose for at least 8 weeks prior to initiation of study drug (Day 1).
9. Subjects who had 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 was greater.

10. Had a 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.
11. Had any other cardiac, hepatic, immunologic, pulmonary, rheumatoid disease, other conditions causing rise in LDH (e.g., tumours, muscular dystrophies, liver and bile disease, etc.)

Prior and Concomitant Medications

The following concomitant medications were allowed if given on a stable dose (only for chronic administration) during the study period. However, for the subject's welfare, medications could be adjusted after 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).

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

- Anti-thymocyte globulin, cyclophosphamide, etc.

Subjects who initiated SB12 or Soliris treatment less than 14 days after receiving meningococcal vaccine must have received treatment with appropriate prophylactic antibiotics until 14 days after vaccination.

The subjects received pRBCs transfusion if the Investigator discovered that a subject's haemoglobin warranted a transfusion:

- Haemoglobin value $\leq$ 9 g/dL with signs or symptoms, or
- Haemoglobin value $\leq$ 7 g/dL regardless of signs or symptoms

Inclusion and exclusion criteria, as well as haematological parameter limits at screening, were largely in line with registrational studies for Soliris in PNH (TRIUMPH and SHEPHERD), and are therefore acceptable. Although patients were not evaluated regarding hereditary complement deficiency before inclusion in study, lack of efficacy due to certain C5 genetic variants is listed among the criteria for IP Discontinuation.

- **Treatments**

Test product: SB12 (eculizumab, proposed biosimilar to Soliris)

Reference product: Soliris

SB12 or Soliris was administered intravenously up to Week 50 (a total of 28 administrations of IP) unless they were early discontinued from study treatment. Dosing and treatment schedules were to 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 was 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 was re-scheduled every time based on the date when the previous treatment was given.

The subject who received SB12 or Soliris treatment would require dosing interval adjustment within the recommended 14 ± 2 days dosing schedule during the maintenance period (up to every 12 days) when it was deemed necessary at the discretion of the Investigator, e.g. two consecutive events of elevated LDH $\geq 2 \times$ 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 conflicted with administrative schedules (e.g., holidays or weekends) but a shortened dosing interval was considered necessary for safety of subject, consultation with medical monitor (or Sponsor) was recommended. For subjects whose dosing interval was adjusted to 12 days in Period 1, it was recommended that the dosing interval be switched back to 14 days after switching IP at Week 26. Once the above event had occurred, the Investigator informed 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 provided SB12 instead of Soliris in a blinded manner. Rules for allocation of remaining comparators during the comparator shortage situation were pre-specified prior to execution of the potential change of IP assignment from Soliris to SB12 in a blinded manner. This was to avoid the risk of unblinding and potential bias.

In circumstances of SB12 instead of Soliris was given in Period 2, the data were summarised as follows presented by actual treatment sequence within each period:

- Period 1 data were summarised by treatment sequences from Period 1 (i.e., actual treatment sequence 'Soliris to SB12' and 'SB12 to All'). Where, treatment sequence 'SB12 to All' included subjects from sequences SB12 to Soliris and Unplanned IP Switch.
- Similarly, Period 2 data were summarised by actual treatment sequence namely 'Soliris to SB12', 'SB12 to All', 'SB12 to Soliris' and 'Unplanned IP switch.' Where, treatment sequence 'SB12 to All' included subjects from sequences SB12 to Soliris and Unplanned IP Switch.

Criteria for IP Discontinuation

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

- Consent withdrawal by subject
- Pregnancy (study treatment was immediately stopped when a pregnancy was made known and the pregnant woman was 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 discussed 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 study protocol in terms of their safety or well-being
- Lack of efficacy (e.g., 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
- Investigator discretion or other reasons

Subjects who discontinued from the study at any time post-Day 1 (after the initiation of study drug) before completion of last study treatment at Week 50 was required to have an ET visit. The data were collected at the 8 weeks after the last dose of study drug according to Section *Reporting Serious Adverse Events* of study protocol (V 6.0). When a subject withdrew from the study due to a serious adverse event (SAE), the SAE had to be reported and followed in accordance with the requirements outlined in Section *Reporting Serious Adverse Events* of study protocol (V 6.0).

Route of administration, dosing and schedule are in line with the posology of Soliris for the treatment of PNH.

- **Objectives**

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

Secondary Objectives

- 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

- **Outcomes/endpoints**

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 (for FDA only)

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 infection
- Incidence of infusion-related reactions (IRRs)

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

AE Definitions

Breakthrough haemolysis

The breakthrough haemolysis was 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.

Major Adverse Vascular Events

The MAVE was defined as thrombophlebitis/deep vein thrombosis, pulmonary embolus, cerebral arterial/venous occlusion, myocardial infarction, transient ischaemic attack, unstable angina, renal vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis (Budd-Chiari syndrome), acute mesenteric ischaemia, etc.

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 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

- **Sample size**

The equivalence margin was [−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] was 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) was given 23

completers per treatment sequence after 26 weeks, which was estimated to give 80% power to detect the equivalence within the margin of 268 U/L.

- **Randomisation and Blinding (masking)**

Randomization

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

Subjects were not stratified, and the assigned randomisation numbers were not re-used.

Subjects who were screen failed due to technical issues, not medical issues, were re-screened once based on discussion and agreement between the Investigator and the medical monitor and/or Sponsor.

Blinding (masking)

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

To ensure the blinding for the treatment sequence assignment, one carton contained only one IP vial (SB12 or Soliris). The carton and IP vial were packed and labelled in identical appearance. These IP vials were packed and labelled in a double-blinded manner for clinical use.

The Investigator and/or designee took responsibility for all steps to maintain appropriate records and ensured appropriate supply, storage, handling, distribution, and usage of IPs in accordance with the study protocol and any applicable laws and regulations. A detailed guidance for IP preparation, administration, storage, and destruction were provided in the pharmacy manual.

Emergency unblinding was considered only when knowledge of the treatment assignment is deemed essential for the subject's safety by their Investigator or a regulatory body. The IWRS was be used to break the blind and details on how to do this were provided in the IWRS manual.

- **Statistical methods**

Analysis Sets

- Enrolled Set (ENR): The ENR consists of all subjects who provide informed consent for the study.
- Randomized Set (RAN): The RAN consists of all subjects who have received a randomisation number
- Modified Full Analysis Set (M-FAS): The 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 investigational product (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): The PPS-AUEC consist of all M-FAS subjects who have sufficient LDH assessments for AUEC calculation without any major protocol deviations that have impact on efficacy assessment. Subjects excluded from the primary analysis will be predefined on a case-by-case basis prior to unblinding the treatment sequence assignment for analyses. In addition, subjects who received different treatment from the randomization treatment sequence due to a shortage of the comparator will be excluded from this analysis set.

In addition to the case-by case basis review of protocol deviations and individual LDH profile prior to unblinding the treatment sequence assignment, subjects who met the following criteria were excluded from the PPS-AUEC:

1. Missing LDH assessment results at week 14, 26, 40 or 52
2. Missing LDH assessment results at more than 2 timepoints (>= 3 missing LDH values) from week 14 to week 26 or from week 40 to week 52

- Per-Protocol Set for LDH at a single time point (PPS-single): The PPS-single consists of all M-FAS subjects who have LDH assessment at week 26 without any major protocol deviations that have impact on efficacy assessment. Subjects excluded from the primary analysis were predefined 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 randomized treatment sequence due to a shortage of the comparator will be excluded from this analysis set.

Multiplicity

No formal adjustment of Type I error rates was performed

Primary efficacy analysis

For EMA, Korea MFDS, or other regulatory agency submissions for those who were in favour of the LDH level at a single time point, the primary efficacy analysis was performed for the PPS-single using a linear model with treatment, and gender as a fixed-effect. The analysis was performed with $\log_e$ transformed LDH at Week 26 estimating the difference in least squares means (LSM) and its 95% confidence interval (CI), and the delta method was used to provide the mean difference and 95% CI in original scale. The equivalence was declared if the two-sided 95% CI of the mean difference in LDH level at Week 26 between SB12 and Soliris lied within the pre-defined equivalence margin of [−1.2 × ULN, 1.2 × ULN] = [−337.2, 337.2], where ULN = 281 U/L. Since the normal range of LDH is gender specific, the smallest ULN = 281 U/L was used for the equivalence margin.

For the US FDA or other regulatory agency submissions for those who were in favour of the time-adjusted AUEC of LDH, the primary endpoint of time-adjusted AUEC of LDH from Week 14 to Week 26 and time-adjusted AUEC of LDH from Week 40 to Week 52 were analysed for the PPSAUEC 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 was performed with loge-transformed time-adjusted AUEC of LDH estimating the difference in LSM and its 90% CI, and back transformation of those values provided the ratio of GMs and 90% CI. The equivalence was declared if the two-sided 90% CI of the ratio of GMs in time-adjusted AUEC of LDH between SB12 and Soliris lied within the pre-defined equivalence margin of [0.77, 1.29].

For sensitivity analysis, the primary efficacy analysis was repeated for the M-FAS. Missing data was imputed using multiple imputation method for cases of insufficient values for AUEC calculation or discontinued subjects before Week 26 or Week 52.

Complete case analysis

Complete case analysis based on the M-FAS was performed for both the endpoint of LDH at Week 26 and time-adjusted AUEC of LDH, where time-adjusted AUEC calculation is based on complete LDH data, without imputation on missing LDH data. Complete case for an endpoint of single LDH level at Week 26 was defined as subjects with non-missing LDH values at Week 26. Similarly, complete case for an endpoint of time adjusted AUEC was the subjects with sufficient data to calculate AUEC (non-missing LDH values more than 1) in at least one period.

Multiple Imputation that assumes missing at random (MAR)

Missing LDH data was imputed for subjects who dropped out of the study prior to the primary analysis time point. Missing LDH data was imputed by fully conditional specification (FCS), which is the sequential regression algorithm, multiple imputation method utilising the non-missing LDH data at previous visits and planned treatment sequence, gender as categorical covariates. This imputation model used baseline LDH values as a covariate in imputing values of LDH for subsequent visits. In case of sensitivity analysis of LDH at Week 26, results of linear model based on loge transformed LDH values were combined first using Rubin's rule and then delta method was used later to report mean difference and 95% CI in original scale.

Secondary efficacy analysis

As a secondary efficacy endpoint, the number of units of pRBCs transfused was summarized descriptively by planned treatment sequence and planned treatment sequence within period. Comparison between treatment sequences in the number of units of pRBCs transfused was analysed using Wilcoxon rank-sum test. Combined individual and mean LDH profile were presented over time by planned treatment sequence.

Results

- **Participant flow**

Table 12: subject disposition by planned treatment sequence (enrolled set)

Number of Subjects	Soliris® to SB12 n (%)	SB12 to Soliris® n (%)	Total n (%)
Screened	-	-	68
Screening failures	-	-	18
Reasons for screening failure			
Does not meet eligibility criteria	-	-	15 (83.3)
Consent withdrawal	-	-	1(5.6)
Other	-	-	2 (11.1)
Randomised	25 (100.0)	25 (100.0)	50 (100.0)
Received different treatment from the randomised treatment during Period 2	-	8 (32.0)	8 (16.0)
Completed study treatment for Period 1	23 (92.0)	23 (92.0)	46 (92.0)
Withdrew during Period 1 treatment	2 (8.0)	2 (8.0)	4 (8.0)
Main reasons for withdrawal			
Adverse event (including unacceptable toxicity)	2 (8.0)	1 (4.0)	3 (6.0)
Pregnancy	0 (0.0)	1 (4.0)	1 (2.0)
Completed study treatment for Period 2	23 (92.0)	23 (92.0)	46 (92.0)
Withdrew during Period 2 treatment	0 (0.0)	0 (0.0)	0 (0.0)
Completed Week 52	23 (92.0)	23 (92.0)	46 (92.0)
Completed Study (Including Safety follow-up at Week 58)	23 (92.0)	23 (92.0)	46 (92.0)

- Period 1 treatment included Week 0 to Week 24 study treatment; Period 2 treatment included Week 26 to Week 50 study treatment. Subjects who withdrew after Week 24 study treatment and before Week 26 study treatment were counted as withdrew during Period 2 treatment.
- Completion of Week 52 was defined as completion of activities at Week 52.
- Completion of the study was defined as completion of safety follow-up at Week 58 for the Protocol v5.x and v6.x and completion of pre-dose activities at Week 52 for the Protocol v4.x.
- Unless otherwise specified, percentages were based on the number of subjects in the Randomised Set.
- Percentages for the screening failure reason were based on the number of screening failures. Multiple reasons were possible.
- Two subjects were re-screened, and they were counted only once in 'Screened' and 'Screening failures'.

- **Recruitment**

First Subject Signed Informed Consent Form: Aug 07, 2019

Last Subject Last Visit: Oct 21, 2021

This study was conducted at a total of 24 study centres in 8 countries: 4 centres in India, 1 centre in Republic of Korea, 5 centres in Malaysia, 1 centre in Mexico, 4 centres in Romania, 3 centres in Taiwan, 2 centres in Thailand, and 4 centres in Ukraine.

- **Conduct of the study**

There were five **global amendments** to the original protocol (Version 1.0, dated Jul 31, 2018). Three global amendments were incorporated during the recruitment period (Aug 07, 2019 – Oct 21, 2021). A detailed change history of all global amendments was provided, and changes made to facilitate recruitment, clarify several study procedures and to address issues related to the COVID-19 pandemic.

Global Protocol Amendment 4 (Version 5.0, Aug 21, 2020) included an update on study design in order to minimise the risk of COVID-19 pandemic, which resulted in the **removal of a 2 year extension period** to assess the long-term safety.

Global Protocol Amendment 5 (Version 6.0, Nov 27, 2020) included an update in order to address the **shortage of comparator**, which lasted from Nov 2020 to Mar 2021. This resulted in an unplanned IP switch from Soliris to SB12 in Period 2 for some subjects, who remained on SB12 treatment until study

end, even after the shortage was resolved by providing US-Soliris (Mar 2021) to avoid frequent IP changes. Of the 8 subjects with unplanned IP switch, 5 patients had already received Soliris as planned after transition to Period 2 and were switched back to SB12. Two of the 8 subjects with unplanned IP switch continued on SB12 after transition before they were switched to Soliris. One subject with unplanned IP switch stayed on SB12 throughout the study. The priority of IP switching sequence is described in "The statement for comparator dispensing strategy v2.0".

As some subjects would inevitably confront unplanned IP switch in Period 2 (from the comparator to SB12) for some period in the study, to ensure continuity of study treatment, information about the shortage and mitigation plan was shared with all subjects, Investigators, DSMB, and relevant institutions (including IEC/IRBs, regulatory agency, and others according to local regulations), and was approved if required by regulations before the implementation of unplanned IP switch. In particular, all subjects were thoroughly explained about the possibility, risks, and benefits of an unplanned IP switch and this would only happen after the subjects consented to proceed with the treatment with SB12 instead of Soliris.

At the same time, an **additional source** of the comparator was explored. The manufacturer of Soliris confirmed that US-sourced Soliris had the same quality with EU-sourced Soliris, which was the comparator in this study, and both Soliris from EU and US had been demonstrated equivalent PK profiles with comparable safety, tolerability, immunogenicity, and PD profiles in SB12 Phase I study. After the investigation of additional source, the Sponsor decided to procure US-sourced Soliris in Nov 2020.

As of Mar 2021, the shortage was completely resolved by supplying US-sourced Soliris. All subjects were supplied with the IPs as planned in the study protocol with the exception of some subjects. To prevent any potential immunogenicity risk with frequent IP changes, the subjects who were in "unplanned IP switch" sequence were provided with SB12 until the study end.

Impact of COVID-19

The study protocol was amended on Aug 21, 2020 (Version 5.0) to reflect all recommendations/mitigations on COVID-19.

Regardless of all contingency measures taken, several impacts were inevitable during the study conduct. COVID-19 pandemic had an effect not only on the continuation of treatment of subjects but also on the overall process of study conduct. The impacts of COVID-19 are summarised in the following categories:

1. COVID-19 Infection: A total of 10 subjects were confirmed positive with COVID-19. Each COVID-19 case was reported to the Sponsor via the COVID-19 positive case reporting form and reviewed by the Sponsor to provide recommendations to Investigators for the subject to take appropriate actions. Each subject was managed based on the subject condition and local guidelines for COVID-19. All COVID-19 cases were captured as AEs.
2. Visit/Assessment Delay: During the study period, COVID-19 related issues, including quarantine due to COVID-19 infection, caused several visit/assessment delays. In case of COVID-19 related visit/assessment delay, it was captured as protocol deviation with COVID-19 flag.
    - S01 (out of window): A total of 10 cases in 9 subjects
    - S05 (Visit 1 out of window): A total of 4 cases in 4 subjects

- S07, S08, S09, S12, S14, S16, and S18 (study procedures not done at pre-dose on scheduled visit): A total of 2 cases in 2 subjects (for each protocol deviation code)
- S19 (ET visit out of window): A total of 1 case in 1 subject

3. Local Laboratory Usage as Alternative Procedure: Due to transient shipment restrictions under COVID-19 circumstances, the laboratory samples for some visits were unable to ship out from the investigational site to the central laboratory. Considering the subject safety, the local laboratory tests were conducted as an alternative means to monitor the subject's safety and treatment effect, and the results were captured on the eCRF. These alternative measures were performed on some visits of three subjects in one investigational site.
4. Site Transfer: One investigational site was designated as COVID-19 hospital by the government, and it did not allow visits for non-COVID-19 patients. As a result, one subject was transferred to another investigational site located in the same city.
5. Re-screening: Due to COVID-19 restrictions at the investigational site, the subject inscreening was unable to complete the screening activities. Therefore, one subject was allowed to be re-screened after the restriction was lifted as it was considered as a technical issue. Subjects whose screening failed due to COVID-19 were recorded on eCRF.
6. Remote SDV: The Sponsor initially planned 100% of on-site SDV and source data review (SDR). However, after COVID-19 outbreak, the travel restrictions at some investigational sites prohibited the monitor's on-site visits. As a mitigation plan, the Sponsor adopted partial and remote SDV/SDR approach only for the investigational sites in which the on-site monitoring visit was not allowed. Remote SDV/SDR was conducted under circumstances that a conventional approach of on-site SDV/SDR was not possible while there was the necessity to source-verify critical data points to ensure the integrity of study data. Remote SDV was only implemented to investigational sites or countries where the local privacy law and regulations allowed, and necessary permissions were obtained according to the local requirements. With the implementation of remote SDV/SDR on any certain investigational sites, the SDV approach of those investigational sites was switched to partial SDV from 100% SDV.

Protocol Deviations

PDs by planned treatment sequence for subjects in the RAN are shown in the Table below.

Table 13: summary of protocol deviation by planned treatment sequence (randomised set)

Number of Subjects	Soliris® to SB12 N = 25 n (%)	SB12 to Soliris® N = 25 n (%)	Total N = 50 n (%)
Any protocol deviations	15 (60.0)	13 (52.0)	28 (56.0)
With at least one major protocol deviation	11 (44.0)	11 (44.0)	22 (44.0)
Study Procedures Criteria	11 (44.0)	11 (44.0)	22 (44.0)
Out of visit window	8 (32.0)	7 (28.0)	15 (30.0)
The ICF reconsent was not obtained or not signed by subject at the earliest next visit after effective date of the revised informed consent obtained	3 (12.0)	4 (16.0)	7 (14.0)
Blood and urine sampling for central laboratory was not done at pre-dose on scheduled visit	2 (8.0)	0 (0.0)	2 (4.0)
Blood sampling for immunogenicity assessment was not done at the same day of study drug administration	2 (8.0)	2 (8.0)	4 (8.0)
Blood sampling for PD analysis was not done at the same day of study drug administration	2 (8.0)	1 (4.0)	3 (6.0)
Blood sampling for PK analysis was not done at the same day of study drug administration	2 (8.0)	2 (8.0)	4 (8.0)
Pregnancy test was not done at pre-dose on scheduled visit	2 (8.0)	0 (0.0)	2 (4.0)
With at least one minor protocol deviation	8 (32.0)	8 (32.0)	16 (32.0)
Study Procedures Criteria	8 (32.0)	8 (32.0)	16 (32.0)
12-lead ECG, PNH symptomatology, or physical examination assessments were not done at pre-dose on scheduled visit	5 (20.0)	5 (20.0)	10 (20.0)
Out of window for the initiation of study drug (more than 21 days from randomisation)	2 (8.0)	3 (12.0)	5 (10.0)
Vital sign assessments were not done at pre-dose on dosing day	2 (8.0)	0 (0.0)	2 (4.0)
ET visit was not done or out of visit window	1 (4.0)	0 (0.0)	1 (2.0)
Vaccination was not performed properly according to local guideline during the study period after Day 1	0 (0.0)	1 (4.0)	1 (2.0)
With at least one major protocol deviation related to COVID-19 restriction	7 (28.0)	3 (12.0)	10 (20.0)
Study procedures criteria	7 (28.0)	3 (12.0)	10 (20.0)
Out of visit window	6 (24.0)	3 (12.0)	9 (18.0)
Blood and urine sampling for central laboratory was not done at pre-dose on scheduled visit	2 (8.0)	0 (0.0)	2 (4.0)
Blood sampling for immunogenicity assessment was not done at the same day of study drug administration	2 (8.0)	0 (0.0)	2 (4.0)
Blood sampling for PD analysis was not done at the same day of study drug administration	2 (8.0)	0 (0.0)	2 (4.0)
Blood sampling for PK analysis was not done at the same day of study drug administration	2 (8.0)	0 (0.0)	2 (4.0)
Pregnancy test was not done at pre-dose on scheduled visit	2 (8.0)	0 (0.0)	2 (4.0)

With at least one minor protocol deviation related to COVID-19 restriction	4 (16.0)	3 (12.0)	7 (14.0)
Study Procedures Criteria	4 (16.0)	3 (12.0)	7 (14.0)
12-lead ECG, PNH symptomatology, or physical examination assessments were not done at pre-dose on scheduled visit	2 (8.0)	0 (0.0)	2 (4.0)
Vital sign assessments were not done at pre-dose on dosing day	2 (8.0)	0 (0.0)	2 (4.0)
ET visit was not done or out of visit window	1 (4.0)	0 (0.0)	1 (2.0)
Out of window for the initiation of study drug (more than 21 days from randomisation)	1 (4.0)	3 (12.0)	4 (8.0)

COVID-19 = Coronavirus Disease 2019; ECG = electrocardiogram; ET = early termination; ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; PNH = Paroxysmal nocturnal haemoglobinuria

- Percentages were based on the number of subjects in the Randomised set.

