23 February 2023
EMA/114622/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bekemv

International non-proprietary name: eculizumab

Procedure No. EMEA/H/C/005652/0000

Note

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

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List of abbreviations

ABEC	area between the effect curve
AChR	anti-acetylcholine receptor
ADA/ADAs	antidrug antibody/antidrug antibodies
aHUS	atypical haemolytic uremic syndrome
ALP	alkaline phosphatase
ALQ	above upper limit of quantification
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AQP4	aquaporin-4
AR	assessment report
aRMM	additional risk minimisation measure
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	AUC from time O extrapolated to infinity
AUC_{last}	AUC from time 0 to last quantifiable concentration
AUEC	area under the effect curve
BE	bioequivalence
BLQ	below limit of quantification
BUN	blood urea nitrogen
C1q	complement component 1q
C3	complement component 3
C5	complement component 5
C_{free}	free eculizumab concentration
CH50	50% total haemolytic complement activity
CHO	Chinese hamster ovary cells
CI	confidence interval
C_{max}	maximum observed serum drug concentration
COVID-19	coronavirus disease 2019
CPU	clinical pharmacology unit
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
C_{tot}	total eculizumab concentration
CV	coefficient of variation
DMC	Data Monitoring Committee
eCRF	electronic case report form
EDTA	disodium edetate
EMAP	elastic meta-analytic-predictive
EOI/EOIs	event of interest/events of interest
EOS	end-of-study

EU	European Union
FAS	full analysis set
Fc	fragment crystallizable
FcRn	Fc Receptor
g/L	grams per litre
GCP	good clinical practice
GMP	good manufacturing practice
GLP	good laboratory practice
gMG	refractory generalised myasthenia gravis
GMR	geometric mean ratio
HFI	hereditary fructose intolerance
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin isotype class G
IgG2/4κ	IgG subclass 2/4 kappa
IP	investigational product
IQR	inter-quartile range
ISR	incurred sample reanalysis
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LLN	lower limit of human reference range
LLOQ	lower limit of quantification
LoQ	list of questions
LS	least squares
mAb	monoclonal antibody
MAP	meta analytic-predictive
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified FAS
mg/L	milligrams/L
min	minimum
MoA	mechanism/mode of action
NI	non-inferiority
NMOSD	neuromyelitis optica spectrum disorder
OC	other concern
pcVPC	prediction-corrected visual predictive check
PD	pharmacodynamic
PK	pharmacokinetic
PNH	paroxysmal nocturnal haemoglobinuria
PPC analysis set	per-protocol analysis set for the primary endpoint of AUEC for the crossover comparison

PPP analysis set	per-protocol analysis set for the primary endpoint of LDH at week 27 for the parallel comparison
PRA	PRA Health Sciences
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
QW	once weekly
R	reference
RBC	red blood cell
RC	eculizumab-target complex
R_{free}	free target concentration
R_{tot}	total target concentration
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	system organ class
T	test
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TK	toxicokinetic(s)
t_{max}	time of C_{max}
TMDD	target-mediated drug disposition
U/L	units per litre
US	United States
USPI	United States Prescribing Information
VPC	visual predictive check
WBC	white blood cell
WOCBP	woman of childbearing potential

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Technology (Ireland) Unlimited Company submitted on 3 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Bekemv, 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:

"BEKEMV 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 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 (EU)
- Marketing authorisation number: EU/1/07/393/001

According to the applicant, for Study 20150168, due to restricted distribution of eculizumab, some clinical sites used locally sourced eculizumab and some clinical sites used eculizumab centrally sourced by Amgen. In either case, only US-licensed or EEA-authorised reference medicinal product was used in the study. All Great Britain clinical sites used EEA-authorised reference medicinal product. This material was purchased in Great Britain before and after the UK withdrawal from the EU and the end of the Brexit transition period. All material sourced from Great Britain was labelled with the EMA authorisation number and is therefore EEA authorised and considered as part of an EU comparator arm.