Source: Table 14.1-1.2

- **Baseline data**

Demographics

Overall, demographic characteristics were variable between treatment arms (please see table below).

Table 14: Demographic characteristics by planned treatment sequence (randomised set)

Characteristics	Soliris® to SB12 N = 25	SB12 to Soliris® N = 25	Total N = 50
Age (years)[a]			
n	25	25	50
Mean	36.3	40.0	38.1
SD	13.67	13.44	13.55
Median	34.0	40.0	36.5
Min, Max	18, 79	19, 65	18, 79
Age group, n (%)			
< 65 years	24 (96.0)	24 (96.0)	48 (96.0)
≥ 65 years	1 (4.0)	1 (4.0)	2 (4.0)
Gender, n (%)			
Female	14 (56.0)	8 (32.0)	22 (44.0)
Male	11 (44.0)	17 (68.0)	28 (56.0)
Child bearing potential, n (%)[b]			
Yes	12 (85.7)	6 (75.0)	18 (81.8)
No	2 (14.3)	2 (25.0)	4 (18.2)
Race, n (%)			
Asian	12 (48.0)	15 (60.0)	27 (54.0)
White	11 (44.0)	7 (28.0)	18 (36.0)
Other	2 (8.0)	3 (12.0)	5 (10.0)
Ethnicity, n (%)			
Hispanic or Latino	2 (8.0)	3 (12.0)	5 (10.0)
Indian (Indian subcontinent)	4 (16.0)	2 (8.0)	6 (12.0)
Chinese	3 (12.0)	5 (20.0)	8 (16.0)
Other	16 (64.0)	15 (60.0)	31 (62.0)
Height at Screening (cm)			
n	25	25	50
Mean	164.12	167.56	165.84
SD	8.467	9.794	9.226
Median	163.00	168.00	164.95
Min, Max	146.0, 180.0	149.0, 190.0	146.0, 190.0
Weight at Baseline (kg)			
n	25	25	50
Mean	64.65	68.44	66.54
SD	15.777	14.898	15.306
Median	61.00	65.00	63.00
Min, Max	43.0, 111.0	47.0, 100.0	43.0, 111.0
Body Mass Index (BMI) (kg/m^2)[c]			
n	25	25	50
Mean	23.80	24.20	24.00
SD	4.331	3.805	4.039
Median	23.00	24.30	23.00
Min, Max	16.8, 37.5	17.4, 31.1	16.8, 37.5

BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation
[a] Age was calculated as Age (years) = year of informed consent − year of birth.
[b] Percentages were based on the number of female subjects.
[c] BMI = (body weight in kilograms) / (height in meters)^2
- Percentages were based on the number of subjects in the Randomised Set, unless otherwise specified.
Source: Table 14.1-3.1

Baseline Disease Characteristics

Descriptive statistics of baseline disease characteristics are summarised in the table below.

Table 15: baseline characteristics by planned treatment sequence (randomised set)

Characteristics	Soliris® to SB12 N = 25	SB12 to Soliris® N = 25	Total N = 50
Duration of PNH (years)[a]			
n	25	25	50
Mean	5.065	7.298	6.182
SD	6.2190	7.5906	6.9597
Median	3.760	5.800	4.050
Min, Max	0.00, 22.56	0.14, 29.28	0.00, 29.28
Subject received a prior pRBC transfusion, n (%)			
Yes	14 (56.0)	16 (64.0)	30 (60.0)
No	11 (44.0)	9 (36.0)	20 (40.0)
Total number of pRBCs in 12 months prior to Screening[b]			
n	25	25	50
Mean	3.8	6.4	5.1
SD	4.85	7.80	6.56
Median	1.0	4.0	2.0
Min, Max	0, 18	0, 28	0, 28
LDH (U/L) at Baseline			
n	25	25	50
Mean	2156.0	2220.2	2188.1
GM	1750.6	2001.6	1871.9
SD	1441.51	1054.60	1250.42
Median	2055.0	2115.0	2077.5
Min, Max	546, 6630	678, 5430	546, 6630
PNH clone size of Type II RBCs (%) at Baseline			
n	24	25	49
Mean	7.594	16.264	12.018
SD	11.8608	25.5559	20.3258
Median	2.260	3.980	3.370
Min, Max	0.15, 54.68	0.07, 88.03	0.07, 88.03
PNH clone size of Type III RBCs (%) at Baseline			
n	25	25	50
Mean	42.396	32.698	37.547
SD	23.3097	20.3411	22.1987
Median	43.200	26.880	36.075
Min, Max	1.99, 96.92	4.25, 74.48	1.99, 96.92
Total PNH clone size of RBCs (%) at Baseline			
n	25	25	50
Mean	49.686	48.310	48.998
SD	25.4573	26.1735	25.5625
Median	50.890	44.120	45.905
Min, Max	8.92, 99.62	4.92, 94.61	4.92, 99.62
PNH clone size of Granulocytes (%) at Baseline			
n	25	25	50
Mean	88.659	89.820	89.240
SD	12.8697	18.8196	15.9669
Median	95.820	93.690	94.255
Min, Max	54.77, 99.73	3.33, 99.68	3.33, 99.73

PNH clone size of Monocytes (%) at Baseline			
n	25	25	50
Mean	89.524	92.693	91.109
SD	12.2771	7.5677	10.2195
Median	95.540	96.820	95.580
Min, Max	59.08, 99.78	71.74, 99.55	59.08, 99.78
Reticulocyte count (%) at Baseline			
n	25	25	50
Mean	7.893	8.494	8.193
SD	5.2386	3.7704	4.5273
Median	6.330	9.310	7.305
Min, Max	1.57, 21.60	2.17, 15.00	1.57, 21.60
Haptoglobin (g/L) at Baseline			
n	25	25	50
Mean	0.050	0.050	0.050
SD	0.0000	0.0000	0.0000
Median	0.050	0.050	0.050
Min, Max	0.05, 0.05	0.05, 0.05	0.05, 0.05
Haemoglobin (g/L) at Baseline			
n	25	25	50
Mean	85.9	89.1	87.5
SD	19.96	25.04	22.47
Median	84.0	89.0	88.5
Min, Max	42, 121	38, 145	38, 145

GM = geometric mean; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cells; RBC = red blood cell; SD = standard deviation

[a] Duration of PNH (years) was calculated as the (date of informed consent − diagnosed date of PNH + 1) / 365.25.

[b] For subjects who did not have prior pRBCs, the total number of pRBCs in 12 months prior to Screening was set to 0.

- Percentages were based on the number of subjects in the Randomised Set, unless otherwise specified.
- Total PNH clone size of RBC was calculated as the sum of PNH clone size of Type II and Type III RBC. When PNH clone size of Type II RBC was missing, only PNH clone size of Type III RBC was used to calculated Total PNH clone size of RBC.

Source: Table 14.1-3.2

Medical and Surgical History

Medical and surgical history reported by over 2 subjects in any planned treatment sequence are provided in the table 16 below.

Table 16: Medical and surgical history reported by system organ class and preferred term by ≥2 subjects in planned treatment sequence (randomised set)

Primary System Organ Class Preferred term	Soliris® to SB12 N = 25 n (%)	SB12 to Soliris® N = 25 n (%)	Total N = 50 n (%)
Any medical and surgical history	19 (76.0)	24 (96.0)	43 (86.0)
Blood and lymphatic system disorders			
Anaemia	2 (8.0)	0 (0.0)	2 (4.0)
Haemolytic anaemia	2 (8.0)	1 (4.0)	3 (6.0)
Splenomegaly	2 (8.0)	0 (0.0)	2 (4.0)
Aplastic anaemia	1 (4.0)	3 (12.0)	4 (8.0)
Pancytopenia	0 (0.0)	2 (8.0)	2 (4.0)
Gastrointestinal disorders			
Duodenitis	2 (8.0)	0 (0.0)	2 (4.0)
Pancreatitis chronic	2 (8.0)	0 (0.0)	2 (4.0)
Hepatobiliary disorders			
Cholecystitis chronic	2 (8.0)	1 (4.0)	3 (6.0)
Liver disorder	2 (8.0)	1 (4.0)	3 (6.0)
Cholelithiasis	0 (0.0)	3 (12.0)	3 (6.0)
Hepatic steatosis	0 (0.0)	2 (8.0)	2 (4.0)
Investigations			
Alanine aminotransferase increased	0 (0.0)	2 (8.0)	2 (4.0)
Gamma-glutamyltransferase increased	0 (0.0)	2 (8.0)	2 (4.0)
Platelet count decreased	0 (0.0)	2 (8.0)	2 (4.0)
Metabolism and nutrition disorders			
Hypokalaemia	0 (0.0)	2 (8.0)	2 (4.0)
Musculoskeletal and connective tissue disorders			
Osteoporosis	2 (8.0)	0 (0.0)	2 (4.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Myelodysplastic syndrome	1 (4.0)	2 (8.0)	3 (6.0)
Renal and urinary disorders			
Nephrolithiasis	2 (8.0)	0 (0.0)	2 (4.0)
Chronic kidney disease	1 (4.0)	2 (8.0)	3 (6.0)
Surgical and medical procedures			
Splenectomy	2 (8.0)	1 (4.0)	3 (6.0)
Vascular disorders			
Hypertension	3 (12.0)	4 (16.0)	7 (14.0)

- Percentages were based on the number of subjects in the RAN.
- Medical and surgical history was coded using MedDRA®, Version 21.0 coding dictionary.

Table 17: Thrombosis history by system organ class and preferred term by planned treatment sequence (randomised set)

Primary System Organ Class Preferred term	Soliris® to SB12 N = 25 n (%)	SB12 to Soliris® N = 25 n (%)	Total N = 50 n (%)
Any thrombosis history	2 (8.0)	1 (4.0)	3 (6.0)
Blood and lymphatic system disorders	1 (4.0)	0 (0.0)	1 (2.0)
Splenic thrombosis	1 (4.0)	0 (0.0)	1 (2.0)
Endocrine disorders	1 (4.0)	0 (0.0)	1 (2.0)
Adrenal thrombosis	1 (4.0)	0 (0.0)	1 (2.0)
Hepatobiliary disorders	1 (4.0)	0 (0.0)	1 (2.0)
Budd-Chiari syndrome	1 (4.0)	0 (0.0)	1 (2.0)
Hepatic vein thrombosis	1 (4.0)	0 (0.0)	1 (2.0)
Portal vein thrombosis	1 (4.0)	0 (0.0)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	1 (4.0)	0 (0.0)	1 (2.0)
Pulmonary thrombosis	1 (4.0)	0 (0.0)	1 (2.0)
Vascular disorders	1 (4.0)	1 (4.0)	2 (4.0)
Deep vein thrombosis	1 (4.0)	0 (0.0)	1 (2.0)
Thrombophlebitis superficial	0 (0.0)	1 (4.0)	1 (2.0)

- Thrombosis history was defined as any medical history with high level group terms of 'Embolism and thrombosis' or preferred term of 'Budd-Chiari syndrome' or preferred term of including the term 'thrombosis'.
- Percentages were based on the number of subjects in the Randomised Set.
- Medical and surgical history including thrombosis history was coded using MedDRA®, Version 21.0 coding dictionary.

Prior and Concomitant Medications

A similar proportion of subjects in both actual treatment sequences had taken medications which started and stopped prior to the study (i.e., prior medication): 11 (44.0%) subjects in the actual Soliris to SB12 treatment sequence, 9 (37.5%) subjects in the actual SB12 to All treatment sequence.

A total of 48 (98.0%) subjects received at least 1 concomitant medication (40 subjects in the SB12 treatment group and 40 subjects in the Soliris treatment group, respectively). The most frequently (reported by > 10% subjects in either treatment group) reported concomitant medications by PT in the SB12 and Soliris treatment groups, respectively, were folic acid (16 [34.0%] and 15 [31.9%] subjects), paracetamol (9 [19.1%] and 9 [19.1%] subjects), prednisolone (6 [12.8%] and 8 [17.0%] subjects), danazol (1 [2.1%] and 9 [19.1%] subjects), ciprofloxacin (3 [6.4%] and 6 [12.8%] subjects), and other viral vaccines (3 [6.4%] and 6 [12.8%] subjects).

- **Numbers analysed**

The number of subjects included in each analysis set for planned or actual treatment sequence (i.e. Soliris to SB12 or SB12 to All [SB12 to Soliris and Unplanned IP Switch]) is summarised in table 18 below.

Table 18: Number of (%) of subjects in the analysis sets by treatment sequence (randomised set)

Number of Subjects	Soliris® to SB12 n (%)[a]	SB12 to All n (%)[b]	SB12 to Soliris® n (%)[a]	Unplanned IP Switch n (%)[b]	Total n (%)
Randomised set (RAN)	25 (100.0)		25 (100.0)		50 (100.0)
Modified full analysis set (M-FAS)	25 (100.0)		24 (96.0)		49 (98.0)
Per-Protocol Set for AUEC of LDH (PPS-AUEC)	23 (92.0)		15 (60.0)		38 (76.0)
Per-Protocol Set for LDH at a single time point (PPS-single)	23 (92.0)		23 (92.0)		46 (92.0)
Safety Set (SAF)	25 (100.0)	24 (96.0)	16 (64.0)	8 (32.0)	49 (98.0)
Safety Set for Period 1 (SAF1)	25 (100.0)	24 (96.0)			49 (98.0)
Safety Set for Period 2 (SAF2)	23 (92.0)	23 (92.0)	15 (60.0)	8 (32.0)	46 (92.0)
PK Analysis Set (PKS)	25 (100.0)	24 (96.0)	16 (64.0)	8 (32.0)	49 (98.0)
PD Analysis Set (PDS)	25 (100.0)	24 (96.0)	16 (64.0)	8 (32.0)	49 (98.0)

IP = investigational product; PD = pharmacodynamic; PK = pharmacokinetic

[a] Percentages were based on the number of subjects in the Randomised Set.

[b] Percentages were based on the number of subjects in the Randomised Set for respective planned treatment sequence where unplanned IP switch occurred.

- Safety Set for Period 1, Safety Set for Period 2, PK Analysis Set and PD Analysis Set are summarised by actual treatment sequence; else summarised by planned treatment sequence.

- **Outcomes and estimation**

The **primary efficacy endpoint** was LDH level (U/L) at Week 26.

The primary efficacy analysis was performed for the PPS-single using a linear model with treatment and gender as fixed effects. In the PPS-single, the 2-sided 95% CI of the estimated LSM difference in LDH level at Week 26 between SB12 and Soliris treatment group (SB12 − Soliris: 34.48, 95% CI [−47.66, 116.62]) completely lied within the pre-defined equivalence margin of [−337.2 to 337.2].

Table 19: Analysis of primary endpoint: LDH (U/L) at week (per-protocol set for LDH at a single time point)

Parameter	Treatment	n	Least Squares Mean	Difference (SB12 – Soliris®)[a] Estimate	95% CI
LDH (U/L) at Week 26	SB12 (N=23)	23	284.20	34.48	(−47.66, 116.62)
	Soliris® (N=23)	23	249.72		

CI = confidence interval; LDH = lactate dehydrogenase; n = number of subjects in the analysis; N for SB12 represents the total number of subjects who had been treated with SB12 in Period 1; N for Soliris® represents the total number of subjects who had been treated with Soliris® in Period 1

[a] Least squares mean (LSM) difference and its 95% CI in original scale were obtained by applying delta method to the LSM ratio estimated from a linear model with natural log-transformed LDH at Week 26 as dependent variable, and treatment and gender as fixed effects.

The robustness of LDH (U/L) at Week 26 was explored by performing the same analysis for the M-FAS using complete case analysis and multiple imputation method.

Taking missing data into account, the results from **sensitivity analyses** on the M-FAS by both methods validated the robustness of the primary analysis from the PPS-single.

The complete case analysis was based on the M-FAS where subjects with non-missing LDH values at Week 26 showed that findings of the estimated LSM difference in LDH (U/L) levels at Week 26 between SB12 and Soliris treatment groups (SB12 – Soliris: 34.48, 95% CI [−47.66, 116.62]) were consistent with those from the primary analysis.

Multiple imputation method that assumed missing data were MAR provided the consistent estimated LSM difference in LDH (U/L) level at Week 26 between SB12 and Soliris treatment groups (SB12 – Soliris: 26.91, 95% CI [−56.24, 110.05]) with the primary analysis.

Table 20: Sensitivity analysis of primary endpoint: LDH (U/L) at week 26 (modified full analysis set)

Parameter	Treatment	n	Least Squares Mean	Difference (SB12 – Soliris®)[a] Estimate	95% CI
Method: Complete case analysis					
LDH (U/L) at Week 26	SB12 (N=24)	23	284.20	34.48	(−47.66, 116.62)
	Soliris® (N=25)	23	249.72		
Method: Multiple imputation					
LDH (U/L) at Week 26	SB12 (N=24)	24	282.87	26.91	(−56.24, 110.05)
	Soliris® (N=25)	25	255.96		

CI = confidence interval; LDH = lactate dehydrogenase; n = number of subjects in the analysis; N for SB12 represents the total number of subjects who had been treated with SB12 in Period 1; N for Soliris® represents the total number of subjects who had been treated with Soliris® in Period 1

[a] Least squares mean (LSM) difference and its 95% CI in original scale were obtained by applying delta method to the LSM ratio estimated from a linear model with natural log-transformed LDH at Week 26 as dependent variable, and treatment and gender as fixed effects.

Secondary Endpoints:

LDH Profile Over Time

The mean LDH profile over time for the M-FAS was plotted by planned treatment sequence. The plot of combined individual LDH profile over time using the M-FAS are provide in the Figure 10 below.

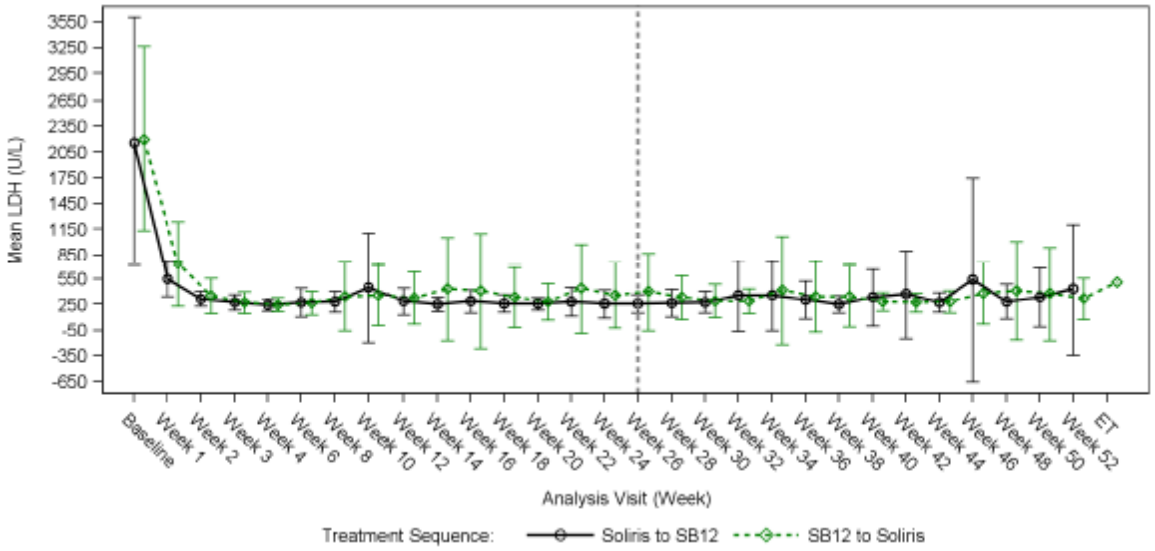


Figure 10: Plot of mean (±SD) LDH profile over time by planned treatment sequence (modified full analysis set)