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 application did submit a critical report, addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant received Scientific Advice from the CHMP on 22 October 2015, 23 February 2017, 07 April 2017, 20 July 2017, 15 November 2018, 26 July 2019, 14 November 2019 and 13 December 2019 pertaining to the quality, non-clinical and clinical aspects of the dossier.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	3 March 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	29 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 June 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	7 July 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 October 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 at Bio-Reliance Biotesting (Sigma-Aldrich Pte Ltd), 2 Science Park Drive, Ascent, Singapore on 09/11/2022. The outcome of the inspection carried out was issued on 15/02/2023.	09 November 2022

The CHMP and PRAC Rapporteur's Joint Assessment Report was circulated to all CHMP and PRAC members on	21 November 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	1 December 2022
The updated CHMP and PRAC Rapporteurs Joint Assessment report was circulated to all PRAC and CHMP members on	8 December 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2023
The CHMP Rapporteur circulated the CHMP Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 February 2022
The CHMP Rapporteur circulated the updated CHMP Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 February 2022
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 Bekemv on	23 February 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Paroxysmal nocturnal haemoglobinuria (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 haemoglobinuria (62%). PNH commonly results in clinically significant hematologic consequences from chronic haemolysis 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

ABP 959 (eculizumab, the proposed name Bekemv) is developed by Amgen Inc. as a biosimilar product to both Soliris-EU and Soliris-US.

Eculizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular haemolysis are blocked with eculizumab treatment.

In most PNH patients, eculizumab serum concentrations of approximately 35 micrograms/mL are sufficient for essentially complete inhibition of terminal complement-mediated intravascular haemolysis.

In PNH, chronic administration of eculizumab resulted in a rapid and sustained reduction in complement-mediated haemolytic activity.

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA25

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:

> Bekemv 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 uraemic 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. This application addresses the PNH indication, including paediatric patients and patients not yet stable on eculizumab (i.e., naïve PNH patients).

In this AR, the name ABP 959 is used for the biosimilar candidate. For the reference product, the name Soliris is used. For EU-authorised Soliris, the name Soliris-EU, and for FDA-licenced Soliris, the name Soliris-US is used.

Excipients

Unlike Soliris, Bekemv contains sorbitol (a type of carbohydrate) as one of its inactive ingredients, while Soliris does not. The function of excipient sorbitol is to provide suitable tonicity and maintain the stability of the product. However when given intravenously Sorbitol may cause serious harm in patients with HFI who lack the enzyme needed to break it down.

For this reason, doctors should exclude HFI before starting treatment. As HFI may not yet be diagnosed in children under 2 years of age) (https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-fructose-sorbitol-used-excipients-medicinal-products-human-use_en.pdf), Bekemv is also contraindicated in this population. Therefore, Bekemv is contraindicated in patients with hereditary fructose intolerance (HFI), a very rare genetic condition, and in children under 2 years of age as follows

"*BEKEMV is contraindicated in subjects with hereditary fructose intolerance (HFI). Prior to initiating treatment HFI should be excluded on age-appropriate clinical grounds (see section 4.4).*

BEKEMV is contraindicated in babies and children below 2 years of age since they may not yet be diagnosed with hereditary fructose intolerance (HFI) (see section 4.4)."

Additional risk minimisation measures have also been introduced to mitigate this risk, consisting of the following educational materials: physician's guide, patient's/parent's information brochure, and patient safety card. The target audience and planned distribution path for the controlled distribution and vaccination reminder also include pharmacists dispensing the drug in addition to prescribing physicians. The risk titled "Sorbitol exposure in patients less than 2 years of age" from RMP has been modified to appear as "Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance" in version 0.5 of the EU RMP.

2.3. Quality aspects

2.3.1. Introduction

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

Other ingredients are: acetic acid, sodium hydroxide, disodium edetate (EDTA), sorbitol (E420), polysorbate 80, water for injections.

The product is available in type I glass vial with an elastomeric stopper and an aluminium seal with flip-off cap.