LDH: lactate dehydrogenase; SD: standard deviation

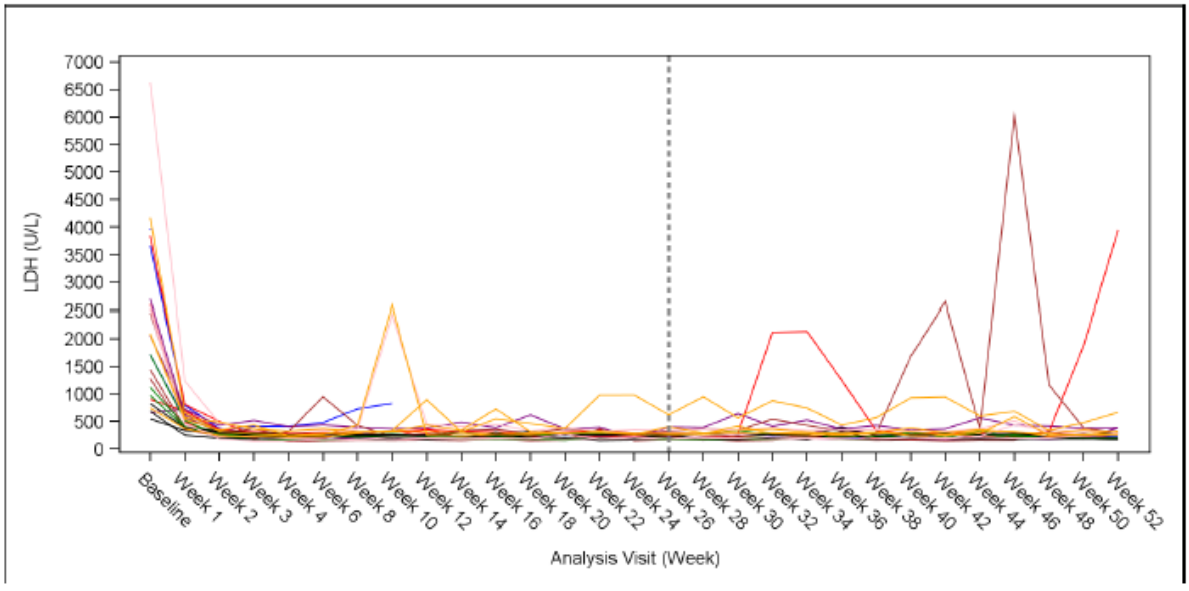
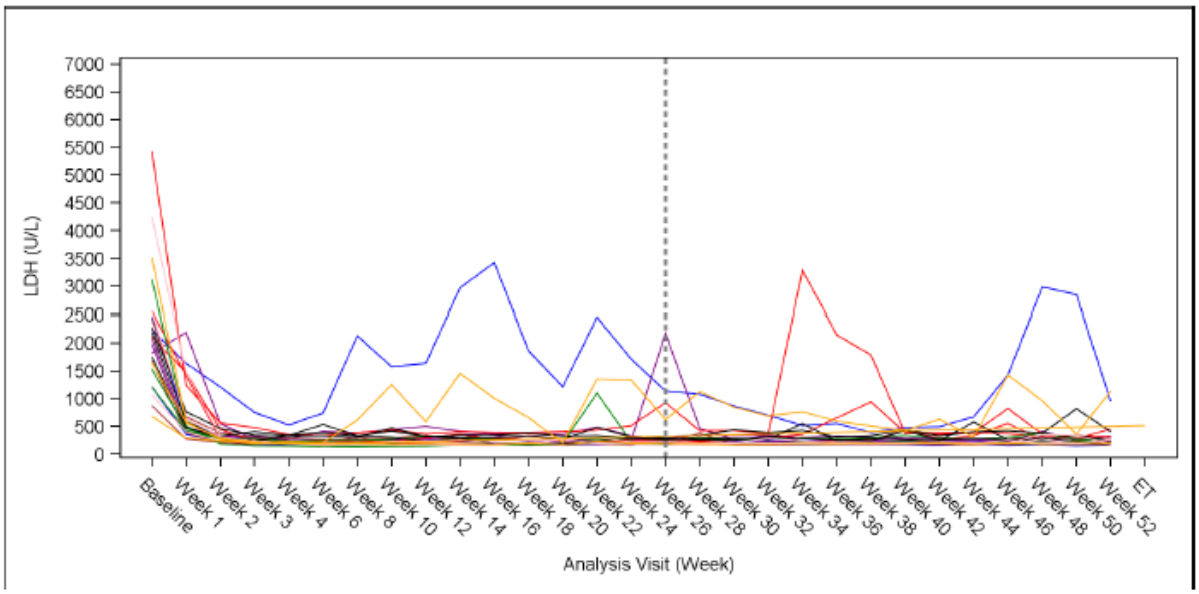


Figure 11: Plot of combined individual LDH profile of planned treatment sequence (Soliris to SB12) in modified full analysis set (M-FAS)



- Source: Listing 16.2.6-1.1b
- LDH: Lactate Dehydrogenase
Program Path: .¥CSR¥f14020101.sas
Data Extraction Date: 11JAN2022
Run date: 17JAN2022 11:16

Figure 12: Combined individual LDH profile of planned treatment sequence (SB12 to Soliris) in modified full-analysis set (M-FAS)

Overall, the number of patients with elevated LDH levels > 2 × ULN was comparable between the actual treatment groups (SB12:Soliris, 11:13), but number of events of elevated LDH levels > 2 × ULN as well as exposure-adjusted event rates (EAER) were higher in patients on SB12 treatment in both periods (events: SB12:Soliris, 49:27; EAER: SB12:Soliris: 2.07:1.39).

Table 21: Summary of patients who experienced elevated LDH≥2.0 *ULN during the maintenance period by actual treatment group within period (safety set, study SB12-3003) (ad hoc analysis)

Category	Period	SB12 N = 47				Soliris N = 47				Total N = 49			
		n/n'	(%)	E	EAER	n/n'	(%)	E	EAER	n/n'	(%)	E	EAER
	Period 1	5/24	(20.8)	23	2.32	7/25	(28.0)	10	1.01	12/49	(24.5)	33	1.67
LDH level > 2 × ULN	Period 2	9/31	(29.0)	26	1.88	6/22	(27.3)	17	1.79	12/46	(26.1)	43	1.85
	Overall	11/47	(23.4)	49	2.07	13/47	(27.7)	27	1.39	17/49	(34.7)	76	1.76

E = number of elevated LDH level > 2.0 × ULN; EAER = Exposure-adjusted Event Rate; LDH = lactate dehydrogenase; N = a total number of patients in the Safety Set; n = number of patients who experienced elevated LDH level > 2.0 × ULN; n' = number of patients in each period; ULN = upper limit of normal
Percentages were based on the n'
EAER was calculated as number of events/ total exposure time in patient-years; where total exposure time in patient-years = Sum of treatment exposure in years across all patients in each treatment group and period.
Source: Section 5.3.5.1 CSR SB12-3003, Listing 16.2.5-1.1a, Listing 16.2.6-1.1b

Number of Units of pRBCs Transfused throughout the Study Period

The overall units of pRBC transfused were decreased after study treatment initiation in both planned treatment sequences. There was no statistically significant difference in the median number of units of pRBCs transfused between the planned Soliris to SB12 and SB12 to Soliris treatment sequences throughout the study duration.

Table 22: Summary statistics for number of units of pRBCs transfused throughout the study duration by planned treatment sequence (modified full analysis set)

Study Overall/ Study Period	Soliris® to SB12 N = 25	SB12 to Soliris® N = 24	Total N = 49
Study Overall			
n	25	24	49
Mean	2.7	2.9	2.8
SD	4.85	8.05	6.55
Median	0.0	0.0	0.0
Min, Max	0, 22	0, 39	0, 39
p-value[a]	0.4704		
Pre-treatment			
n	25	24	49
Mean	0.8	0.7	0.8
SD	1.37	1.08	1.23
Median	0.0	0.0	0.0
Min, Max	0, 5	0, 4	0, 5
p-value[a]	> 0.9999		
Study Period 1			
n	25	24	49
Mean	0.9	1.1	1.0
SD	2.06	3.72	2.96
Median	0.0	0.0	0.0
Min, Max	0, 8	0, 18	0, 18
p-value[a]	0.4592		
Study Period 2			
n	23	23	46
Mean	1.0	1.1	1.1
SD	2.61	4.05	3.37
Median	0.0	0.0	0.0
Min, Max	0, 12	0, 19	0, 19
p-value[a]	0.4282		

IP = investigational product; Max = maximum; Min = minimum; N = total number of subjects in the Modified Full Analysis Set; pRBC = packed red blood cells; SD = standard deviation

[a] *p*-values were based on the Wilcoxon rank-sum test for the testing of the treatment sequence difference.

- Within each treatment sequence, n of 'Study Overall': The total number of subjects with available data in that treatment sequence; n of 'Study Period 1' / 'Pre-treatment': The number of subjects with available data in Period 1; n of 'Study Period 2': The number of subjects with available data in Period 2. 'Pre-treatment' period refers to the period from date of informed consent and prior to first IP dosing.

Other Efficacy Results

According to the applicant, the 90% CI lied within the pre-defined equivalence range [0.77 to 1.29], as required by FDA.

Table 23: Analysis of primary endpoint: time adjusted AUEC values (per protocol set for AUEC of LDH)

				Ratio (SB12/Soliris®)	
Parameter	Treatment	n	Geometric Least Squares Mean[a]	Estimate	90% CI
Time-adjusted AUEC (U/L) of LDH	SB12 (N=38)	38	279.65	1.08	(0.95, 1.23)
	Soliris® (N=38)	38	258.73		

AUEC = area under the effect curve; CI = confidence interval; n = number of subjects in the analysis; N for SB12 represents the total number of pooled subjects in PPS-AUEC who belonged to SB12 treatment group in either Periods 1 or 2; N for Soliris® represents the total number of pooled subjects in PPS-AUEC who belonged to Soliris® treatment group in either Periods 1 or 2

[a] Geometric means ratio and 90% CI was obtained by performing back transformation of least squares mean difference and its 90% CI from the linear mixed model with natural log-transformed time-adjusted AUEC of LDH as dependent variable, and treatment, sequence, period and gender as fixed effects and subject nested within sequence as a random effect.

Disease-related Laboratory Parameters

A trend of mean reduction from baseline in LDH was comparable between planned Soliris to SB12 and planned SB12 to Soliris treatment sequences.

Table 24: Summary statistics for disease related laboratories parameters by planned treatment sequence (modified full analysis set)

Visit	Soliris® to SB12 N = 25		SB12 to Soliris® N = 24		Total N = 49	
Statistics	Value	Change	Value	Change	Value	Change
Lactate Dehydrogenase (U/L)						
Baseline						
n	25	-	24	-	49	-
Mean	2156.0	-	2195.2	-	2175.2	-
SD	1441.51	-	1069.69	-	1260.02	-
GM	1750.6	-	1973.3	-	1856.3	-
Median	2055.0	-	2100.0	-	2070.0	-
Min	546	-	678	-	546	-
Max	6630	-	5430	-	6630	-
Week 26						
n	23	23	23	23	46	46
Mean	260.2	−1836.7	402.6	−1858.6	331.4	−1847.7
SD	103.67	1449.64	456.73	1094.43	335.29	1270.07
GM	245.5	N/A	299.2	N/A	271.0	N/A
Median	244.0	−1658.0	247.0	−1802.0	247.0	−1763.0
Min	164	−6293	169	−4504	164	−6293
Max	618	−125	2175	360	2175	360
Week 52						
n	23	23	23	23	46	46
Mean	431.9	−1665.0	317.7	−1943.4	374.8	−1804.2
SD	773.14	1455.47	241.43	1069.77	569.26	1270.81
GM	289.1	N/A	272.0	N/A	280.4	N/A
Median	267.0	−1538.0	244.0	−1758.0	253.5	−1687.5
Min	169	−6363	161	−5118	161	−6363
Max	3945	105	1134	−516	3945	105
PNH clone size of Type II RBC (%)						
Baseline						
n	24	-	24	-	48	-
Mean	7.594	-	16.934	-	12.264	-
SD	11.8608	-	25.8804	-	20.4668	-
Median	2.260	-	4.080	-	3.375	-
Min	0.15	-	0.07	-	0.07	-
Max	54.68	-	88.03	-	88.03	-
Week 26						
n	20	20	22	22	42	42
Mean	11.242	3.453	19.211	4.388	15.416	3.942
SD	17.3129	15.4892	27.5523	20.1248	23.3228	17.8563
Median	4.040	0.360	3.450	−0.030	3.450	0.165
Min	0.07	−8.88	0.07	−36.60	0.07	−36.60
Max	67.38	66.62	92.51	78.69	92.51	78.69
Week 52						
n	22	22	22	22	44	44
Mean	11.257	3.723	17.335	2.512	14.296	3.118
SD	16.0857	11.7777	25.4164	20.4562	21.2439	16.5070
Median	3.925	0.665	4.540	−0.270	3.925	0.200
Min	0.20	−17.66	0.07	−42.46	0.07	−42.46
Max	61.30	41.95	81.09	76.98	81.09	76.98

PNH clone size of Type III RBC (%)						
Baseline						
n	25	-	24	-	49	-
Mean	42.396	-	33.135	-	37.860	-
SD	23.3097	-	20.6583	-	22.3170	-
Median	43.200	-	27.510	-	36.570	-
Min	1.99	-	4.25	-	1.99	-
Max	96.92	-	74.48	-	96.92	-
Week 26						
n	21	21	23	23	44	44
Mean	48.875	7.522	41.412	7.507	44.974	7.514
SD	29.1507	19.1509	24.3698	22.1217	26.7078	20.5173
Median	42.340	6.090	45.300	9.960	43.735	8.240
Min	9.35	−24.88	2.03	−56.41	2.03	−56.41
Max	97.90	52.71	93.66	44.80	97.90	52.71
Week 52						
n	23	23	23	23	46	46
Mean	48.812	5.113	43.352	9.447	46.082	7.280
SD	27.2211	15.1142	24.9244	24.8654	25.9536	20.4635
Median	40.870	4.870	43.040	9.480	41.955	6.435
Min	14.85	−25.32	1.99	−56.72	1.99	−56.72
Max	98.53	32.58	93.73	50.45	98.53	50.45
Total PNH clone size of RBC (%)						
Baseline						
n	25	-	24	-	49	-
Mean	49.686	-	49.390	-	49.541	-
SD	25.4573	-	26.1616	-	25.5346	-
Median	50.890	-	45.000	-	45.930	-
Min	8.92	-	4.92	-	4.92	-
Max	99.62	-	94.61	-	99.62	-
Week 26						
n	21	21	23	23	44	44
Mean	61.109	12.338	59.787	11.703	60.418	12.006
SD	29.5036	24.8653	23.1164	19.8665	26.0520	22.1270
Median	63.070	7.730	58.730	10.170	60.900	10.065
Min	16.65	−30.83	15.02	−31.19	15.02	−31.19
Max	99.98	63.45	94.99	50.24	99.98	63.45
Week 52						
n	23	23	23	23	46	46
Mean	61.087	10.182	59.933	11.850	60.510	11.016
SD	28.0349	18.2165	23.7627	23.8484	25.7030	20.9999
Median	63.570	7.980	64.300	11.640	63.705	10.560
Min	16.90	-30.81	16.04	-46.23	16.04	-46.23
Max	99.42	40.21	100.00	49.69	100.00	49.69

PNH clone size of WBC, Granulocytes (%)						
Baseline						
n	25	-	24	-	49	-
Mean	88.659	-	89.628	-	89.134	-
SD	12.8697	-	19.1992	-	16.1146	-
Median	95.820	-	92.750	-	94.070	-
Min	54.77	-	3.33	-	3.33	-
Max	99.73	-	99.68	-	99.73	-
Week 52						
n	23	23	23	23	46	46
Mean	86.463	−1.342	87.635	−1.903	87.049	−1.623
SD	14.9842	5.9737	19.9793	7.6036	17.4720	6.7670
Median	93.870	−0.390	95.320	0.190	94.595	−0.030
Min	51.21	−13.42	4.22	−25.36	4.22	−25.36
Max	99.70	11.27	99.40	5.84	99.70	11.27
PNH clone size of WBC, Monocytes (%)						
Baseline						
n	25	-	24	-	49	-
Mean	89.524	-	92.483	-	90.973	-
SD	12.2771	-	7.6552	-	10.2799	-
Median	95.540	-	95.575	-	95.540	-
Min	59.08	-	71.74	-	59.08	-
Max	99.78	-	99.55	-	99.78	-
Week 52						
n	23	23	23	23	46	46
Mean	87.152	−1.660	92.841	0.198	89.997	−0.731
SD	13.5323	3.8771	7.9632	3.0854	11.3490	3.5896
Median	93.530	−0.870	95.840	0.490	95.725	−0.085
Min	57.61	−12.24	72.03	−11.86	57.61	−12.24
Max	99.05	3.25	99.82	5.53	99.82	5.53
Reticulocytes (%)						
Baseline						
n	25	-	24	-	49	-
Mean	7.893	-	8.625	-	8.252	-
SD	5.2386	-	3.7925	-	4.5552	-
Median	6.330	-	9.330	-	7.470	-
Min	1.57	-	2.17	-	1.57	-
Max	21.60	-	15.00	-	21.60	-
Week 26						
n	17	17	20	20	37	37
Mean	7.187	0.094	8.620	−0.190	7.962	−0.059
SD	4.7444	2.1362	4.2000	3.7793	4.4540	3.0963
Median	5.120	0.430	8.575	−0.070	7.080	−0.060
Min	2.00	−4.27	3.55	−8.22	2.00	−8.22
Max	19.43	3.45	18.48	9.13	19.43	9.13
Week 52						
n	19	19	21	21	40	40
Mean	7.152	−0.667	8.458	−0.144	7.838	−0.393
SD	3.6737	3.8526	4.4370	3.7116	4.0941	3.7397
Median	7.750	0.090	7.210	−0.170	7.420	−0.100
Min	1.66	−11.40	3.01	−8.20	1.66	−11.40
Max	15.00	5.63	18.89	9.54	18.89	9.54

Haptoglobin (g/L)						
Baseline						
n	25	-	24	-	49	-
Mean	0.050	-	0.050	-	0.050	-
SD	0.0000	-	0.0000	-	0.0000	-
Median	0.050	-	0.050	-	0.050	-
Min	0.05	-	0.05	-	0.05	-
Max	0.05	-	0.05	-	0.05	-
Week 26						
n	23	23	23	23	46	46
Mean	0.144	0.094	0.110	0.060	0.127	0.077
SD	0.2278	0.2278	0.2203	0.2203	0.2223	0.2223
Median	0.050	0.000	0.050	0.000	0.050	0.000
Min	0.05	0.00	0.05	0.00	0.05	0.00
Max	0.98	0.93	1.06	1.01	1.06	1.01
Week 52						
n	23	23	23	23	46	46
Mean	0.093	0.043	0.093	0.043	0.093	0.043
SD	0.1280	0.1280	0.1252	0.1252	0.1252	0.1252
Median	0.050	0.000	0.050	0.000	0.050	0.000
Min	0.05	0.00	0.05	0.00	0.05	0.00
Max	0.60	0.55	0.50	0.45	0.60	0.55
Free Haemoglobin (g/L)						
Baseline						
n	25	-	24	-	49	-
Mean	0.92	-	0.85	-	0.88	-
SD	1.166	-	0.497	-	0.894	-
Median	0.50	-	0.75	-	0.70	-
Min	0.2	-	0.2	-	0.2	-
Max	5.8	-	2.3	-	5.8	-
Week 26						
n	23	23	23	23	46	46
Mean	0.36	−0.58	0.57	−0.31	0.46	−0.45
SD	0.204	1.097	0.435	0.352	0.352	0.817
Median	0.30	−0.20	0.40	−0.30	0.35	−0.20
Min	0.1	−5.0	0.1	−1.0	0.1	−5.0
Max	0.8	0.1	1.8	0.5	1.8	0.5
Week 52						
n	23	23	22	22	45	45
Mean	0.44	−0.50	0.63	−0.25	0.54	−0.38
SD	0.298	1.252	0.643	0.820	0.501	1.058
Median	0.40	−0.20	0.40	−0.25	0.40	−0.20
Min	0.1	−5.5	0.2	−1.9	0.1	−5.5
Max	1.5	0.6	3.1	2.4	3.1	2.4

Change = change from baseline; GM = geometric mean; Max = maximum; Min = minimum; N = total number of subjects in the Modified Full Analysis Set; N/A = not applicable; PNH = Paroxysmal nocturnal haemoglobinuria; RBC = red blood cell; WBC = white blood cell; SD = standard deviation

- Total PNH clone size of RBC was calculated as the sum of PNH clone size of Type II and Type III RBC. When PNH clone size of Type II RBC was missing, only PNH clone size of Type III RBC was used to calculate Total PNH clone size of RBC.
- GM was not calculated for change from baseline values.

Source: Table 14.2-1.5.1

PNH-related Symptoms

A trend of mean reduction from baseline in severity scores (0-10 scale) for all PNH-related symptoms (fatigue, haemoglobinuria, chest pain, abdominal pain, dyspnoea, dysphagia, erectile dysfunction) was observed at Week 26 and Week 52 in both treatment groups.

Table 25: PNH-related symptoms subject questionnaire by planned treatment sequence (modified full analysis set)

Symptom	Soliris® to SB12 N = 25	SB12 to Soliris® N = 24	Total N = 49
Abdominal pain			
Baseline			
n	25	24	49
Mean	1.3	1.2	1.2
SD	2.05	1.95	1.98
Median	0.0	0.0	0.0
Min, Max	0, 7	0, 8	0, 8
Week 26			
n	23	23	46
Mean	0.6	0.2	0.4
SD	2.10	0.39	1.51
Median	0.0	0.0	0.0
Min, Max	0, 10	0, 1	0, 10
Week 52			
n	23	23	46
Mean	0.5	0.3	0.4
SD	1.12	0.69	0.93
Median	0.0	0.0	0.0
Min, Max	0, 4	0, 3	0, 4
Chest pain			
Baseline			
n	25	24	49
Mean	1.0	1.3	1.1
SD	1.81	1.94	1.86
Median	0.0	0.0	0.0
Min, Max	0, 8	0, 7	0, 8
Week 26			
n	23	23	46
Mean	0.4	0.5	0.5
SD	0.94	1.70	1.36
Median	0.0	0.0	0.0
Min, Max	0, 4	0, 8	0, 8
Week 52			
n	23	23	46
Mean	0.3	0.4	0.4
SD	0.65	1.12	0.90
Median	0.0	0.0	0.0
Min, Max	0, 2	0, 5	0, 5
Dysphagia			
Baseline			
n	25	24	49
Mean	0.4	1.3	0.9
SD	0.92	2.26	1.75
Median	0.0	0.0	0.0
Min, Max	0, 3	0, 8	0, 8
Week 26			
n	23	23	46
Mean	0.0	0.0	0.0
SD	0.21	0.21	0.21
Median	0.0	0.0	0.0
Min, Max	0, 1	0, 1	0, 1

Week 52			
n	23	23	46
Mean	0.1	0.1	0.1
SD	0.34	0.46	0.40
Median	0.0	0.0	0.0
Min, Max	0, 1	0, 2	0, 2
Dyspnoea (shortness of breath)			
Baseline			
n	25	24	49
Mean	1.4	1.8	1.6
SD	1.96	2.23	2.08
Median	0.0	1.0	1.0
Min, Max	0, 7	0, 7	0, 7
Week 26			
n	23	23	46
Mean	0.9	0.7	0.8
SD	1.65	1.66	1.64
Median	0.0	0.0	0.0
Min, Max	0, 7	0, 6	0, 7
Week 52			
n	23	23	46
Mean	0.4	0.5	0.5
SD	0.79	1.16	0.98
Median	0.0	0.0	0.0
Min, Max	0, 2	0, 5	0, 5
Erectile dysfunction (if male)			
Baseline			
n	11	16	27
Mean	1.6	1.8	1.7
SD	2.50	2.91	2.70
Median	0.0	0.0	0.0
Min, Max	0, 7	0, 9	0, 9
Week 26			
n	10	16	26
Mean	0.1	1.1	0.7
SD	0.32	2.21	1.78
Median	0.0	0.0	0.0
Min, Max	0, 1	0, 7	0, 7
Week 52			
n	10	16	26
Mean	0.1	0.9	0.6
SD	0.32	1.78	1.45
Median	0.0	0.0	0.0
Min, Max	0, 1	0, 5	0, 5
Fatigue			
Baseline			
n	25	24	49
Mean	3.3	4.2	3.8
SD	2.44	2.38	2.43
Median	3.0	4.0	3.0
Min, Max	0, 7	0, 8	0, 8

Week 26			
n	23	23	46
Mean	1.9	1.9	1.9
SD	1.87	2.20	2.02
Median	2.0	1.0	1.0
Min, Max	0, 8	0, 7	0, 8
Week 52			
n	23	23	46
Mean	2.0	1.7	1.8
SD	2.14	2.04	2.08
Median	1.0	1.0	1.0
Min, Max	0, 8	0, 8	0, 8
Haemoglobinuria (discolouration of urine)			
Baseline			
n	25	24	49
Mean	3.1	3.4	3.2
SD	2.56	2.99	2.76
Median	3.0	2.0	2.0
Min, Max	0, 8	0, 9	0, 9
Week 26			
n	23	23	46
Mean	0.8	1.1	0.9
SD	1.09	1.53	1.32
Median	0.0	0.0	0.0
Min, Max	0, 3	0, 5	0, 5
Week 52			
n	23	23	46
Mean	1.0	0.6	0.8
SD	2.18	0.94	1.68
Median	0.0	0.0	0.0
Min, Max	0, 10	0, 3	0, 10

Max = maximum; Min = minimum; N = total number of subjects in the Modified Full Analysis Set; PNH = Paroxysmal nocturnal haemoglobinuria; SD = standard deviation

Breakthrough Haemolysis

TEAEs related to BTH were reported more frequently in more subjects in the SB12 treatment group [22 TEAEs in 8/47 (17.0%) subjects vs 3 TEAEs in 1/47 (2.1%) subject in the Soliris treatment group; Table below].

According to the narratives provided, 4 subjects reported TEAEs related to BTH in the SB12 treatment group during Period 1 (vs 0 in the Soliris group). During Period 2, 3 subjects had TEAEs related to BTH while receiving SB12 treatment, and 1 subject had TEAEs related to BTH while treated with Soliris and again after the unplanned IP switch back to SB12. In addition, one subject, who had experienced TEAEs related to BTH during Period 1, had another TEAE related to BTH during Period 2 after the unplanned IP switch back to SB12.

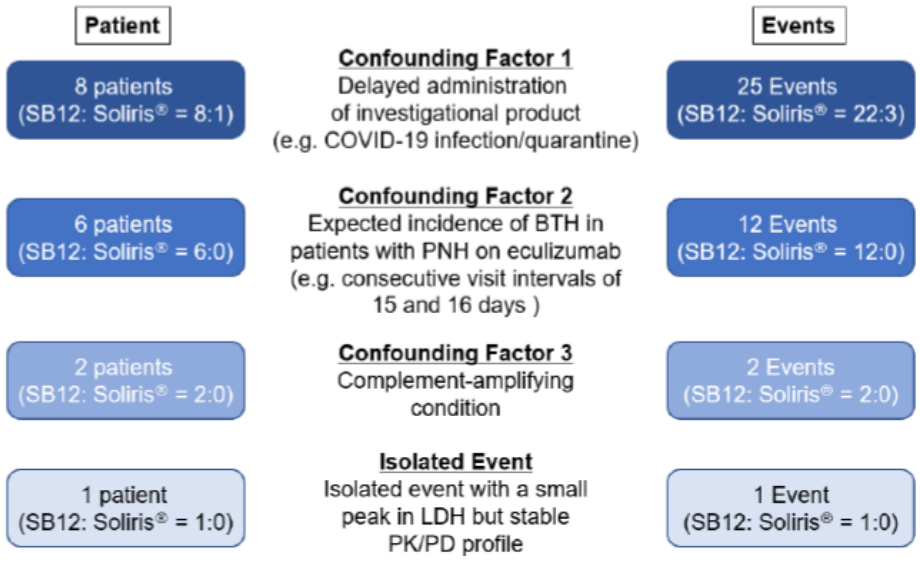
The majority of TEAEs were of Grade 1 (13 of 25 TEAEs in 5 [62.5%] subjects) or Grade 2 (11 of 25 TEAEs in 5 [62.5%] subjects) in severity, and most of TEAEs were resolved during the study period. One (12.5%) subject who had serious TEAE (of haemolysis) was of Grade 3 while treated with SB12 during Period 2, which did not lead to permanent IP discontinuation.

Table 26: TEAEs related to breakthrough haemolysis by system organ class, preferred term and treatment group (safety set)

System Organ Class Preferred Term	SB12 N = 47 n (%)	E	Soliris® N = 47 n (%)	E	Total N = 49 n (%)	E
Any TEAEs related to breakthrough haemolysis	8 (17.0)	22	1 (2.1)	3	8 (16.3)	25
Blood and lymphatic system disorders	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Haemolysis	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Gastrointestinal disorders	2 (4.3)	4	1 (2.1)	2	3 (6.1)	6
Abdominal pain	2 (4.3)	4	1 (2.1)	1	3 (6.1)	5
Dysphagia	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Hepatobiliary disorders	2 (4.3)	2	0 (0.0)	0	2 (4.1)	2
Jaundice	2 (4.3)	2	0 (0.0)	0	2 (4.1)	2
Renal and urinary disorders	8 (17.0)	15	1 (2.1)	1	8 (16.3)	16
Haemoglobinuria	8 (17.0)	15	1 (2.1)	1	8 (16.3)	16

E = frequency of TEAEs; n = number of subjects with event; N for SB12 represents the total number of pooled subjects who had been treated with SB12 in either Periods 1 or 2; N for Soliris® represents the total number of pooled subjects who had been treated with Soliris® in either Periods 1 or 2; N for Total represents the total number of subjects in the Safety Set; Percentages were based on N in each column; TEAE = treatment-emergent adverse event
- System organ classes (SOC) were presented alphabetically; preferred terms (PTs) were sorted within each SOC in descending order of subject frequency in SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.
- An event was reported under the treatment the subject was last received prior to the event.

The applicant performed a *post-hoc* assessment on individual patients to identify any confounding factors related to suboptimal C5 inhibition, complement-amplifying conditions or delayed administration of IP which may have contributed to the numerical imbalance of BTH event between the two treatment groups observed in Study SB12-3003.



Two patients experienced BTHs by COVID-19 infection/quarantine and consecutive visit intervals of 15 and 16 days. Although these two patients had COVID-19, BTH events also occurred before COVID-19 infection due to consecutive visit interval of 15 and 16 days, thus, excluded from confounding factor 2.

Figure 13: Confounding factors leading to numerical imbalance of BTH event

Comparison tables showing the incidences of proposed confounding factors #1 and #2 for BTH events in patients on SB12 or Soliris are shown in the Tables below.

Table 27: Incidence of confounding factor #1 with breakthrough haemolysis (BTH) in all patients by treatment group (safety set, study SB12-3003) (ad hoc analysis)

Reason for Delay	Breakthrough Hemolysis	SB12		Soliris		Total	
		n	E	n	E	n	E
COVID-19 Infection	Yes	4	4	1	1	5	5
	No	3	3	2	2	4[a]	5
	Total	7	7	3	3	9	10
Personal Reason	Yes	0	0	0	0	0	0
	No	4	4	4	5	7[b]	9
	Total	4	4	4	5	7	9
Total	Yes	4	4	1	1	5	5
	No	7	7	6	7	11	14
	Total	11	11	7	8	16[c]	19

E = number of events of confounding factor #1; n = number of patients for each category
[a] Patient had dose delay due to quarantine by COVID-19 infection both during SB12 and Soliris treatment
[b] Patient had dose delay due to personal reason both during SB12 and Soliris treatment
[c] A total of 2 patients had dose delay both during SB12 and Soliris treatment

Table 28: Incidence of confounding factor #2 with breakthrough Haemolysis (BTH) in all patients by treatment group (safety set, study SB12-3003) (ad hoc analysis)

Breakthrough Hemolysis	SB12		Soliris		Total	
	n	E	n	E	n	E
Yes	3	3	0	0	3	3
No	6	7	8	11	10	18
Total	9	10	8	11	13[a]	21

E = number of events of confounding factor #2; n = number of patients for each category
[a] A total of 4 patients had consecutive dosing intervals of 15 or 16 days during both SB12 and Soliris treatment

Major Adverse Vascular Events

One MAVE (portal vein thrombosis) as serious TEAE of Grade 5 in severity was reported in the Soliris treatment group during the study period. The event occurred in the same patient who died during the study.

An adult received a total of 8 IP administrations (Soliris) after the most recent IP administration, the subject had an adverse event of portal vein thrombosis of Grade 5 in severity. This event was determined to be serious and considered as a major adverse vascular event (MAVE) that was not related to breakthrough haemolysis. The adverse event of portal vein thrombosis led to death on Study Day 165.

- **Ancillary analyses**

Subgroup Analysis of Primary Efficacy Endpoint

There were no **ADA positive**/inconclusive subjects in the PPS-single; hence, no subgroup analysis was possible.

For the primary endpoint, LDH at Week 26, subgroup statistics by **gender** were presented.

Table 29: Subgroup analysis of primary efficacy endpoint: summary statistics of LDH (U/L) by gender per-protocol set for LDH at a single time point (PPS-single)

Gender: Male

Visit		SB12 N=16			Soliris N=10			Total N=26	
Statistics	Base	Value	Change	Base	Value	Change	Base	Value	Change
Week 26									
n	16	16	16	10	10	10	26	26	26
Mean	2255.7	477.6	-1778.1	2691.6	280.6	-2411.0	2423.3	401.8	-2021.5
SD	1190.72	534.52	1245.48	1738.22	85.81	1712.14	1408.96	428.52	1443.82
GM	2012.8	336.5	NA	2261.3	268.2	NA	2105.0	308.4	NA
Median	2100.0	258.0	-1647.0	2265.0	280.5	-1967.0	2100.0	261.5	-1797.0
Min	872	169	-4504	897	164	-6293	872	164	-6293
Max	5430	2175	360	6630	403	-614	6630	2175	360

Table 30: Subgroup analysis of primary efficacy endpoint: summary statistics of LDH (U/L) by gender per-protocol set for LDH at a single time point (PPS-single)

Gender: Female

Visit		SB12 N=7			Soliris N=13			Total N=20	
Statistics	Base	Value	Change	Base	Value	Change	Base	Value	Change
Week 26									
n	7	7	7	13	13	13	20	20	20
Mean	2273.6	231.1	-2042.4	1639.5	244.5	-1395.0	1861.5	239.9	-1621.6
SD	664.18	36.22	676.08	1036.36	116.49	1080.70	955.99	95.01	991.13
GM	2196.7	228.7	NA	1352.7	229.3	NA	1602.9	229.1	NA
Median	2190.0	246.0	-1904.0	1440.0	217.0	-1220.0	1845.0	219.5	-1639.5
Min	1530	185	-3325	546	165	-3623	546	165	-3623
Max	3510	286	-1342	3840	618	-125	3840	618	-125

Source: Listing 16.2.6-1.1b
- Base: Baseline; Change: Change from Baseline; GM: Geometric Mean
- N represents the total number of subjects in the Per-Protocol Set for LDH at a single time point (PPS-Single)
- GM is not calculated for change from baseline values.

Program Path: .¥CSR¥t1402010304.sas
Data Extraction Date: 11JAN2022 Run date: 17JAN2022 11:28

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 31: Summary of efficacy for trial SB12-3003

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	
Study identifier	EudraCT Number: 2018-002857-31
Design	1:1 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 who were randomised to initially receive SB12 were switched to receive Soliris and subjects who were randomised to initially receive Soliris were switched to receive SB12 at Week 26. SB12 or Soliris was given until Week 50.
Duration of main phase:	Aug 07, 2019 - Oct 21, 2021
Duration of Run-in phase:	not applicable
Duration of Extension phase:	not applicable
Hypothesis	Equivalence

Treatment groups	Sequence I: SB12 to Soliris		Intravenous administration of 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 (total of 28 administrations), IP switch at Week 26
	Sequence II: Soliris to SB12		Intravenous administration of 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 (total of 28 administrations), IP switch at Week 26
Endpoints and definitions	Primary endpoint	LDH level (U/L) at Week 26	Clinical equivalence is demonstrated if the 2-sided 95% CI of the of the estimated LSM difference in LDH level at Week 26 is contained within the pre-defined equivalence range [−337.2 to 337.2] U/L
	Secondary endpoints	LDH profile over time (no equivalence range has been pre-defined)	
		Number of units of pRBCs transfused throughout the study period (no equivalence range has been pre-defined)	
	Other efficacy endpoint	Time-adjusted area under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52 (primary endpoint for FDA)	
Database lock	Nov 16, 2021		

Results and Analysis

Analysis description	**Primary Analysis: LDH level (U/L) at Week 26 (M-FAS)**		
Analysis population	Modified Full Analysis Set (M-FAS): all randomized subjects who received IP (multiple imputation method that assumed missing data were MAR)		
Descriptive statistics	Treatment group	SB12	Soliris
	Number of subjects	24	25
	LDH level (U/L) at Week 26 (LSM)	282.87	255.96
Effect estimate per comparison	Primary endpoint: **LDH level (U/L) at Week 26**	Comparison groups	SB12 vs Soliris
		Estimated LSM difference	26.91
		95% confidence interval for difference	[-56.24, 110.05]
Notes	Clinical equivalence is demonstrated if the 2-sided 95% CI of the estimated LSM difference in LDH level at Week 26 is contained within the pre-defined equivalence range [−337.2 to 337.2] U/L		
Analysis description	**Primary Analysis: LDH level (U/L) at Week 26 (PPS-single)**		
Analysis population	Per-Protocol Set (PPS): The PPS-single consisted of all M-FAS subjects who had LDH assessment at Week 26 without any major protocol deviations that had impact on efficacy assessment.		
Descriptive statistics	Treatment group	SB12	Soliris
	Number of subjects	23	23
	LDH level (U/L) at Week 26 (LSM)	284.20	249.72
Effect estimate per comparison	Primary endpoint: **LDH level (U/L) at Week 26**	Comparison groups	SB12 vs Soliris
		Estimated LSM difference	34.48
		95% confidence interval for difference	[-47.66, 116.62]
Notes	Clinical equivalence is demonstrated if the 2-sided 95% CI of the estimated LSM difference in LDH level at Week 26 is contained within the pre-defined equivalence range [−337.2 to 337.2] U/L		
Analysis description	**Secondary endpoint: LDH profile over time**		
Analysis population	Modified full analysis set (M-FAS)		

Descriptive statistics and estimate variability	Treatment group	Sequence I (SB12 to Soliris)	Sequence II (Soliris to SB12)
	Number of subjects	23	23
	Mean (SD) LDH level at Week 26	402.60 (456.73)	260.20 (103.67)
	Number of subjects	23	23
	Mean (SD) LDH level at Week 52	317.70 (241.43)	431.90 (773.14)
Notes	No equivalence range has been pre-defined. Interpretation of Period 2 (Week 52) results is hampered due to unplanned IP switch of 8 subjects in the Soliris treatment arm		
Analysis description	**Secondary endpoint: Number of units of pRBCs transfused throughout the study period**		
Analysis population	Modified full analysis set (M-FAS)		
Descriptive statistics and estimate variability	Treatment group	Sequence I (SB12 to Soliris)	Sequence II (Soliris to SB12)
	Number of subjects	24	25
	Mean (SD) number of units of pRBCs study Period 1	1.1 (3.72)	0.9 (2.06)
	Number of subjects	23	23
	Mean (SD) number of units of pRBCs study Period 2	1.1 (4.05)	1.0 (2.61)
Notes	No equivalence range has been pre-defined. Interpretation of Period 2 results is hampered due to unplanned IP switch of 8 subjects in the Soliris treatment arm		
Analysis description	**Other efficacy endpoint: Time-adjusted area under the effect curve (AUEC) of LDH from Week 14 to Week 26 and from Week 40 to Week 52 (primary endpoint for FDA)**		
Analysis population	Per-Protocol Set for AUEC of LDH		
Descriptive statistics	Treatment group	SB12	Soliris
	Number of subjects	38	38
	Geometric LSM of time-adjusted AUEC (U/L) of LDH	279.65	258.73
Effect estimate per comparison	Other efficacy endpoint: **Time-adjusted AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52**	Comparison groups	SB12 vs Soliris
		Estimated ratio	1.08
		90% confidence interval for ratio	[0.95, 1.23]
Notes	According to the applicant, the 90% CI lied within the pre-defined equivalence range [0.77 to 1.29], as required by FDA. As this endpoint was not required by EMA, and hence no equivalence range has been defined, the results can only be regarded as supportive for the current MAA.		

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not Applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not Applicable.

2.6.5.6. Supportive study

Not Applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

SB12-3003 was a randomized, double-blind, multicentre, comparative clinical Phase III study (SB12-3003) in treatment-naïve patients with PNH to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB12 and Soliris. Fifty subjects were randomised 1:1 to treatment sequence I (SB12 to Soliris) or treatment sequence II (Soliris to SB12). Subjects who were randomised to initially receive SB12 were switched to receive Soliris and subjects who were randomised to initially receive Soliris were switched to receive SB12 at Week 26. Study treatment was given until Week 50. Although in general the study duration of 52 weeks is acceptable, the cross-over design was strongly discouraged during EMA Scientific Advice, mainly due to the short observation period of 26 weeks for efficacy and safety evaluation.

Due to shortage of the comparator, 8 subjects received SB12 instead of Soliris at some visits during Period 2, while others received US-sourced Soliris instead of EU-Soliris, to ensure the continuity of study treatment. The shortage of EU-sourced comparator is acknowledged and the resulting events of unplanned switch to SB12 or US-Soliris in Period 2 to maintain treatment are considered appropriate given the circumstances. No specific concerns arise from using US-sourced Soliris, as biosimilarity between EU- and US-sourced Soliris could be demonstrated based on quality and clinical pharmacology data. As the unplanned switch and/or use of US-sourced Soliris only occurred during Period 2, after assessment of the primary endpoint, the primary evaluation regarding efficacy would not be impacted.

Inclusion and exclusion criteria were largely in line with registrational studies for Soliris in PNH (TRIUMPH and SHEPHERD). The enrolment of treatment-naïve patients with PNH was also the preferred study population in EMA Scientific Advice and is therefore accepted.

The primary endpoint was to compare LDH levels, which is acceptable given the absence of a suitable clinical endpoint to assess the efficacy of eculizumab in PNH. However, an earlier timepoint for the primary assessment (currently Week 26), before treatment response has reached the plateau, would have been more appropriate. In addition, due to its low specificity, including a more specific and predictive PD marker for clinical efficacy and pharmacological action of eculizumab is considered essential. Although the applicant could justify the use of the terminal complex ELISA to assess PD, the absence of the functional CH50 adds some uncertainty regarding the comparability of efficacy. LDH profile over time and number of units of pRBC transfused as secondary efficacy endpoints are accepted.

The sample size calculation is reproducible under the given parameters. The applicant could satisfactorily justify the discrepancies between the ULN used for the sample size calculation of [−1.2 × ULN, 1.2 × ULN], where ULN = 223 U/L, and the equivalence margin of the primary the primary efficacy analysis, where ULN = 281 U/L; sample size calculation was based on the ULN from the reference study (TRIUMPH [Hillmen *et al.,* 2006]), and the ULN to define the limits for the demonstration of equivalence in the primary efficacy endpoint was based on the specification of laboratory parameters chosen for the study. The use of different cut-offs is acceptable, but the use of

ULN to derive a margin for equivalence as such is questioned, and the justification for the clinical irrelevance of [−1.2 × ULN, 1.2 × ULN] based on the SD and the absolute LDH level observed in pivotal Soliris studies is not agreed. Given the high fluctuations of LDH levels in PNH patients in general, a high SD on the population level is to be expected, and does not indicate clinical irrelevance on an individual patient level. Moreover, no rationale for interpreting the difference of LDH levels based on the ULN as clinically irrelevant has been provided, but in general, this strategy is considered not meaningful.

The overall process for randomization appears appropriate. No stratification was included, which is acceptable, given the limited sample size.

Strategies to ensure double-blinding for the treatment sequence assignment are appropriate.

The overall statistical approach is considered acceptable. However, the handling of missing data is not considered optimal. The missing at random assumption is strong and could lead to the attenuation of difference between the treatment arms. Nevertheless, considering that the vast majority of randomized patients (92%) completed Period 1 of the study, the impact on the primary analysis of efficacy is considered minimal, therefore, no concern is raised.

There were five global amendments to the original protocol, mainly to facilitate recruitment, clarify several study procedures and to address issues related to the COVID-19 pandemic, which are acknowledged and overall appropriate. With Amendment 4 (Version 5.0), a 2 year extension period to assess the long-term safety was removed and replaced by an open-label extended supply of SB12. Further details on participating subjects were requested. The applicant has provided the requested information on the status of the subjects from the open-label extension period. All patients completing the week 50 treatment (n=46) were enrolled into the extension period. As of Oct 15, 2022, 2 patients completed the extension period, and 7 patients discontinued from the extension period, with the majority of reasons being moving to another country due to the war in Ukraine. Amendment 5 (Version 6.0) included the update to address the shortage of comparator. The overall strategy for the selection of subjects receiving unplanned IP switch appear appropriate. A summary showing the recruitment timeline of subjects with unplanned IP switch compared to subjects who did not have unplanned IP switch was provided upon request and the sequence of events could be followed.