2.3.2. Active Substance

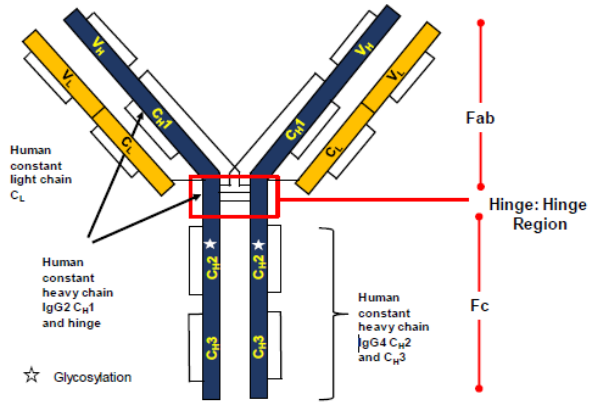
2.3.2.1. General information

The active substance (AS) eculizumab (also referend in this report as ABP 959) is a recombinant humanised monoclonal antibody of the immunoglobulin isotype class G 2/4 (IgG2/4) subclass, that binds to human complement component 5 (referred to C5) with high affinity and inhibits its cleavage, thereby blocking pro-inflammatory and cytolytic effects of terminal complement activation. Activation of the complement protein C5 by C5 convertase initiates the spontaneous assembly of the late complement components, C5b-C9, into a structure known as the membrane attack complex (MAC), or terminal complement complex (TCC), which is the final step in the complement cascade.

ABP 959 is expressed in a Chinese Hamster Ovary (CHO) cell line. ABP 959 contains 36 total cysteine residues, which are involved in both intra-chain and inter-chain disulfide bonds. Each heavy chain contains 448 amino acids with 4 intra-chain disulfides. Each light chain contains 214 amino acids with 2 intra-chain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 298.

A schematic depiction of the ABP 959 molecule displaying the most prominent disulfide mediated structural isoform (IgG2-B) is shown in *Figure 1*, including the antigen-binding fragment (Fab), hinge, and fragment crystallizable (Fc) regions, the expected IgG2 disulfide bonding pattern, and the glycosylation sites observed for ABP 959.

Figure 1 A schematic depiction of the ABP 959 molecule



The theoretical mass is 144 981 Da. The predominant glycan moiety is A2G0F, thus, the theoretical mass of glycosylated ABP 959 containing 2 predominant glycans (1 A2G0F per heavy chain) is 147 869 Da.

ABP 959 has been developed as a biosimilar to the reference product Soliris, originally approved in the EU in June 2007 (EMEA/H/C/000791).

2.3.2.1. Manufacture, characterisation and process controls

Description of manufacturing process and process controls
ABP 959 is produced at Amgen Singapore Manufacturing (ASM). The respective GMP certificates are included in dossier.

The process steps follow a standard monoclonal antibody platform technology. Upstream process consists of several cell expansion steps and a harvest step In the downstream process the harvested cell culture fluid is purified using a series of chromatography purification steps.. All manufacturing steps are adequately described and flow-charts with process controls are provided, including critical input process parameters and critical in-process tests.

Control of materials
Information on the source of the cell substrate and analysis of the expression construct used to develop the Master Cell Bank (MCB) and Working Cell Bank (WCB) is adequately described. Chinese hamster ovary cells were used to generate the transfected cell line. The ABP 959 amino acid sequence was derived from publicly available information on the amino acid sequence of Soliris (eculizumab). The synthesised DNA was then inserted into an expression vector pDC323 to generate the eculizumab expression plasmids, separately for heavy and light chain. Origin and function of expression vector components are adequately described, and sequences of heavy and light chains are provided. Production of the active substance during development and creation of MCB and WCB utilises selection process of single cell clone, which is described adequately.

A common two-tiered cell banking system consisting of a Master Cell Bank and Working Cell Bank, is used. The genetic stability of the production cell line is demonstrated. The presented protocol for the qualification of future working cell banks is acceptable. Overall, the cell banking system, including characterisation and testing is adequately described and in line with ICH Q5D.

Constituents of the culture medium are described in satisfactory detail. No raw materials of animal origin are used in the manufacturing process.

Control of critical steps and intermediates
Critical parameters controlled by in-process controls (IPCs) include quality related testing for glycosylation and fragmentation, pH, osmolality, host cell protein (HCP), polysorbate and protein concentration. Safety/microbiological related critical controls include parameters such as Mycoplasma, adventitious virus, pH, filter integrity, bioburden and endotoxin. The applicant has explained the criteria for the choice of the criticality of a process parameter and control. In the process design studies, the applicant has explained the establishment of the acceptable process parameter ranges. Relevant process parameters are set to control the manufacturing process. Process validation studies support the established process parameters.