Major protocol deviations were observed at similar frequencies between treatment sequences, except deviations related to COVID-19 restrictions, which occurred more frequently in the Soliris to SB12 treatment sequence [7/25 (28%) vs 3/25 (12%) in the SB12 to Soliris sequence]. These protocol deviations included out of visit window [6/25 (24%) vs 3/25 (12%) in the SB12 to Soliris sequence]. Upon request, the applicant provided information of the distribution of protocol deviations related to COVID-19 restrictions. Most COVID-19-related deviations occurred during Period 2, which coincided with regional COVID-19 outbreaks (Nov 2020 to Dec 2020), which can be followed. During Period 1, more patients on Soliris treatment (3 patients, 12%) had COVID-19-related deviations compared to 1 (4.2%) patient on SB12 treatment. During Period 2, more patients on SB12 treatment (6 patients, 19.4%) had COVID-19-related deviations compared to 2 (9.1%) patients on Soliris treatment. Thus, an imbalance between treatments was observed during both periods, but favouring different treatments in different periods. The overall imbalance observed is therefore likely a chance finding.

Demographic characteristics and baseline disease characteristics were overall variable between treatment arms, which is likely attributed to the very limited sample size due to the orphan nature of the disease. The study was conducted predominantly in an Asian population (54% of subjects). Upon request, the applicant performed subgroup analyses of efficacy and safety between Asian vs Non-Asian to detect any potential differences between two subgroups in Study SB12-3003. The analysis showed that distribution of demographic characteristics of Race and Ethnicity is comparable between the planned treatment sequences. Moreover, no difference in primary efficacy (LDH at Week 26) result

between Asian and Non-Asian patients was observed. Thus, the extrapolation of the efficacy results obtained in Study SB12-3003 to Non-Asian population is reasonable. Reassuringly, overall mean LDH levels at baseline were comparable [2156.0 U/L (Soliris to SB12) vs 2220.2 U/L (SB12 to Soliris)]. Nevertheless, the applicant was asked to discuss and contextualize the differences in baseline characteristics including, but not limited to, PNH clone size in the treatment arms. The applicant confirmed that there were numerical differences observed in certain baseline characteristics, but that there was no significant difference in all baseline disease characteristics. Regarding the clinical importance of the baseline differences observed in Type II RBCs PNH clone size and Type III RBCs PNH clone size between the treatment sequences, the applicant provided literature showing that analysis of PNH clone size of white blood cells might be more informative than analysis of PNH clone size of RBC alone when assessing PNH patients. This is acknowledged. Of note, the white blood clone size was very similar between the two treatment sequences. Regarding the numerical differences observed in total number of packed red blood cell 12 months prior to Screening between the two treatment sequences, the applicant clarified that this might be due to 2 patients with the highest number of packed red blood cell received being randomized to the SB12 to Soliris sequence.

While most prior and concomitant medications were overall comparable between treatment groups, more patients in the Soliris group received concomitant danazol treatment [9/47 (19.1%) vs 1/47 (2.1%) in SB12 group]. Upon request, the applicant clarified that all of the patients with concomitant danazol treatment (in total 9 patients) were on this treatment before study start. Out of the 9 patients, 8 were randomized to the Soliris to SB12 sequence and 1 patient was randomized to the SB12 to Soliris sequence. Most of the patients stopped danazol treatment within a few months from study start. It is agreed, that the observed discrepancy in danazol treatment frequencies might have rather been by chance due to the randomization process. In addition, the applicant provided a sensitivity analysis of the primary efficacy endpoint with danazol treatment as a covariate. The results suggest that danazol might not have had an impact on the primary efficacy analysis. Furthermore, patients on danazol treatment did not report any clinically significant laboratory findings nor relevant TEAEs throughout the study. Thus, the impact on safety also seems to be negligible. Overall, due to the cross-over study design, pre-existing factors potentially confounding the efficacy outcome could likely be distinguished from study variables that influence the outcome.

Efficacy data and additional analyses

The primary efficacy endpoint evaluation, LDH levels at Week 26, was performed on the PPS-single analysis set. The LSM LDH levels at Week 26 were 284.20 U/L in the SB12, and 249.72 U/L in the Soliris treatment group, which is in the range of what would be expected from registrational studies for Soliris. The 2-sided 95% CI of the estimated LSM difference between SB12 and Soliris treatment group (SB12 − Soliris: 34.48, 95% CI [−47.66, 116.62]) completely lied within the pre-defined equivalence margin of [−337.2 to 337.2]. Results from sensitivity analyses on the M-FAS, taking missing data into account, validated the robustness of the primary analysis from the PPS-single. While the complete case analysis results on the M-FAS were identical to the results from PPS-single analysis, the M-FAS with multiple imputation method provided an estimated LSM difference in LDH (U/L) level at Week 26 between SB12 and Soliris treatment groups (SB12 − Soliris: 26.91, 95% CI [−56.24, 110.05]), consistent with the primary analysis. Although the clinical irrelevance of the proposed equivalence margin is questionable, the observed 2-sided 95% CI of the estimated LSM difference was clearly below the suggested margin [−1.2 × ULN, 1.2 × ULN] in all analysis sets. Therefore, despite remaining uncertainties, confirmation of biosimilarity is provided from the primary endpoint.

Secondary efficacy endpoints, LDH profile over time and number of pRBC units transfused, were descriptively summarised and appeared similar between treatment groups. However, a trend of higher

mean LDH levels in patients treated with SB12 was observed at Week 26, Week 52 and for time-adjusted AUEC from Week 14 to Week 26 and from Week 40 to Week 52 (primary endpoint for FDA, which formally demonstrated biosimilarity). Furthermore, LDH levels of individual patients indicated more frequently a pronounced increase while on SB12 treatment compared to patients on Soliris treatment. Upon request, the applicant presented a summary of subjects who experienced LDH levels > 2 x ULN during the maintenance phase, i.e. excluding the induction phase up to Week 4. Although the number of patients with elevated LDH levels > 2 × ULN was comparable between the actual treatment groups (SB12:Soliris, 11:13), the number of events of elevated LDH levels > 2 x ULN was higher in patients on SB12 treatment in both periods (total: 49 vs 27 events in SB12 and Soliris, respectively), as was the exposure-adjusted event rate (EAER; SB12:Soliris: 2.07:1.39) to account for different exposure due to the unplanned IP switch back to SB12 in Period 2. The applicant identified 3 subjects who experienced the majority of total events of LDH levels > 2 x ULN (47/76, 62% of reported events). When excluding events from these patients, the numerical imbalance of events of elevated LDH levels > 2 × ULN between patients on SB12 and Soliris became narrowed to 17 events (SB12) versus 12 events (Soliris). Hence, the frequency of elevated LDH levels > 2 x ULN was still 42% higher during SB12 vs Soliris for the remaining patients. Moreover, although all 3 identified subjects who experienced the majority of total events had these events during SB12 and Soliris treatment, a clear imbalance towards more frequent events while on SB12 treatment even in those 3 subjects is noted. In many instances, elevated LDH levels > 2 x ULN were associated with extended dosing intervals and patients without dose delay were less likely to have elevated LDH level > 2 x ULN (overall 28.1%) compared to patients who had a dose interval of 17 days or more at least once (50.0%). Hence, despite numerical imbalances, it is agreed that elevated LDH levels are more likely to occur after extended dosing intervals and are manageable by shortening the dosing intervals in most cases.

Higher LDH levels may indicate lower eculizumab exposure, e.g. due to dose delays, and may be associated with the occurrence of breakthrough haemolysis (BTH), which could point towards reduced efficacy. Indeed, TEAEs related to BTH were reported more frequently in more subjects in the SB12 treatment group [22 TEAEs in 8/47 (17.0%) subjects vs 3 TEAEs in 1/47 (2.1%) subject in the Soliris treatment group], which is also reflected in a lower reduction from baseline in haemoglobinuria severity scores in both periods. Upon request to provide more details about the 2 year open-label extension period, the applicant noted that, as of Oct 15, 2022, 6 out of 8 patients who experienced BTH were still receiving SB12 and none of the patients discontinued from the study due to 'lack of efficacy'.

Moreover, according to the applicant, most BTH events can be explained by 1 of 3 confounding factors, which include complement-amplifying conditions, such as infections, and delayed administration of IP. Upon request, the applicant provided an extended overview on subjects experiencing breakthrough haemolysis, including baseline characteristics, individual LDH levels over time and at the time of the event, and details on the treatment (dose, time of dose, treatment duration). Furthermore, a comparison showing the incidence of proposed confounding factors #1 (dose delay ≥ 17 days) and #2 (consecutive dosing intervals of 15 or 16 days) for BTH across both treatment groups, irrespective of the occurrence of BTH events, was provided. The incidence of confounding factor #1 (dose delay ≥ 17 days due to quarantine by COVID-19 infection) was higher in patients on SB12 compared to patients on Soliris, as more patients on SB12 (7 patients) were infected to COVID-19 compared to patients on Soliris (3 patients). The proportion of patients with dose delay due to quarantine by COVID-19 infection and reported BTH events was 4/7 patients for SB12 and 1/3 patient for Soliris. Since it is agreed that the overall higher incidence of COVID-19 infections in SB12 treated patients is likely caused by local outbreaks, it appears that COVID-19-related dose delays ≥ 17 days favour the occurrence of BTH events, independent of treatment. The incidence of confounding factor #2 (consecutive dosing intervals of 15 or 16 days) was comparable between patients on SB12 and Soliris,

but only patients on SB12 reported BTH events (3/9 vs 0/8 on Soliris), all of which occurred during Period 2. These findings suggest that BTH events are independent of extended dosing intervals of 15 or 16 days. However, as overall numbers are low, this may be a chance finding and a final conclusion cannot be drawn.

2.6.7. Conclusions on the clinical efficacy

Although uncertainties remain regarding the clinical irrelevance of the equivalence margin for the primary endpoint, and occurrence of more frequent BTH events during SB12 treatment, biosimilarity is supported by a narrow 95% CI of the primary efficacy endpoint and results from secondary endpoints LDH profile over time and number of pRBC units transfused.

2.6.8. Clinical safety

The clinical safety of SB12 has been assessed in two clinical studies, a clinical Phase I pharmacokinetic (PK) study in healthy subjects (SB12-1001) and a clinical Phase III efficacy and safety study in patients with PNH (SB12-3003). Safety of SB12 in these studies was assessed by monitoring adverse events (AEs), serious AEs (SAEs), adverse events special interest (AESI) (e.g. meningococcal infection, other systemic infection, infusion-related reaction), vital signs, and laboratory evaluations as well as immunogenicity, which is an important safety aspect of therapeutic proteins. The AEs were coded using Medical Dictionary for Regulatory Activities version (MedDRA version 21.0) and guided by the grading of the NCI-CTCAE version 5.0.

A pooled safety analysis of the two clinical studies is not applicable due to heterogeneity of the study population (healthy subjects versus patients with PNH) and duration of treatment/exposure (multiple-dose versus single-dose). Due to the low number of included subjects/patients and the design of the studies, the safety data collected from these studies can only provide limited information on comparability of safety and immunogenicity of SB12 and the reference products.

2.6.8.1. Patient exposure

Phase I study SB12-1001

In the clinical Phase I study SB12-1001, a total of 240 subjects were randomized to receive a single IV dose of eculizumab with 80 subjects in each three treatment groups (SB12, EU Soliris, or US Soliris), respectively. The Safety Set (SAF) consisted of all subjects who received investigational product (IP).

Phase III study SB12-3003

In clinical Phase III study SB12-3003, a total of 50 subjects were randomly allocated to each treatment sequence.

Table 32: Summary of exposure to study drug by treatment group (safety set)

Statistics	SB12	Soliris®	Total
Study Period 1	**N = 24**	**N = 25**	**N = 49**
Duration of exposure (day)[a]			
n	24	25	49
Mean	164.1	160.4	162.2
SD	25.84	39.06	32.96
Median	169.0	169.0	169.0
Min, Max	43, 175	1, 183	1, 183
Cumulative dose of IP (mg)			
n	24	25	49
Mean	11962.5	11568.0	11761.2
SD	1653.41	2663.76	2213.01
Median	12300.0	12300.0	12300.0
Min, Max	4200, 12300	300, 12300	300, 12300
Number of IV infusions of IP			
n	24	25	49
Mean	14.6	14.2	14.4
SD	1.84	3.08	2.53
Median	15.0	15.0	15.0
Min, Max	6, 15	1, 15	1, 15
Number of subjects with IP infusion interruption	0 (0.0)	1 (4.0)	1 (2.0)
Subjects with 1 infusion interruption	0 (0.0)	1 (4.0)	1 (2.0)
Subjects with 2 infusion interruptions	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with more than 2 infusion interruptions	0 (0.0)	(0.0)	0 (0.0)
Study Period 2	**N = 23**	**N = 15**	**N = 38**
Duration of exposure (day)[a]			
n	23	15	38
Mean	171.6	169.5	170.8
SD	4.37	2.36	3.82
Median	169.0	169.0	169.0
Min, Max	168, 183	166, 176	166, 183
Cumulative dose of IP (mg)			
n	23	15	38
Mean	11700.0	11700.0	11700.0
SD	0.00	0.00	0.00
Median	11700.0	11700.0	11700.0
Min, Max	11700, 11700	11700, 11700	11700, 11700
Number of IV infusions of IP			
n	23	15	38
Mean	13.0	13.0	13.0
SD	0.00	0.00	0.00
Median	13.0	13.0	13.0
Min, Max	13, 13	13, 13	13, 13
Number of subjects with IP infusion interruption	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with 1 infusion interruption	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with 2 infusion interruptions	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with more than 2 infusion interruptions	0 (0.0)	0 (0.0)	0 (0.0)

IP = investigational product; IV = intravenous; Max = maximum; Min = minimum; N = total number of subjects in Safety Set for each study period; SD = standard deviation.

[a] Duration of exposure (day) in Period x = Date of last dose in Period x − Date of first dose in Period x + 1, where x = 1, 2.

- Percentages were based on N in each column.
- Subjects with unplanned IP switch during Period 2 were excluded from the Period 2 table.

2.6.8.2. Adverse events

Phase I study SB12-1001

A summary of all AEs in study SB12-1001 is presented in the Table below and TEAEs occurring in ≥ 5.0% of the subjects in any treatment group are summarised for the SAF by PT in the Table below.

Table 33: Summary of adverse events (safety set)

Treatment	SB12 N=80		EU sourced Soliris® N=80		US sourced Soliris® N=80		Total N=240	
Category	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any AEs	58 (72.5)	161	54 (67.5)	138	59 (73.8)	169	171 (71.3)	468
Any TEAEs	56 (70.0)	149	52 (65.0)	125	57 (71.3)	153	165 (68.8)	427
TEAE severity								
Mild	36 (45.0)	110	28 (35.0)	89	24 (30.0)	94	88 (36.7)	293
Moderate	19 (23.8)	38	23 (28.8)	34	32 (40.0)	58	74 (30.8)	130
Severe	1 (1.3)	1	1 (1.3)	2	1 (1.3)	1	3 (1.3)	4
TEAE causality								
Related	25 (31.3)	39	17 (21.3)	36	29 (36.3)	47	71 (29.6)	122
Not related	31 (38.8)	110	35 (43.8)	89	28 (35.0)	106	94 (39.2)	305
Any TEAEs leading to discontinuation of IP	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Any SAEs	1 (1.3)	1	0 (0.0)	0	1 (1.3)	1	2 (0.8)	2
Any AESIs	6 (7.5)	6	4 (5.0)	4	3 (3.8)	3	13 (5.4)	13
Meningococcal infection	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Other systemic infection	0 (0.0)	0	0 (0.0)	0	2 (2.5)	2	2 (0.8)	2
Infusion-related reaction	6 (7.5)	6	4 (5.0)	4	1 (1.3)	1	11 (4.6)	11
Any TEAEs leading to death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

AE = adverse event; AESI = AE of special interest; E = frequency of AEs; IP = investigational product; N = number of subjects in the Safety Set; n = number of subjects with event; SAE = serious AE; TEAE = treatment-emergent AE
Percentages were based on the number of subjects in the Safety Set.
If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality).

Table 34: Number (%) of subjects with treatment-emergent adverse events in ≥ 5.0 % of subjects in any treatment and number of events (safety set)

Treatment	SB12 N=80		EU sourced Soliris® N=80		US sourced Soliris® N=80		Total N=240	
Preferred term	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE	56 (70.0)	149	52 (65.0)	125	57 (71.3)	153	165 (68.8)	427
Headache	17 (21.3)	29	12 (15.0)	17	19 (23.8)	30	48 (20.0)	76
Nasopharyngitis	18 (22.5)	20	18 (22.5)	21	10 (12.5)	10	46 (19.2)	51
Rhinitis	7 (8.8)	9	7 (8.8)	7	4 (5.0)	4	18 (7.5)	20
Back pain	8 (10.0)	8	4 (5.0)	5	5 (6.3)	7	17 (7.1)	20
Upper respiratory tract infection	1 (1.3)	1	7 (8.8)	7	5 (6.3)	6	13 (5.4)	14
Infusion related reactions	6 (7.5)	6	4 (5.0)	4	1 (1.3)	1	11 (4.6)	11
Diarrhoea	2 (2.5)	2	2 (2.5)	2	7 (8.8)	7	11 (4.6)	11
Nausea	4 (5.0)	4	1 (1.3)	3	4 (5.0)	4	9 (3.8)	11
Influenza like illness	2 (2.5)	2	2 (2.5)	2	5 (6.3)	5	9 (3.8)	9
Oropharyngeal pain	2 (2.5)	2	4 (5.0)	4	3 (3.8)	3	9 (3.8)	9
Pain in extremity	2 (2.5)	2	1 (1.3)	1	5 (6.3)	6	8 (3.3)	9
Dizziness	1 (1.3)	1	0 (0.0)	0	5 (6.3)	6	6 (2.5)	7

E = frequency of TEAEs; N = number of subjects in the Safety Set; n = number of subjects with event; TEAE = treatment-emergent adverse event
Percentages are based on the number of subjects in the Safety Set.
Adverse events were coded by preferred term using the MedDRA version 21.0 coding dictionary.

Phase III study SB12-3003

An overview of AEs in study SB12-3003 by actual treatment group in the SAF is presented in Table 38. Exposure-adjusted event rate (EAER), which is the number of events/total exposure time in subject-years; where total exposure time in subject-years was sum of treatment exposure in years across all subjects in each treatment group, was used to calibrate imbalanced drug exposure due to unplanned IP switch.

An overall summary of AEs by actual treatment sequence within Period 1 and Period 2 in the SAF is provided below. Severity Grade of NCI-CTCAE used for a classification of the severity of the AEs is provided in the table below.

Table 35: 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 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

Table 36: Overall Summary of all AEs by treatment group (safety set)

	SB12 N = 47 Person-years = 23.4			Soliris® N = 47 Person-year = 19.6			Total N = 49 Person-year = 43.1		
Subjects Experiencing	**n (%)**	**E**	**EAER**	**n (%)**	**E**	**EAER**	**n (%)**	**E**	**EAER**
Any Treatment-emergent adverse events (TEAEs)	34 (72.3)	119	5.09	32 (68.1)	99	5.05	42 (85.7)	218	5.06
TEAE Severity									
Grade 1	1 (2.1)	38	1.62	6 (12.8)	28	1.43	3 (6.1)	66	1.53
Grade 2	27 (57.4)	73	3.12	23 (48.9)	67	3.42	30 (61.2)	140	3.25
Grade 3	6 (12.8)	8	0.34	2 (4.3)	3	0.15	8 (16.3)	11	0.26
Grade 4	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
Grade 5	0 (0.0)	0	0	1 (2.1)	1	0.05	1 (2.0)	1	0.02
TEAE Causality									
Related	3 (6.4)	5	0.21	8 (17.0)	15	0.77	11 (22.4)	20	0.46
Not Related	31 (66.0)	114	4.87	24 (51.1)	84	4.29	31 (63.3)	198	4.59
TEAE Outcome									
Recovered/Resolved		103	4.4		84	4.29		187	4.34
Recovered/Resolved With Sequelae		0	0		2	0.1		2	0.05
Recovering/Resolving		3	0.13		5	0.26		8	0.19
Not Recovered/ Not Resolved		11	0.47		7	0.36		18	0.42
Fatal		0	0		1	0.05		1	0.02
Unknown		2	0.09		0	0		2	0.05
TEAEs leading to IP discontinuation	0 (0.0)	0	0	1 (2.1)	1	0.05	1 (2.0)	1	0.02
TEAEs leading to death	0 (0.0)			1 (2.1)			1 (2.0)		
Adverse Events of Special Interest	0 (0.0)	0	0	4 (8.5)	5	0.26	4 (8.2)	5	0.12
Meningococcal infection	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
Other systemic infection	0 (0.0)	0	0	1 (2.1)	1	0.05	1 (2.0)	1	0.02
Infusion-related reaction	0 (0.0)	0	0	3 (6.4)	4	0.2	3 (6.1)	4	0.09
Serious TEAEs	3 (6.4)	3	0.13	2 (4.3)	3	0.15	5 (10.2)	6	0.14
Serious TEAE Severity									
Grade 1	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
Grade 2	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
Grade 3	3 (6.4)	3	0.13	1 (2.1)	2	0.1	4 (8.2)	5	0.12
Grade 4	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
Grade 5	0 (0.0)	0	0	1 (2.1)	1	0.05	1 (2.0)	1	0.02
Serious TEAE Causality									
Related	0 (0.0)	0	0	2 (4.3)	2	0.1	2 (4.1)	2	0.05
Not Related	3 (6.4)	3	0.13	0 (0.0)	1	0.05	3 (6.1)	4	0.09

COVID-19 infection									
Any TEAEs for COVID-19	8 (17.0)	8	0.34	3 (6.4)	3	0.15	10 (20.4)	11	0.26
TEAEs among COVID-19 infected subjects	10 (21.3)	43	1.84	6 (12.8)	23	1.17	10 (20.4)	66	1.53
Any Serious TEAEs for COVID-19	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
Serious TEAEs among COVID-19 infected subjects	1 (2.1)	1	0.04	0 (0.0)	0	0	1 (2.0)	1	0.02

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of TEAEs; EAER = exposure-adjusted event rate; IP = investigational product; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = total number of subjects in Safety Set for each study period; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event

- EAER was calculated as number of events / total exposure time in subject-years, where total exposure time in subject-years was sum of treatment exposure in years across all subjects in each treatment group.
- Percentages were based on N in each column.
- AEs were coded to system organ class and preferred term using MedDRA®, Version 21.0 coding dictionary.
- Severity assessment was done in accordance with NCI-CTCAE 5.0.
- If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n). Subjects with missing severity (or causality) were counted at the most severe (related) category and also the 'Missing' category separately in the summary.

Table 37: Overall summary of all AEs by actual treatment sequence within period 1 (safety set)

	Soliris® to SB12 N = 25		SB12 to All N = 24		Total N = 49	
Subjects Experiencing	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any Treatment-emergent adverse events (TEAEs)	18 (72.0)	55	18 (75.0)	62	36 (73.5)	117
TEAE Severity						
Grade 1	3 (12.0)	11	0 (0.0)	18	3 (6.1)	29
Grade 2	12 (48.0)	40	17 (70.8)	42	29 (59.2)	82
Grade 3	2 (8.0)	3	1 (4.2)	2	3 (6.1)	5
Grade 4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 5	1 (4.0)	1	0 (0.0)	0	1 (2.0)	1
TEAE Causality						
Related	6 (24.0)	11	3 (12.5)	5	9 (18.4)	16
Not Related	12 (48.0)	44	15 (62.5)	57	27 (55.1)	101
TEAE Outcome						
Recovered/Resolved		47		53		100
Recovered/Resolved with Sequelae		2		0		2
Recovering/Resolving		3		1		4
Not Recovered/Not Resolved		2		8		10
Fatal		1		0		1
TEAEs leading to IP discontinuation	1 (4.0)	1	0 (0.0)	0	1 (2.0)	1
TEAEs leading to death	1 (4.0)		0 (0.0)		1 (2.0)	
Adverse Events of Special Interest	3 (12.0)	3	0 (0.0)	0	3 (6.1)	3
Meningococcal infection	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Other systemic infection	1 (4.0)	1	0 (0.0)	0	1 (2.0)	1
Infusion-related reaction	2 (8.0)	2	0 (0.0)	0	2 (4.1)	2
Serious TEAEs	2 (8.0)	3	0 (0.0)	0	2 (4.1)	3
Serious TEAE Severity						
Grade 1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 3	1 (4.0)	2	0 (0.0)	0	1 (2.0)	2
Grade 4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 5	1 (4.0)	1	0 (0.0)	0	1 (2.0)	1
Serious TEAE Causality						
Related	2 (8.0)	2	0 (0.0)	0	2 (4.1)	2
Not Related	0 (0.0)	1	0 (0.0)	0	0 (0.0)	1
COVID-19 infection						
Any TEAEs for COVID-19	1 (4.0)	1	1 (4.2)	1	2 (4.1)	2
TEAEs among COVID-19 infected subjects	3 (12.0)	10	3 (12.5)	11	6 (12.2)	21
Any serious TEAEs for COVID-19	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious TEAEs among COVID-19 infected subjects	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of TEAEs; IP = investigational product; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = total number of subjects

in Safety Set for each study period; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event
- Percentages were based on N in each column.
- AEs were coded to system organ class and preferred term using MedDRA®, Version 21.0 coding dictionary.
- Severity assessment was done in accordance with NCI-CTCAE 5.0.
- If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n). Subjects with missing severity (or causality) were counted at the most severe (related) category and also the 'Missing' category separately in the summary.

Table 38: Overall summary of all AEs by actual sequence within period 2 (safety set)

	Soliris® to SB12 N = 23		SB12 to All N = 23		SB12 to Soliris® N = 15		Unplanned IP Switch N = 8		Total N = 46	
Subjects Experiencing	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any TEAEs	15 (65.2)	46	16 (69.6)	55	10 (66.7)	32	6 (75.0)	23	31 (67.4)	101
TEAE Severity										
Grade 1	1 (4.3)	14	3 (13.0)	23	3 (20.0)	16	0 (0.0)	7	4 (8.7)	37
Grade 2	10 (43.5)	27	12 (52.2)	31	7 (46.7)	16	5 (62.5)	15	22 (47.8)	58
Grade 3	4 (17.4)	5	1 (4.3)	1	0 (0.0)	0	1 (12.5)	1	5 (10.9)	6
Grade 4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAE Causality										
Related	0 (0.0)	0	2 (8.7)	4	1 (6.7)	2	1 (12.5)	2	2 (4.3)	4
Not Related	15 (65.2)	46	14 (60.9)	51	9 (60.0)	30	5 (62.5)	21	29 (63.0)	97
TEAE Outcome										
Recovered/Resolved		43		44		27		17		87
Recovered/Resolved with Sequelae		0		0		0		0		0
Recovering/Resolving		2		2		2		0		4
Not Recovered/Not Resolved		1		7		3		4		8
Fatal		0		0		0		0		0
Unknown		0		2		0		2		2
TEAEs leading to IP discontinuation	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAEs leading to death	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Adverse Events of Special Interest	0 (0.0)	0	1 (4.3)	2	0 (0.0)	0	1 (12.5)	2	1 (2.2)	2
Meningococcal infection	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Other systemic infection	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Infusion-related reaction	0 (0.0)	0	1 (4.3)	2	0 (0.0)	0	1 (12.5)	2	1 (2.2)	2
Serious TEAEs	3 (13.0)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (6.5)	3
Serious TEAE Severity										
Grade 1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 3	3 (13.0)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (6.5)	3
Grade 4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious TEAE Causality										
Related	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Not Related	3 (13.0)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (6.5)	3
COVID-19 infection										
Any TEAEs for COVID-19	7 (30.4)	7	2 (8.7)	2	1 (6.7)	1	1 (12.5)	1	9 (19.6)	9
TEAEs among COVID-19 infected subjects	7 (30.4)	26	3 (13.0)	19	1 (6.7)	7	2 (25.0)	12	10 (21.7)	45
Any Serious TEAEs for COVID-19	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious TEAEs among COVID-19 infected subjects	1 (4.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.2)	1

AE = adverse event; COVID-19 = Coronavirus Disease 2019; E = frequency of TEAEs; IP = investigational product; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = total number of subjects in Safety Set for each study period; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event
- Percentages were based on N in each column.
- AEs were coded to system organ class and preferred term using MedDRA®, Version 21.0 coding dictionary.
- Severity assessment was done in accordance with NCI-CTCAE 5.0.
- If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n). Subjects with missing severity (or causality) were counted at the most severe (related) category and also the 'Missing' category separately in the summary.

Source: Table: 14.3.1-1.1

Table 39: TEAEs with incidence >5 % of preferred term by System Organ Class, preferred term, and treatment group (safety set)

System Organ Class Preferred Term	SB12 N = 47		Soliris® N = 47		Total N = 49	
	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	34 (72.3)	119	32 (68.1)	99	42 (85.7)	218
Any TEAEs with incidence > 5% of subjects	18 (38.3)	40	11 (23.4)	14	26 (53.1)	54
Gastrointestinal disorders	4 (8.5)	6	2 (4.3)	2	5 (10.2)	8
Diarrhoea	4 (8.5)	6	2 (4.3)	2	5 (10.2)	8
Infections and infestations	8 (17.0)	8	3 (6.4)	3	10 (20.4)	11
Corona virus infection	8 (17.0)	8	3 (6.4)	3	10 (20.4)	11
Investigations	3 (6.4)	3	2 (4.3)	2	5 (10.2)	5
Alanine aminotransferase increased	3 (6.4)	3	2 (4.3)	2	5 (10.2)	5
Nervous system disorders	2 (4.3)	4	3 (6.4)	5	5 (10.2)	9
Headache	2 (4.3)	4	3 (6.4)	5	5 (10.2)	9
Renal and urinary disorders	8 (17.0)	15	2 (4.3)	2	9 (18.4)	17
Haemoglobinuria	8 (17.0)	15	2 (4.3)	2	9 (18.4)	17
Vascular disorders	3 (6.4)	4	0 (0.0)	0	3 (6.1)	4
Hypertension	3 (6.4)	4	0 (0.0)	0	3 (6.1)	4

E = frequency of TEAEs; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = N for SB12 represents the total number of pooled subjects who had been treated with SB12 in either Periods 1 or 2; N for Soliris® represents the total number of pooled subjects who had been treated with Soliris® in either Periods 1 or 2; N for Total represents the total number of subjects in the Safety Set; TEAE = treatment-emergent adverse event

- Percentages were based on N in each column.
- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA®, Version 21.0 coding dictionary.
- SOC were presented alphabetically; PTs were sorted within each SOC in descending order of subject frequency in SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.
- Only TEAEs with PTs that were with > 5% incidence of subjects in either pooled treatment group were included in this summary.
- An event was reported under the treatment the subject was last received prior to the event.

A summary of TEAEs by NCI-CTCAE 5.0 Grade ≥ 3 is presented in the Table below.

Overall, the majority of TEAEs were of Grade 1 (66 of 218 TEAEs in 3 [6.1%] subjects) or Grade 2 (140 of 218 TEAEs in 30 [61.2%] subjects). The frequency of ≥ Grade 3 TEAEs was higher while on SB12 treatment [6/47 (12.8%) vs 2/47 (4.3%) Soliris]. No TEAEs of Grade 4 (life-threatening event) were reported during the study period. One (2.1%) subject had TEAE of Grade 5 (fatal) portal vein thrombosis in the Soliris treatment group. The fatal event was considered not related to the IP.

Table 40: Summary of grade ≥3 treatment emergent adverse events by system organ class, preferred term and treatment group (Safety set)

System Organ Class	SB12 N = 47		Soliris® N = 47		Total N = 49	
Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any Grade ≥ 3 TEAEs*	6 (12.8)	8	2 (4.3)	3	8 (16.3)	11
Blood and lymphatic system disorders	2 (4.3)	2	0 (0.0)	0	2 (4.1)	2
Anaemia	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Haemolysis	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
General disorders and administration site conditions	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Infusion site hypersensitivity	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Hepatobiliary disorders	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Portal vein thrombosis	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Infections and infestations	1 (2.1)	1	1 (2.1)	1	2 (4.1)	2
Wound infection bacterial	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Cellulitis	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Injury, poisoning and procedural complications	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Hand fracture	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Investigations	1 (2.1)	2	0 (0.0)	0	1 (2.0)	2
Neutrophil count decreased	1 (2.1)	2	0 (0.0)	0	1 (2.0)	2
Nervous system disorders	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Headache	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Renal and urinary disorders	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Chronic kidney disease	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Vascular disorders	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Hypertension	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1

E = frequency of TEAEs; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = for SB12 represents the total number of pooled subjects who had been treated with SB12 in either Period 1 or 2; N for Soliris® represents the total number of pooled subjects who had been treated with Soliris® in either Period 1 or 2; N for Total represents the total number of subjects in the Safety Set. Percentages were based on N in each column; TEAE = treatment-emergent adverse event

- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA®, Version 21.0 coding dictionary.
- If a subject had multiple events with different severity, then the subject was counted only once at the worst severity for the number of subjects (n). Subjects with missing severity were counted at the most severe category and also the 'Missing' category separately in the summary.
- SOC were presented alphabetically; PTs were sorted within each SOC in descending order of subject frequency in SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.
- An event was reported under the treatment the subject was last received prior to the event.

A summary of IP-related TEAEs is presented in the Table below.

The majority (198 of 218) of TEAEs were considered not related to IP in study overall. Treatment-related events were reported more frequently during Soliris treatment [8/47 (17.0%), 0.77 EAER] compared to SB12 treatment [3/47 (6.4%), 0.21 EAER].

Table 41: Summary of IP-related treatment-emergent adverse events by system organ class, preferred term and treatment group (safety set)

System Organ Class	SB12 N = 47		Soliris® N = 47		Total N = 49	
Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any treatment-related adverse events	3 (6.4)	5	8 (17.0)	15	11 (22.4)	20
General disorders and administration site conditions	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Infusion site hypersensitivity	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Infections and infestations	0 (0.0)	0	1 (2.1)	4	1 (2.0)	4
Abscess limb	0 (0.0)	0	1 (2.1)	2	1 (2.0)	2
Cellulitis	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Scrotal abscess	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Investigations	0 (0.0)	0	2 (4.3)	3	2 (4.1)	3
Alanine aminotransferase increased	0 (0.0)	0	2 (4.3)	2	2 (4.1)	2
Gamma-glutamyltransferase increased	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Nervous system disorders	2 (4.3)	4	2 (4.3)	4	4 (8.2)	8
Headache	2 (4.3)	4	2 (4.3)	4	4 (8.2)	8
Psychiatric disorders	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Libido decreased	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Dyspnoea	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Skin and subcutaneous tissue disorders	0 (0.0)	0	2 (4.3)	2	2 (4.1)	2
Urticaria	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Rash	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1

E = frequency of TEAEs; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = for SB12 represents the total number of pooled subjects who had been treated with SB12 in either Period 1 or 2; N for Soliris® represents the total number of pooled subjects who had been treated with Soliris® in either Period 1 or 2; N for Total represents the total number of subjects in the Safety Set. Percentages were based on N in each column; TEAE = treatment-emergent adverse event

- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA®, Version 21.0 coding dictionary.
- If a subject had multiple events with different causality, then the subject was counted only once at the most related category for the number of subjects (n). Subjects with missing causality were counted at the most related category and also the 'Missing' category separately in the summary.
- SOC were presented alphabetically; PTs were sorted within each SOC in descending order of subject frequency in SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.
- An event was reported under the treatment the subject was last received prior to the event.

All TEAEs of special interest were summarised in the table below.

During the study, there were 5 TEAEs of special interest (infusion site hypersensitivity, cellulitis, dyspnoea, rash, and urticaria) reported in 4 (8.5%) subjects, and all TEAEs of special interest were reported in the Soliris treatment group. Among these 5 TEAEs of special interest, 1 subject with infusion site hypersensitivity was discontinued. All TEAEs of special interest were related to IP.

- Infusion site hypersensitivity and cellulitis reported in one subject each and were considered as SAEs of Grade 3 severity. Cellulitis was not resolved at the time of subject's withdrawal from the study due to death.
- Dyspnoea and rash reported in one subject and were considered as Grade 2 in severity.
- Urticaria reported in one subject and was considered as Grade 2 in severity.

Table 42: Treatment-emergent adverse events of special interest by system organ class, preferred term and treatment group (Safety set)

System Organ Class Preferred Term	SB12 N = 47		Soliris® N = 47		Total N = 49	
	n (%)	E	n (%)	E	n (%)	E
Any TEAEs of Special Interest	0 (0.0)	0	4 (8.5)	5	4 (8.2)	5
General disorders and administration site conditions	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Infusion site hypersensitivity	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Infections and infestations	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Cellulitis	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Dyspnoea	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Skin and subcutaneous tissue disorders	0 (0.0)	0	2 (4.3)	2	2 (4.1)	2
Rash	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Urticaria	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1

E = frequency of TEAEs; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N for SB12 represents the total number of pooled subjects who had been treated with SB12 in either Period 1 or 2; N for Soliris® represents the total number of pooled subjects who had been treated with Soliris® in either Period 1 or 2; N for Total represents the total number of subjects in the Safety Set. Percentages were based on N in each column; TEAE = treatment-emergent adverse event

- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA®, Version 21.0 coding dictionary.
- SOC were presented alphabetically; PTs were sorted within each SOC in descending order of subject frequency in SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.
- An event was reported under the treatment the subject was last received prior to the event.

COVID-19 Infections

Any TEAEs for COVID-19 [8/47 (17.0%), 0.34 EAER] and TEAEs among COVID-19 infected subjects [10/47 (21.3%), 1.84 EAER] were more frequently reported in patients during SB12 treatment compared to Soliris [3/47 (6.4%), 0.15 EAER and 6/47 (12.8%), 1.17 EAER, respectively].

All TEAEs for COVID-19 were of Grade 1 (5 of 11 TEAEs in 4 [8.2%] subjects) or Grade 2 (6 of 11 TEAEs in 6 [12.2%] subjects) in severity and were not considered related to IP by Investigator/Sponsor. Only 3 TEAEs for COVID-19 were reported as symptomatic (fever), and rest of them were reported as asymptomatic. All of them were resolved during the study period.

No serious TEAEs for COVID-19 were reported, and one serious TEAEs among COVID-19 infected subject was reported in the SB12 treatment group (haemolysis; TEAEs related to breakthrough haemolysis, see below).

Breakthrough Haemolysis and Major Adverse Vascular Events

A total of 22 TEAEs related to breakthrough haemolysis were reported in 8 (17.0%) subjects in the SB12 treatment group and 3 TEAEs related to breakthrough haemolysis were reported in 1 (2.1%) subject in the Soliris treatment group (Table below).

Table 43: TEAEs related to breakthrough haemolysis by system organ class, preferred term and treatment group (safety set)

System Organ Class Preferred Term	SB12 N = 47 n (%)	E	Soliris® N = 47 n (%)	E	Total N = 49 n (%)	E
Any TEAEs related to breakthrough haemolysis	8 (17.0)	22	1 (2.1)	3	8 (16.3)	25
Blood and lymphatic system disorders	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Haemolysis	1 (2.1)	1	0 (0.0)	0	1 (2.0)	1
Gastrointestinal disorders	2 (4.3)	4	1 (2.1)	2	3 (6.1)	6
Abdominal pain	2 (4.3)	4	1 (2.1)	1	3 (6.1)	5
Dysphagia	0 (0.0)	0	1 (2.1)	1	1 (2.0)	1
Hepatobiliary disorders	2 (4.3)	2	0 (0.0)	0	2 (4.1)	2
Jaundice	2 (4.3)	2	0 (0.0)	0	2 (4.1)	2
Renal and urinary disorders	8 (17.0)	15	1 (2.1)	1	8 (16.3)	16
Haemoglobinuria	8 (17.0)	15	1 (2.1)	1	8 (16.3)	16

E = frequency of TEAEs; n = number of subjects with event; N for SB12 represents the total number of pooled subjects who had been treated with SB12 in either Periods 1 or 2; N for Soliris® represents the total number of pooled subjects who had been treated with Soliris® in either Periods 1 or 2; N for Total represents the total number of subjects in the Safety Set; Percentages were based on N in each column; TEAE = treatment-emergent adverse event
- System organ classes (SOC) were presented alphabetically; preferred terms (PTs) were sorted within each SOC in descending order of subject frequency in SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.
- An event was reported under the treatment the subject was last received prior to the event.

One MAVE (portal vein thrombosis) as serious TEAE of Grade 5 in severity was reported in Soliris treatment group during the study period.

2.6.8.3. Serious adverse event/deaths/other significant events

Phase I study SB12-1001

There were no deaths and no discontinuations due to TEAEs in study SB12-1001. Two SAEs were reported, and both were considered not related to IP by the Investigator. One subject in the SB12 group had renal colic and one subject in the US-sourced Soliris group had back pain. Thus, the proportion of subjects with SAEs was comparable among the treatment groups, and no concerns regarding biosimilarity arise.

Phase III study SB12-3003

Deaths

One death occurred due to a MAVE that was not related to breakthrough haemolysis in the Soliris arm. The male subject received 8 doses of Soliris during Period 1, before the subject withdrew from the study due to death led by the AE of portal vein thrombosis (Grade 5) on study day 165, 70 days after the most recent IP administration at Week 10. According to the applicant, the event was considered not related to the IP. No safety concerns arise from this event regarding SB12 treatment, since the subject has not received any SB12 treatment.

Other Serious Adverse Events

The SAEs are summarised for the SAF by actual treatment sequence in the Table below.

Three serious TEAEs were reported in 3 (6.4%) in the SB12 treatment group and 3 serious TEAEs in 2 (4.3%) subjects in the Soliris treatment group. Haemolysis, wound infection bacterial and hand fracture as serious TEAEs in the SB12 treatment group were reported as not related to IP. Two serious TEAEs (cellulitis and infusion site hypersensitivity) in the Soliris treatment group were considered to be related to the IP. Outcome of a serious TEAE of portal vein thrombosis was fatal and other 5 serious TEAEs were considered as Grade 3 in severity. All serious TEAEs were resolved except a serious TEAE of cellulitis which was not resolved.

Table 44: Serious Adverse Events by system organ class, preferred term and actual treatment sequence (safety set)

System Organ Class Preferred Term	Soliris® to SB12 N =25		SB12 to All N = 24		SB12 to Soliris® N = 16		Unplanned IP Switch N = 8		Total N = 49	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any Serious Adverse Events	5 (20.0)	6	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	5 (10.2)	6
Blood and lymphatic system disorders	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Haemolysis	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
General disorders and administration site conditions	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Infusion site hypersensitivity	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Hepatobiliary disorders	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Portal vein thrombosis	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Infections and infestations	2 (8.0)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (4.1)	2
Cellulitis	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Wound infection bacterial	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Injury, poisoning and procedural complications	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1
Hand fracture	1 (4.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.0)	1

E = frequency of SAEs; MedDRA® = Medical Dictionary for Regulatory Activities; n = number of subjects with event; N = total number of subjects in each treatment sequence in the Safety Set; SAE = serious adverse event.
- Percentages were based on N in each column.
- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA®, Version 21.0 coding dictionary.
- SOC were presented alphabetically; PTs were sorted within each SOC in descending order of subject frequency in Soliris® to SB12. If the frequency of the PTs were tied, the PTs were ordered alphabetically.

2.6.8.4. Laboratory findings

Phase I study SB12-1001

Haematology

Mean and median values of all parameters of hematology did not show any relevant changes over time. A few subjects had shifts from normal hematology values at baseline to values outside the normal range post-baseline. There were no clinically significant changes from baseline in hematology values in any treatment group.

Biochemistry

Mean and median values of all parameters of biochemistry did not show any relevant changes over time. A few subjects had shifts from normal biochemistry values at baseline to values outside the normal range post-baseline. Except for Serum C-reactive protein (CRP) in 1 subject (EU Soliris treatment group), with reported TEAE of upper respiratory tract infection on day 38 which resolved on day 47), there were no clinically significant changes from baseline in biochemistry values in any treatment group.