Process validation and/or verification
Process validation data from commercial scale batches is provided. The established process parameters and process indicators met the predetermined criteria. The process validation results support the control strategy and demonstrate that the manufacturing process is able to produce AS with desired quality.

Small-scale characterisation studies were conducted to evaluate the chemical stability of in-process product pools utilising commercial analytical methods. According to these studies, hold times were set and are considered acceptable.

Reprocessing at the AS filtration step has been validated. Reprocessing is conducted in the same manner as the original AS filtration using a new filter. Description of conditions for which reprocessing could be applied

and data to demonstrate demonstration that the reprocessing step does not impact on the quality of the active substance is provided and thus, reprocessing considered acceptable.

Filter validation studies were conducted both by the filter provider and by the applicant; it can be concluded based on the provided information that the filter can be regarded suitable for its intended use and the filter do not decrease the quality of the finished product (FP).

Validation was performed and is ongoing to demonstrate the effectiveness and chromatography performance over the lifetime of the resins. The lifetime of the membranes is validated and the approaches are acceptable.

Concerning the transportation of AS, the company has qualified insulated shipping containers comprised of various sizes and durations. A short summary of the qualification programme is provided in the dossier. Based on provided results, the transportation of the AS can be performed without impact to product quality during validated period at controlled conditions.

Manufacturing process development
ABP 959 was initially manufactured at the Amgen process development facility (. The AS manufacturing process was subsequently transferred to the clinical manufacturing facility (to generate lots to support the pharmacokinetic/pharmacodynamic (PK/PD) similarity Study 20150164.

To enable long-term frozen storage and to facilitate future development, the AS formulation was changed to a different protein concentration and the manufacturing process was subsequently transferred to ATO CMF to generate lots to support the clinical similarity Study 20150168.

The AS manufacturing process was transferred to Amgen Singapore Manufacturing (ASM) for commercial manufacturing. Comparability assessments included lots manufactured at the proposed commercial scale i.e. 2000 L scale. Phase- and risk-based comparability evaluations were performed as appropriate to support manufacturing changes. The development of the manufacturing process and the comparability studies conducted are adequately described. The applicant has performed comparability studies concerning manufacturing site and formulation changes. Overall, comparability between manufacturing sites and composition change is adequately performed and acceptable.

Characterisation
Characterisation studies were performed using commercial scale and process active substance material or FP material. Both the AS and FP lots were in the final commercial formulation. The clinical representativeness (material used in characterisation vs. clinical material) was shown. Characterisation results includes determination of structure (primary, secondary, and higher-order), glycosylation (N- and O-linked glycans), disulfide structure, charge variants, size variants and hydrophobic variants. Biological characterisation of ABP 959 was conducted to assess the structure-function properties of the molecule. These included demonstration of the mechanism of action, assessment of Fc functionality, and assessment of the *in vitro* biological activity of stressed ABP 959 and product variants. Overall, the performed characterisation studies are considered relevant and cover a wide variety of physicochemical and biological characterisation studies. Justification of the identification and classification of the product-related impurities can be agreed.

Impurities
Product-related impurities/substances as well as process-related impurities have been identified. Impurities are characterised at sufficient level. Biological activities of the product-related impurities/substances and safety aspects were discussed.

Process-related impurities (host cell proteins (HCP), DNA, residual protein A and process reagents) were observed in low levels and the presented data demonstrate that the manufacturing process for commercial production is able to clear process-related impurities to acceptable levels.

Control of mycoplasma and adventitious viruses were assessed in section A.2. Adventitious agents safety evaluation.

Elemental impurities and potential risk of nitrosamines were assessed in the finished product part of the dossier.

Container closure system
The AS container closure system (CCS) is a bag with associated lines and has been adequately described.. Sterility is according to ISO 11137. The specification and a representative certificate of analysis are available. Integrity of the CCS was confirmed by microbial aerosol challenge test.