Urinalysis

Mean and median values of all continuous parameters of urinalysis did not show any relevant changes over time. Categorical parameters of urinalysis did not show any relevant changes over time. A few subjects had shifts from normal urinalysis values at baseline to values outside the normal range post-

baseline. There were no clinically significant changes from baseline in urinalysis values in any treatment group.

Vital Signs

Mean and median values of all vital sign parameters (body temperature, systolic and diastolic blood pressure, and pulse) did not show any changes over time.

12-lead Electrocardiogram

ECG values and changes from baseline of heart rate, RR interval, PR interval, QRS interval, QT interval, QTcF interval, and QTcB interval were presented. Mean and median values of all ECG parameters did not show any relevant changes over time. Minor alterations were similar to those usually observed in healthy subjects.

One subject (SB12 treatment group) had a QTcF interval > 450 msec and ≤ 480 msec on Day 3; all other QTcF interval readings were ≤ 450 msec during the study.

An absolute change from baseline of QTcF > 30 msec was observed in 3 subjects on Day 3 (all 3 subjects were in the SB12 treatment group) and in 4 subjects on Day 64 (1 subject in the SB12 treatment group, 2 subjects in the EU sourced Soliris treatment group, and 1 subject in the US sourced Soliris treatment group). QTcF absolute changes from baseline > 60 msec were not observed in any of the subjects.

Interpretation of ECG recordings showed some abnormalities, but none of these abnormalities reached clinical relevance as judged by the Investigator.

Physical Examination Findings

A total of 24 subjects had 40 abnormal findings for the physical examination results evaluated as clinically significant by the Investigator (14 events in 9 subjects in the SB12 treatment group, 12 events in 6 subjects in the EU sourced Soliris treatment group, and 14 events in 9 subjects in the US sourced Soliris treatment group, respectively). The most frequently reported clinically significant physical examination abnormalities were reported in the body system of skin; i.e., 8 events were reported in 4 subjects in the SB12 treatment group, 6 events were reported in 2 subjects in the EU sourced Soliris treatment group, and 5 events were reported in 5 subjects in the US sourced Soliris treatment group.

Pregnancy

All female subjects had negative results for pregnancy.

A case of pregnancy was reported for the female partner of one subject. The subject received US sourced Soliris. Contraception measures as instructed were not followed; condom only was used as method of contraception. The Investigator was informed that the female partner had undergone elective termination of the pregnancy, for private reasons. No complications were reported. The pregnancy outcome was reported by the male participant; the female partner refused further contacts and/or provision of the hospital discharge report.

Phase III study SB12-3003

Haematology

There were no notable differences in mean and median values for haematology parameters observed, and changes in mean values from baseline were comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

Haemoglobin at Baseline was 85.9 g/L and 88.5 g/L in actual Soliris to SB12 and actual SB12 to All treatment sequences, respectively. Haemoglobin at Week 26 was 106.7 g/L and 108.2 g/L and haemoglobin at Week 52 was 113.8 g/L and 109.2 g/L in actual Soliris to SB12 and actual SB12 to All treatment sequences, respectively. Hence, mean haemoglobin levels were increased to a similar extent in both treatment groups at Weeks 26 and 52.

For each haematology parameter, observed shift patterns were comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

Clinically significant abnormalities of haemoglobin were reported in 11 (22.4%) subjects at baseline (6 [24.0%] subjects in actual Soliris to SB12 treatment sequence and 5 [20.8%] subjects in actual SB12 to All treatment sequence). Upon completion of the initial phase, clinically significant level of haemoglobin was reported in 3 (7.0%) subjects at Week 6 (2 [9.1%] subjects and 1 [4.8%] subject in each actual treatment sequence, respectively). At Week 52, no subject was reported with clinically significant level of haemoglobin. There were no notable trends in clinically significant abnormalities of other haematology parameters.

Chemistry

There were no notable differences in mean and median values for chemistry parameters observed, and changes in mean values from baseline were comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

For each chemistry parameter, observed shift patterns were comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

Few subjects had clinically significant abnormalities in some chemistry parameters (i.e. creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase) in both actual Soliris to SB12 and actual SB12 to All treatment sequences during the study period. There were no notable trends in clinically significant abnormalities of chemistry parameters.

Coagulation

There were no notable differences in mean and median values for coagulation parameters observed between actual Soliris to SB12 and actual SB12 to All treatment sequences.

For each coagulation parameter, observed shift patterns were comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

Few subjects had clinically significant abnormalities in prothrombin time (i.e., 3 subjects with prothrombin time above the significant abnormal range at week 14) and active partial thromboplastin time (i.e., 2 subjects at baseline, 1 subject at week 14 and also at week 26 and 3 subjects at week 52, all subjects had active partial thromboplastin time above the significant abnormal range) in both actual Soliris to SB12 and actual SB12 to All treatment sequences. There were no notable trends in clinically significant abnormalities of coagulation parameters.

Urinalysis

There were no notable changes in mean values from baseline for continuous parameters between actual Soliris to SB12 and actual SB12 to All treatment sequences. The proportion of subjects with each result for categorical parameters was comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

Other laboratory parameters

There were no notable changes in median values for ferritin, vitamin B12, and folate observed between actual Soliris to SB12 and actual SB12 to All treatment sequences.

For ferritin, vitamin B12, and folate, the observed shift patterns were comparable between actual Soliris to SB12 and actual SB12 to All treatment sequences.

Vital Signs and Weight

There were minimal changes in mean systolic and diastolic blood pressure, heart rate, and body temperature from baseline to Week 26 and Week 52 with no marked differences among treatment sequences. At Week 52, there were no clinically significant abnormalities (high/low) in vital signs were reported in any treatment sequence.

Twelve-lead Electrocardiogram Results

No clinically significant abnormal 12-lead ECG results were observed during the study period.

Physical Examination

There were no notable changes in physical examination assessments during the study period.

Pregnancy

One subject in the SB12 treatment group was reported with pregnancy. There was no previous known maternal history. Contraception measures used at the time were oral contraceptives and condoms. At subject's will, the subject decided with abortion by taking abortion medication (mifepristone). The subject was withdrawn from the study due to pregnancy. Pregnancy reports for this subject were provided.

Other Observations Related to Safety

All subjects were vaccinated within 3 years prior to or on Day 1.

All subjects were HIV negative at Screening.

Disease-related laboratory parameters are described in section *3.3.4. Outcomes and estimation*.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not Applicable.

2.6.8.6. Safety in special populations

Not Applicable.

2.6.8.7. Immunological events

Bioanalytical assays – immunogenicity

A bridging ligand-binding assay was used for the detection of ADAs in the clinical Phase I study (SB12-1001) and clinical Phase III study (SB12-3003). ADAs against eculizumab (SB12 and Soliris) in human serum were detected and confirmed in human serum using a multi-tiered approach in an ECL assay. In this assay, the qualitative and quasi-quantitative determination of ADAs in human serum samples was conducted by using a validated MSD platform. At confirmatory assay (Tier 2), the assay is based on the use of excess unlabeled SB12 in a competitive binding format to demonstrate the specificity of the binding interactions in the antibody/labeled drug complex.

In tier 3, a competitive ligand binding assay was also used for detection of NAbs in the clinical Phase I in addition to the titration assay. NAbs against eculizumab (SB12 and Soliris) in human serum were detected using a single tier acid dissociation, competitive ligand binding ECL assay using BEAD.

Phase I study SB12-1001

Evaluation of immunogenicity was secondary objective of the study SB12-1001.

The incidence of ADA and NAb to eculizumab for all analysed subjects at each time point are summarised in the Table below.

Overall, the incidence of ADA to eculizumab was low and comparable across all the 3 treatment groups of eculizumab. One subject in the US-sourced Soliris group was ADA positive pre-dose. Three subjects had a post-dose ADA positive result. Two of the positive ADA subjects were in the SB12 treatment group and one in the EU-sourced Soliris group. There were no ADA positive subjects in the US-sourced Soliris group.

None of the subjects with post-dose ADA to eculizumab had a positive result for NAb.

No concerns arise from immunogenicity findings regarding biosimilarity.

Table 45: Incidence of anti-drug antibodies and neutralising antibodies to eculizumab by visit and treatment group (safety set)

Parameter	Result	SB12 N=80		EU sourced Soliris® N=80		US sourced Soliris® N=80		Total N=240	
Time point		n/n'	(%)	n/n'	(%)	n/n'	(%)	n/n'	(%)
ADA									
Day 1 pre-dose (BL)	Positive	0/80	(0.0)	0/80	(0.0)	1/80	(1.3)	1/240	(0.4)
	Negative	80/80	(100.0)	80/80	(100.0)	79/80	(98.8)	239/240	(99.6)
Day 15	Positive	2/80	(2.5)	1/79	(1.3)	0/80	(0.0)	3/239	(1.3)
	Negative	78/80	(97.5)	78/79	(98.7)	80/80	(100.0)	236/239	(98.7)
Day 29	Positive	1/80	(1.3)	0/79	(0.0)	0/80	(0.0)	1/239	(0.4)
	Negative	79/80	(98.8)	79/79	(100.0)	80/80	(100.0)	238/239	(99.6)
Day 64/EOS	Positive	1/80	(1.3)	0/79	(0.0)	0/80	(0.0)	1/239	(0.4)
	Negative	79/80	(98.8)	79/79	(100.0)	80/80	(100.0)	238/239	(99.6)
Post-dose	Positive[a]	2/80	(2.5)	1/79	(1.3)	0/80	(0.0)	3/239	(1.3)
	Negative	78/80	(97.5)	78/79	(98.7)	80/80	(100.0)	236/239	(98.7)
NAb[b]									
Day 1 pre-dose (BL)	Positive	0/0	(0.0)	0/0	(0.0)	0/1	(0.0)	0/1	(0.0)
	Negative	0/0	(0.0)	0/0	(0.0)	1/1	(100.0)	1/1	(100.0)
Day 15	Positive	0/2	(0.0)	0/1	(0.0)	0/0	(0.0)	0/3	(0.0)
	Negative	2/2	(100.0)	1/1	(100.0)	0/0	(0.0)	3/3	(100.0)
Day 29	Positive	0/1	(0.0)	0/0	(0.0)	0/0	(0.0)	0/1	(0.0)
	Negative	1/1	(100.0)	0/0	(0.0)	0/0	(0.0)	1/1	(100.0)
Day 64/EOS	Positive	0/1	(0.0)	0/0	(0.0)	0/0	(0.0)	0/1	(0.0)
	Negative	1/1	(100.0)	0/0	(0.0)	0/0	(0.0)	1/1	(100.0)
Post-dose	Positive[c]	0/2	(0.0)	0/1	(0.0)	0/0	(0.0)	0/3	(0.0)
	Negative	2/2	(100.0)	1/1	(100.0)	0/0	(0.0)	3/3	(100.0)

ADA = anti-drug antibody; BL = baseline; EOS = end of study; N = number of subjects in the Safety Set; n' = number of subjects with available assessment at each time point and category; n = number of subjects with that observation; NAb = neutralising antibody

[a] Post-dose ADA result was defined as positive if at least one positive ADA on post-baseline (Day 15, Day 29, or Day 64/EOS).

[b] NAb results only for subjects with ADA positive were used for the summary.

[c] Post-dose NAb result was defined as positive if at least one positive NAb on post-baseline (Day 15, Day 29, or Day 64/EOS).

Percentages were based on n'.

Phase III study SB12-3003

Evaluation of immunogenicity was a secondary objective of study SB12-3003.

No ADA or NAb were detected throughout the study duration of 52 weeks.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not Applicable.

2.6.8.9. Discontinuation due to adverse events

Phase I study SB12-1001

None of the subjects discontinued IP due to TEAEs.

Phase III study SB12-3003

One TEAE of infusion-related hypersensitivity leading to IP discontinuation due to infusion-related hypersensitivity was reported in Soliris treatment group (at week 0 = first dose of IP). This event was Grade 3 in severity and was considered related to IP, classified as an AESI, occurred during Period 1 and was resolved. No safety concerns regarding SB12 treatment arise from this event.

2.6.8.10. Post marketing experience

Not Applicable.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The safety of SB12 has been evaluated in two clinical studies (Phase I study SB12-1001 and Phase III study SB12-3003). Due to the heterogeneity of the studied population, the safety data of the two clinical studies has not been pooled, but provided separately for the two studies. This is regarded acceptable.

Phase I study SB12-1001

A total of 240 subjects were randomized in 1:1:1 ratio among the treatment groups SB12, EU-sourced Soliris and US-sourced Soliris (80 per treatment group). All of the subjects were included in the SAF. This is acceptable.

The proportion of subjects with any AEs was similar among the groups: In the SB12 group, 72.5 % of the subjects had any AEs, in the EU-sourced Soliris group, 67.5% of the subjects had any AEs and in the US-sourced Soliris group, 73.8% of the subjects had any AEs. The proportion of subjects with any TEAEs was also similar among the groups (70.0% SB12, 65.0% EU Soliris and 71.3% US Soliris). Most of the TEAEs were mild or moderate. None of the TEAEs led to subject discontinuation. The proportion of subjects with any AESIs was also low and comparable among the treatment groups. No subject died during the study. In conclusion, there were no notable differences in the pattern of adverse events among the treatment groups.

Two SAEs were reported. One subject in the SB12 group had renal colic and one subject in the US-sourced Soliris group had back pain, both SAEs were considered not related to IP by the Investigator. Thus, the proportion of subjects with SAEs was comparable among the treatment groups.

There were no notable differences in the laboratory findings (including haematology, biochemistry and urinalysis parameters) among the treatment groups in the Phase I study SB12-1001. The same holds true for the vital signs and physical examination parameters.

Immunogenicity was also assessed in the Phase I study SB12-1001. The assay validation for the

immunogenicity assays has been conducted and summaries as well as the detailed validation reports have been provided. The results of the validation work confirm that these assays are suitable for their intended use. The same holds true for the assay used in the Phase III study. One subject in the US-sourced Soliris group was ADA positive pre-dose. The number of subjects with ADAs throughout the study was low, with only three subjects having a post-dose ADA positive result. Two of the positive ADA subjects were in the SB12 treatment group and one in the EU-sourced Soliris group. There were no ADA positive subjects in the US-sourced Soliris group. All of the positive ADA subjects had a negative NAb result. The proportion of subjects with ADAs was similar among the treatment groups in the Phase I study SB12-1001 and no concerns arise from the immunogenicity findings.

Phase III SB12-3003

In clinical Phase III study SB12-3003, a total of 50 subjects were randomly allocated to each treatment sequence. A total of 49 subjects (SB12: 24 subjects; Soliris: 25 subjects) received at least 1 administration of SB12 or Soliris in Period 1. Hence, the safety data set for Period 1 is considered appropriate for the biosimilarity assessment regarding safety for the limited duration of 26 weeks, as numbers of subjects were in accordance with the pre-planned sample size target of 23 subjects per group.

However, adequate interpretation/comparison of long term safety and immunogenicity data is compromised due to the cross-over design, which was strongly discouraged during EMA Scientific Advice. Although different N-glycan patterns between SB12 and Soliris have been identified (see Quality Section), no clinical concern was raised. From the reference product it is known that eculizumab has low immunogenic potential (infrequent and low antibody titre responses and no neutralizing antibodies were observed, see EPAR and PI Soliris). During the clinical development of SB12 there were only few subjects in the phase I study developing antibodies, of whom no subject had neutralising antibodies. The patient population included in the phase III study was treatment-naïve and can therefore be considered a sensitive population for detecting the occurrence of immunogenicity, albeit the overall number of subjects was low. Therefore, no issue was raised from a clinical perspective.

In Period 2, after transition to other treatment at week 26, a total of 46 subjects received at least one study drug administration, but only 38 subjects (n=23 in SB12 group, n=15 in Soliris group) did not have unplanned IP switch during this period. Hence, the safety data set for Period 2 is even more reduced due to unplanned IP switch. The percentage of subjects with TEAEs in the Unplanned IP Switch treatment sequence (75.0%; 6 of 8 subjects) was comparable to the percentage of subjects with TEAEs in other treatment sequences (range from 65.2% to 69.6%) and no apparent safety concerns were observed for this subgroup of patients.

During Period 1, the number of subjects reporting any TEAEs was comparable between treatment arms, but more subjects reported ⩾ Grade 3 TEAEs in the Soliris treatment arm [3/25 (12%)] compared to SB12 [1/24 (4.2%)]. Treatment-related events were also reported more frequently in the Soliris group [6/25 (24.0%) compared to the SB12 group [3/24 (12.5%], as were AESI in the Soliris group [3/25 (12%); vs 0/24 (0%) in the SB12 group]. COVID-19 infections were observed at similar frequencies between study arms during Period 1.

Although similar trends were observed during Period 1 compared to the overall summary including both Periods, there were also differences, highlighting the limitations of a short observation period in a small number of patients. For example, the overall frequency of ⩾ Grade 3 TEAEs was higher while on SB12 treatment [6/47 (12.8%)] compared to Soliris [2/47 (4.3%)]. Similarly, COVID-19 related TEAEs were more frequently reported in patients during SB12 treatment [8/47 (17.0%)] compared to Soliris

[3/47 (6.4%)].

During the whole study duration, the incidences of the most frequent TEAEs by SOC and PT were higher in the SB12 group compared to the Soliris group (corona virus infection, haemoglobinuria, diarrhoea, alanine aminotransferase (ALT) increased, hypertension), except headache, which was more frequent in the Soliris group. Hence, corona virus infections occurred overall more frequently during SB12 treatment, which were attributed to local outbreaks. COVID-19 related dose delays may be associated with events of breakthrough haemolysis.

Overall, the majority of TEAEs were of Grade 1 or Grade 2. No TEAEs of Grade 4 (life-threatening event) were reported during the study period. One (2.1%) subject had TEAE of Grade 5 (fatal) portal vein thrombosis (MAVE) in the Soliris treatment group, which was considered not related to IP. Serious TEAEs were reported at similar frequencies, 3 in 3/47 (6.4%) subjects in the SB12 treatment group and 3 serious TEAEs in 2/47 (4.3%) subjects in the Soliris treatment group.

No notable differences or abnormalities were observed in haematology parameters, chemistry, coagulation, urinalysis and other laboratory parameters. No safety concerns arise from laboratory parameters regarding biosimilarity.

No ADA or NAb were detected throughout the study duration of 52 weeks. However, the limited sample size is too small to draw any final conclusions regarding the actual frequency of ADA following SB12 treatment, and it cannot be excluded that neutralising antibodies may occur after more patients have been treated.

2.6.10. Conclusions on the clinical safety

In the Phase I study, there were no notable differences in the safety profile of SB12 and the reference product. In the Phase III study, some imbalances may indicate a worse safety profile for SB12, while others would suggest otherwise. Due to the obvious limitations of the design and conduct of the study, it appears likely that these are chance findings. Although data on immunogenicity are very limited, no clinical concern is raised.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• *Meningococcal* infections • Serious infections (including sepsis) • *Aspergillus* infection • Infusion reactions
Important potential risks	• Serious haemolysis after drug discontinuation in PNH patients • Immunogenicity • Malignancies and haematologic abnormalities in PNH patients • Serious infections in neonates after maternal exposure to eculizumab
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Meningococcal infections	Routine risk minimisation measures: − SmPC sections 4.3, 4.4 and 4.8 − PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guides

Safety concern	Risk minimisation measures
	− Patient's/Parent's information brochure − Patient safety card Controlled distribution Vaccination reminder
Serious infections (including sepsis)	Routine risk minimisation measures: − SmPC sections 4.4 and 4.8 − PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guides − Patient's/Parent's information brochure − Patient safety card
Aspergillus infection	Routine risk minimisation measures: − SmPC sections 4.4 and 4.8 − PL section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guides
Infusion reactions	Routine risk minimisation measures: − SmPC sections 4.2, 4.4, and 4.8 − PL sections 2, 3, and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures:

Safety concern	Risk minimisation measures
	Educational Materials − Physician's guides − Patient's/ Parent's information brochure
Serious haemolysis after drug discontinuation in PNH patients	Routine risk minimisation measures: − SmPC section 4.4 − PL section 3 Monitoring of patients who discontinued SB12 recommended in SmPC section 4.4 and PL section 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guides − Patient's/Parent's information brochure
Immunogenicity	Routine risk minimisation measures: − SmPC sections 4.4 and 4.8 − PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guides (PNH)
Malignancies and haematologic abnormalities in PNH patients	Routine risk minimisation measures: − SmPC section 4.8 − PL section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: None

Safety concern	Risk minimisation measures
Serious infections in neonates after maternal exposure to eculizumab	Routine risk minimisation measures: − SmPC section 4.6 − PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Flixabi PL (regarding design/layout/format) and Soliris PL (regarding content), Soliris. The bridging report submitted by the applicant has been found acceptable.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The claimed therapeutic indication for the treatment of PNH is the same as for the reference product Soliris:

Epysqli is indicated in adults and children for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).

Soliris is also indicated in the treatment of atypical haemolytic uremic syndrome (aHUS), refractory generalised myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive, and neuromyelitis optica spectrum disorder (NMOSD), but these indications are still protected by orphan exclusivity and not applied for in this MAA.

Summary of quality comparability data

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. Throughout the SB12 development program, EU Soliris was used as the reference product in quality exercises and clinical studies while US Soliris was inevitably used in clinical phase III study.

In order to support a determination that SB12 is highly similar to EU Soliris and to establish a scientific bridge between EU Soliris and US Soliris, a three-way comparison was performed at quality level between SB12, EU and US Soliris.

Summary of nonclinical comparability data

The pharmacology program was focused on primary PD. A series of *in vitro* PD studies was performed to assess any potential differences in biological activity between SB12 and EU or US Soliris. Given that SB12 is developed as a proposed biosimilar, secondary PD, safety pharmacology and PD drug interaction studies were not deemed necessary, which is in accordance with EMA guideline [EMA/CHMP/BMWP/403543/2010]. Toxicological *in vivo* studies were not performed.

The clinical development plan consists of two studies:

Clinical Phase I study (SB12-1001) was the pivotal PK similarity study. This was a double-blind, three-arm, parallel group, and single-dose study to demonstrate similarity in PK, safety, tolerability, immunogenicity, and PD between SB12 and Soliris. A total of 240 healthy subjects aged 18-55 years were enrolled and randomised in a ratio of 1:1:1 to receive a 300 mg single dose IV of either SB12, EU sourced Soliris, or US sourced Soliris.

The design of the clinical study has been discussed in EMA Scientific Advice, which was largely adhered to, except the recommended exclusion of female participants and the use of the functional CH50 assay for PD assessment.

Clinical Phase III study (SB12-3003) aimed to confirm clinical equivalence between SB12 and Soliris in a representative indication. This was a randomized, double-blinded, multicentre, cross-over study to compare the efficacy, safety, PK, and immunogenicity in patients with PNH between SB12 and Soliris. A total of 50 subjects were randomised in a 1:1 ratio to treatment sequence I (SB12 to Soliris) or treatment sequence II (Soliris to SB12). Subjects who were randomised to initially receive SB12 were

switched to receive Soliris and subjects who were randomised to initially receive Soliris were switched to receive SB12 at Week 26. Study drug was given according to the posology of Soliris until Week 50 (4 x 600 mg weekly, followed by 900 mg bi-weekly).

EMA Scientific Advice was followed concerning enrolment of a treatment-naïve study population, as well as primary (LDH levels) and secondary (LDH profile over time, number of pRBC transfusions) efficacy endpoints. The equivalence range and time point for the primary assessment have not been conclusively discussed. The cross-over design including an IP switch after 26 Weeks was strongly discouraged as this would hamper adequate interpretation/comparison of long term safety and immunogenicity data.

3.2. Results supporting biosimilarity

Quality

A comprehensive and well-established biosimilarity exercise has been conducted. EU-sourced RMP lots and US-sourced comparators lots have been included into the similarity exercise and compared against several produced batches of Epysqli. These Epysqli batches were comprised of PPQ DP, clinical DP and PPQ DS batch. DP batches included into the biosimilarity exercise were manufactured from independent DS batches. The number of RMP lots (and comparator lots for the 3-way comparison) is agreed as it forms a solid basis for evaluation of the variability in quality attributes of RMP.

A broad panel of standard and state-of-the-art methods has been applied for similarity evaluation and addresses all relevant physicochemical and biological characteristics of the eculizumab molecule. In principle, the results support the applicant's conclusion that similarity for the relevant physicochemical and biological quality attributes has been demonstrated. For the majority of the compared quality attributes the data for Epysqli were within the pre-established similarity ranges. Slight differences detected in N-glycosylation, oxidation, deamidation, and charged variants have been appropriately addressed and do not raise any doubts on the biosimilarity claim. In addition to comprehensive and state-of-the-art characterisation study, comparative stress stability studies, performed for SB12, EU and US Soliris to assess similarity in terms of degradation profiles, support the biosimilarity claim. Results of all comparative stability studies showed similar degradation profiles supporting similarity across SB12, EU and US Soliris.

Nonclinical

Comparative *in vitro* studies to evaluate similarity between Epysqli and EU/US Soliris with regard to biological properties were conducted and generally showed similar biological properties between both products. Additional biological properties of SB12 (e.g. C5 binding by SPR (surface plasmon resonance), Fcγ receptors, C1q binding, C5 polymorphic variants binding) were also compared to EU/US Soliris in side-by-side analyses. Study reports of those studies were submitted in Module 3 of the dossier and were thus assessed and discussed in detail in the Quality section of the assessment report.

Clinical data

Pharmacokinetics

Phase I study SB12-1001

Biosimilarity in pharmacokinetics of SB12 and Soliris was shown in healthy volunteers in the single-dose Phase I study SB12-1001. The geometric LSMean ratio (90% CI) for SB12 and EU sourced Soliris

in AUCinf was 0.991 (0.9541 to 1.0285), for SB12 and US sourced Soliris 0.951 (0.9140 to 0.9904), and for EU sourced Soliris and US sourced Soliris 0.960 (0.9216 to 1.0010), which were all within the pre-defined equivalence margin of 0.8 to 1.25. Thus, the primary endpoint of the study was met.

In addition, summary statistics of the other PK parameters revealed that most of the PK parameters, such as AUC_{last}, C_{max}, V_z, CL and $t_{1/2}$ were similar among the three treatment groups.

The profiles for mean terminal complement activity among SB12, EU-sourced Soliris and US-sourced Soliris group were also similar, supporting PD similarity.

Phase III study SB12-3003

The mean (SD) eculizumab C_{trough} at Week 26 was 150.041 (62.6232) µg/mL in the Soliris group and 133.807 (71.6412) µg/mL in the SB12 group. At Week 52 mean (SD) eculizumab C_{trough} levels were 127.102 (60.2749) µg/mL (Soliris) and 129.084 (52.5487) µg/mL (SB12). Hence, eculizumab levels appeared similar with overlapping SD bars.

Clinical Efficacy (Phase III study SB12-3003)

The **primary efficacy analysis** was performed for the PPS-single using a linear model with treatment and gender as fixed effects. In the PPS-single, the 2-sided 95% CI of the estimated LSM difference in LDH level at Week 26 between SB12 and Soliris treatment group (SB12 − Soliris: 34.48, 95% CI [−47.66, 116.62]) completely lied within the pre-defined equivalence margin of [−337.2 to 337.2].

In the M-FAS, using multiple imputation method that assumed missing data were MAR, the 2-sided 95% CI of the estimated LSM difference in LDH (U/L) level at Week 26 between SB12 and Soliris treatment groups (SB12 − Soliris: 26.91, 95% CI [−56.24, 110.05]) also completely lied within the pre-defined equivalence margin.

Secondary efficacy endpoints:

The mean LDH profile over time indicated a marked decrease 2 weeks after treatment initiation and appeared similar between treatment arms when plotted by treatment sequence.

The overall units of pRBC transfused were decreased after study treatment initiation in both planned treatment sequences to a similar extent.

Other efficacy results:

The primary efficacy endpoint for FDA, the estimated ratio of geometric LSM in time-adjusted AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52 between SB12 and Soliris treatment groups (SB12/Soliris) was 1.08, and the 2-sided 90% CI of [0.95, 1.23] was within the pre-defined equivalence range [0.77 to 1.29], according to the applicant.

Mean proportions of PNH clone size of RBC were increased at Week 26 and remained increased up to Week 52 in both treatment groups. Mean haptoglobin increased in both treatment groups at Week 26, slightly decreased up to Week 52, but remained clearly above baseline levels. Opposite trends were observed in mean free haemoglobin levels, suggesting similar effects of eculizumab on disease-related laboratory parameters in both treatment groups.

A trend of mean reduction from baseline in severity scores (0-10 scale) for PNH-related symptoms (fatigue, haemoglobinuria, chest pain, abdominal pain, dyspnoea, dysphagia, erectile dysfunction) was observed at Week 26 and Week 52 in both treatment groups.

Clinical Safety

Phase I study SB12-1001

The safety profile of SB12 and Soliris was highly similar in healthy subjects in the single-dose Phase I study SB12-1001. The proportion of subjects with any AEs and TEAEs was similar among the groups. Most of the TEAEs were mild or moderate. The proportion of subjects with any AESI was low and comparable among the treatment groups. The proportion of subjects with SAEs was low and comparable among the treatment groups (each 1 event in the SB12 and US-Soliris group).

The number of subjects with ADAs throughout the study was small, with only three subjects having a post-dose ADA positive result. Two of the positive ADA subjects were in the SB12 treatment group and one in the EU-sourced Soliris group. There were no ADA positive subjects in the US-sourced Soliris group. All of the positive ADA subjects had a negative NAb result.

Phase III study SB12-3003

During Period 1, the number of subjects reporting any TEAEs was comparable between treatment arms. COVID-19 infections were observed at similar frequencies between study arms during Period 1.

Overall, the majority of TEAEs were of Grade 1 or Grade 2. Serious TEAEs were reported at similar frequencies, 3 in 3/47 (6.4%) subjects in the SB12 treatment group and 3 serious TEAEs in 2/47 (4.3%) subjects in the Soliris treatment group. No ADA or NAb were detected throughout the study duration of 52 weeks.

3.3. Uncertainties and limitations about biosimilarity

Quality

None.

NonClinical

None.

Clinical data

The terminal complement complex ELISA was used as a PD endpoint in both the Phase I and Phase III trial. The initially proposed and endorsed CH50 was not included. This is not regarded optimal. The inclusion of CH50 as a secondary PD endpoint would have provided further valuable information and support for the Phase III study. Due to the small Phase III study, from which only limited data regarding efficacy, safety, PK and PD can be expected, it would have been even more important to retrieve as much information as possible from the Phase I study in order to provide a conclusive biosimilarity exercise. Thus, it is not considered optimal that important PD data, such as CH50, have not been evaluated in this study.

Phase I study SB12-1001

It is not considered optimal that only total eculizumab levels have been measured for the evaluation of PK characteristics. The measurement of free eculizumab concentrations could have provided additive data in support for the demonstration of biosimilarity. Although this is not regarded optimal, a request at this point in time would not be regarded fruitful. Therefore, no concern is raised.

Phase III study SB12-3003

As no equivalence range has been pre-defined for PK evaluation in study SB12-3003, only descriptive statistics are available. Eculizumab C_{trough} concentrations were consistently lower in the SB12 group

compared to Soliris throughout Period 1 (mean 150.041 µg/mL in the Soliris group and 133.807 µg/mL in the SB12 group at Week 26). Eculizumab levels over time were also lower for SB12 at most time points during Period 2 compared to Soliris.

Furthermore, it appears that reduction of terminal complement activity is lower in patients treated with SB12 compared to Soliris.

Clinical Efficacy (Phase III study SB12-3003)

Primary efficacy endpoint:

At Week 26, the LSM of LDH was higher in the SB12 group (284.20 U/L) compared to Soliris (249.72 U/L). Although formally the primary efficacy endpoint met pre-defined criteria to show biosimilarity, the low specificity of LDH, questionable clinical irrelevance of the equivalence margin, and likely not optimal time point of primary assessment in the study population represent remaining uncertainties.

Secondary endpoints:

The number of events of elevated LDH levels > 2 x ULN and exposure-adjusted event rates (EAER) were higher in patients on SB12 treatment during both treatment periods.

Other efficacy results:

The geometric LSM in time-adjusted AUEC of LDH from Week 14 to Week 26 and from Week 40 to Week 52 was higher for SB12 (279.65 U/L) compared to Soliris (258.73 U/L).

The mean LDH at Week 26 was higher in the SB12 treatment group (402.6 U/L) compared to Soliris (260.2 U/L). At Week 52, after the planned switch, mean LDH was again higher in patients receiving SB12 (431.9 U/L) compared to Soliris (317.7 U/L).

The mean reduction from baseline in haemoglobinuria severity scores was more pronounced during Soliris treatment compared to SB12 treatment in both periods (sequence I: 3.1 at baseline, 0.8 (Soliris) at Week 26, 1.0 (SB12) at Week 52; sequence II: 3.4 at baseline, 1.1 (SB12) at Week 26, 0.6 (Soliris) at Week 52].

Breakthrough haemolysis:

TEAEs related to BTH were reported more frequently in more subjects in the SB12 treatment group [22 TEAEs in 8/47 (17.0%) subjects vs 3 TEAEs in 1/47 (2.1%) subject in the Soliris treatment group] across both treatment periods, which may indicate a potential reduced efficacy of SB12. The applicant provided possible confounding factors, i.e. dose delays, which partially explain this imbalance.

Clinical Safety

Phase III study SB12-3003

In Period 2, 8/23 (34.8%) subjects in the Soliris treatment arm had an unplanned IP switch. Hence, the safety data set for patients receiving Soliris in Period 2 is considerably reduced.

During Period 1 more subjects reported ≥ Grade 3 TEAEs in the Soliris treatment arm [3/25 (12%)] compared to SB12 [1/24 (4.2%)]. Treatment-related events were also reported more frequently in the Soliris group [6/25 (24.0%) compared to the SB12 group [3/24 (12.5%], as were AESI in the Soliris group [3/25 (12%); vs 0/24 (0%) in the SB12 group].

During the whole study duration, the overall frequency of ≥ Grade 3 TEAEs was higher while on SB12 treatment [6/47 (12.8%)] compared to Soliris [2/47 (4.3%)]. Similarly, COVID-19 related TEAEs were more frequently reported in patients during SB12 treatment [8/47 (17.0%)] compared to Soliris [3/47 (6.4%)].

During the whole study duration, the incidences of the most frequent TEAEs by SOC and PT were higher in the SB12 group compared to the Soliris group (corona virus infection, haemoglobinuria, diarrhoea, alanine aminotransferase (ALT) increased, hypertension), except headache, which was more frequent in the Soliris group.

Adequate interpretation/comparison of long term safety and immunogenicity data is compromised due to the cross-over design, which was strongly discouraged during EMA Scientific Advice.

3.4. Discussion on biosimilarity

Quality

A well-established biosimilarity exercise has been conducted, which confirms similarity of SB12 with its reference product EU Soliris.

Nonclinical

Comparative *in vitro* studies support the biosimilarity of SB12 versus the Soliris EU.

Clinical

In clinical Phase I study SB12-1001 conducted in healthy volunteers, PK biosimilarity was formally demonstrated between SB12, EU-sourced Soliris and US-sourced Soliris. For the primary PK parameter AUCinf, the 90% CI for the ratio of test/reference product fell within the acceptance range of 80.00-125.00%. This was supported by similar summary statistic of other PK parameters in this study and similar $C_{through}$ levels between SB12 and Soliris in the Phase III study SB12-3003.

Terminal complement activity was measured as PD marker in Phase I and Phase III studies. Although the assessment of this marker pointed towards similar PD among SB12, EU-sourced Soliris and US-sourced Soliris in healthy volunteers in the Phase I study, it is not considered optimal that CH50 has not been included as PD marker in both the Phase I and Phase III study. This would have provided further valuable information regarding PD similarity of the test and reference product. Thus, the conclusions on PD similarity are considered limited.

In clinical Phase III study SB12-3003, the primary endpoint LDH levels at Week 26 supports biosimilarity, as the 95% CI for the LSM difference between SB12 and Soliris completely lied within the pre-defined equivalence margin. As already highlighted during Scientific Advice, the use of LDH as primary endpoint has its limitations, as measuring LDH levels is considered to have low specificity. Moreover, in a treatment-naïve study population, an earlier time point for LDH evaluation may have been more appropriate, as the reduction in LDH levels has already reached the plateau at Week 26. Although the clinical irrelevance of the proposed equivalence margin is questionable, confirmation on biosimilarity is provided from the narrow 95% CI of the primary efficacy endpoint and similar results from secondary endpoints LDH profile over time and pRBC units transfused.

Due to the inevitable limitations of LDH as primary endpoint, the importance of clinical pharmacology outcomes to demonstrate biosimilarity has been highlighted. In the Phase I study SB12-1001 biosimilarity regarding PK was adequately demonstrated in healthy volunteers.

A considerably higher proportion of subjects with TEAEs related to breakthrough haemolysis [22 TEAEs in 8/47 (17.0%) subjects vs 3 TEAEs in 1/47 (2.1%) subject in the Soliris treatment group] raised concerns regarding a potentially reduced efficacy of SB12. Although several flaws in study design and conduct hamper adequate interpretation of results, the marked difference concerning breakthrough haemolysis is consistent across both study periods.

Confounding factors were proposed by the applicant, which partially explain the higher incidence of breakthrough haemolysis in patients treated with SB12. These include dose delays of ≥ 17 days (confounding factor #1), which were caused by COVID-19 infections during local outbreaks and occurred more frequently during SB12 treatment. Elevated LDH levels or BTH events may also be caused by dose delays of 15 or 16 days (confounding factor #2) that result in a lower eculizumab exposure, which is manageable by a narrower dosing interval for affected patients, and are therefore of no concern.

The clinical data regarding safety is limited and can only provide supportive information on comparability of safety and immunogenicity. In the Phase I study conducted in 240 healthy volunteers, the safety profiles of SB12, EU-sourced Soliris and US-sourced Soliris was very similar, with similar proportion of subjects with AEs and TEAEs. The number of subjects with ADAs was low and also comparable among the groups. Thus, no concerns regarding different safety profiles arise from this study.

However, in Phase III study SB12-3003, in addition to the already very limited sample size (n=49), adequate interpretation/comparison of long term safety and immunogenicity data is even more compromised due to the cross-over design, which was strongly discouraged during EMA Scientific Advice. Different N-glycan patterns between SB12 and Soliris have been identified, but concluded to have no impact on efficacy and safety. From the reference product it is known that eculizumab has low immunogenic potential (infrequent and low antibody titre responses and no neutralising antibodies were observed, see EPAR and PI Soliris). During the clinical development of SB12 there were only few subjects in the phase I study developing antibodies, of whom no subject had neutralizing antibodies. The patient population included in the phase III study was treatment-naïve and can therefore be considered a sensitive population for detecting the occurrence of immunogenicity, albeit the overall number of subjects was low. Therefore, no issue was raised from a clinical perspective.

3.5. Extrapolation of safety and efficacy

Soliris is currently indicated for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uremic syndrome (aHUS), generalised myasthenia gravis (gMG), and neuromyelitis optica spectrum disorder (NMOSD). The applicant has provided a justification for extrapolation to other indications. However, as with the current marketing authorisation the applicant only claims PNH, no assessment of the justification for extrapolation will be done at the very moment. The applicant is asked to provide these data during future variation procedures, when extension of indication is sought for.

3.6. Additional considerations

It should be noted that the manufacturing process for drug substance and drug product has been changed after conduct of the clinical studies meaning that the PPQ and intended commercial material is derived from a process version, which slightly differs from the clinical process. A sound comparability exercise to demonstrate a comparable quality profile of material from the different process versions was performed. Comparability between drug substance materials and drug product derived from the different process versions could be demonstrated. Some minor issues identified during the initial assessment were sufficiently addressed.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Epysqli is considered biosimilar to Soliris. Therefore, a

benefit/risk balance comparable to the reference product can be concluded.

Divergent position is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Epysqli is not similar to Aspaveli within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Epysqli is favourable in the following indication:

SB12 is indicated in adults and children for the treatment of Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree the details of a controlled drug distribution system and educational material including a patient safety card with each National Competent Authority and must implement such programmes nationally to ensure that:

1. All healthcare practitioners who may prescribe eculizumab receive the appropriate educational material.
2. All patients being treated with eculizumab receive a patient safety card.
3. Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis.
4. Vaccination reminders are sent to the prescribers.

The educational material should be agreed with the National Competent Authority and should contain the following:

- Summary of product characteristics
- Physician's guides to prescribing
- Package leaflet
- Patient's/parent's information brochures
- Patient safety card

The physician's guides to prescribing should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- All patients must be monitored for signs of meningococcal infection.
- The need for patients to be vaccinated against *Neisseria meningitidis* two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis.
- The requirement to vaccinate children against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- There is an important risk of Aspergillus infection in patients treated with eculizumab. The healthcare professionals should be advised to look for risk factors and signs and symptoms of Aspergillus infection. Practical advice should be included to mitigate the risk.
- The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring.
- The risk of developing antibodies to eculizumab.
- Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
- The need to explain to and ensure understanding of by patients/carers:
    - the risks of treatment with eculizumab

- the signs and symptoms of sepsis/severe infection and what action to take
- the patient's/carer's guides and their contents
- the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab
- the requirement for vaccinations/antibiotic prophylaxis

The patient's/parent's guides should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- Signs and symptoms of severe infection and the need to obtain urgent medical care.
- The patient safety card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab.
- The importance of meningococcal vaccination prior to treatment with eculizumab and/or to receive antibiotic prophylaxis.
- The need for children to be vaccinated against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion.
- Risk of serious haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations.

The patient safety card should contain:

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

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense eculizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against *Neisseria meningitidis* is needed for his/her patients on eculizumab.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not Applicable.

5. Appendix - Divergent position to the majority recommendation

DIVERGENT POSITION DATED 30 March 2023

Epysqli EMEA/H/C/006036/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation for the biosimilar Epysqli (eculizumab, reference product: Soliris) for the following indication:

Epysqli is indicated in adults and children for the treatment of:

- *Paroxysmal nocturnal haemoglobinuria (PNH)*

Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).

The reasons for divergent opinion were the following:

In study SB12-3003, treatment-emergent adverse events (TEAEs) related to breakthrough haemolysis (BTH) were reported more frequently and in more subjects in the Epysqli treatment group than in the Soliris treatment group [22 TEAEs in 8/47 (17.0%) subjects vs 3 TEAEs in 1/47 (2.1%) subject in the Soliris treatment group]. While the observed imbalance in BTH events may be partly explained by differences in the frequency of dose delays ≥17 days between treatment groups, related to local COVID-19 outbreaks, dose delays of 15 or 16 days occurred at similar frequencies between the treatment groups and are thus not considered to be a strong confounding factor. After removing BTH events due to dose delays ≥17 days, the remaining imbalance between treatment groups is still concerning [12 TEAEs in 6/47 (13%) subjects in Epysqli vs 0 TEAEs in 0/47 (0%) subjects in Soliris]. Since the marked imbalance in BTH events occurred in both study periods of this cross-over study, and even recurred upon re-challenge after unplanned IP switch back to Epysqli in one subject, it appears independent of study participant characteristics. Furthermore, all BTH events involved haemoglobinuria, which is a major symptom of PNH, and may be indicative for a true lower efficacy of Epysqli compared to Soliris. Furthermore, although the primary endpoint, LDH levels at Week 26, has formally been met, the equivalence margin of [−337.2 to 337.2] and timepoint are considered questionable and lack sound clinical justification. The primary endpoint is thus not considered to provide reassurance on similar efficacy. Moreover, the number of events of elevated LDH levels > 2 x ULN was also higher in patients on SB12 treatment, again during both treatment periods adding further support for suspected lower efficacy based on LDH level data.

The applicant has not provided a convincing alternative explanation for the observed imbalance in TEAEs of BTH and this raises major concerns about the conclusion on biosimilarity. In view of the above considerations, the undersigned delegates consider that biosimilarity of Epysqli and the reference product Soliris has not been conclusively demonstrated.

Daniela Philadelphy

Jayne Crowe