The applicant has performed various pharmacopoeial tests for the container closure system including biological reactivity, physicochemical tests, bacterial endotoxins, particulates and sterility. Test results comply with the limits. Additionally, the applicant has performed extractables and leachables studies. the levels are below the permitted daily exposure (PDE) for both extractables and leachables; all leachables were below the concentration of toxicological concern.
In summary, the CCS is considered suitable and the presented information adequate.

2.3.2.2. Specification

The AS release and shelf life specifications presented in Table 1, include tests for physical characteristics (physical appearance, colour), identity (immunoassay), purity and impurities (SE-UHPLC, HCP), adventitious agents (bacterial endotoxins, bioburden) and potency (bioassay).

The end-of-shelf-life specification is identical to the release specification, except for certain parameters which have been justified sufficiently as not necessary for end of shelf life. The acceptance criteria have been established based on product-specific knowledge and release/stability data that have been used in development, clinical, process validation, stability and comparability studies. Batch analysis results from AS lots used in clinical studies (meet the current commercial specification results and thus are considered representative for setting specifications and clinically justified. The applicant applied a statistical analysis to estimate ranges (tolerance intervals) that was considered acceptable.

Overall, the set of quality attributes tested at release and at shelf-life complies with ICH Q6B and are acceptable.

Analytical procedures
For the in-house methods, system suitability and sample acceptance criteria (SE-HPLC, HCP-ELISA, potency, bioburden) are provided, relevant reagents and equipment listed and representative chromatograms (SE-HPLC/HMW, UHPLC/Glycan map) provided. Overall, the used analytical methods are adequately described. Validation of the analytical procedures are adequately performed. For the potency testing an enzyme-linked immunosorbent assay (ELISA) format is used..

Reference standards
The reference standards used during the product development to routine batch release use have been adequately described. A two-tiered reference standard system is used for commercial manufacturing including primary reference standard (PRS) and working reference standards (WRS). The WRS is used for

routine lot release and stability testing. A protocol for qualification of future reference standard is presented. The protocol is found acceptable.

Batch analyses
Batch analyses data were presented for batches manufactured with the PBS formulation (development, clinical and stability studies), and for batches manufactured with the sorbitol formulation (development, clinical and stability studies). All results comply with the specifications valid at time of testing and also comply with the current valid specifications

2.3.2.3. Stability

The applicant proposed a shelf life of 48 months for ABP 959 stored at the recommended storage condition of -30°C.

Real time stability data for 48 months at -30°C is provided for three batches with the current proposed sorbitol formulation. For the same batches, also stability data for 6 months at 5°C and for 3 months at 25°C is provided. Additionally, stability data up to 24 months is provided for one batch for the same conditions as for the 3 batches. For the commercial production site ASM (Amgen Singapore) 18 months data is provided for all three storage conditions. Stability study results are ready and available for all sites at storage conditions 5°C and at 25°C.

The container closure system used for the primary stability batches are smaller but otherwise identical to the container closure system used during commercial manufacturing. Comparability between different AS manufacturing sites has been shown. The test methods and acceptance criteria used during clinical development for the supporting, primary, and production lot stability studies are same as presented and validated (sections S.4.2 and S.4.3). Specifications used for the initial evaluation of the proposed shelf life differ slightly from the proposed commercial specifications, but were later confirmed with the current proposed commercial specifications.

All samples stored at the recommended storage condition (-30°C) met the stability acceptance criteria. At accelerated conditions, moderate changes in parameters were detected. Based on the presented stability study results, the proposed shelf-life with storage conditions can be approved. Overall, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months years when stored at -30 ºC.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Bekemv is a sterile, single-use, preservative-free concentrate for solution for infusion that is clear to opalescent and colourless to slightly yellow, intended for dilution prior to intravenous infusion, containing 300 mg eculizumab. The FP is supplied in a glass vial with elastomeric stopper, and aluminium seal with flip-off cap. Each vial contains a 30 mL deliverable volume of 10 mg/mL eculizumab (ABP 959) formulated in 10 mM acetate, 0.05 mM disodium edetate (EDTA), 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 80 at pH 5.2.

References to quality standards (Ph.Eur , USP or NF) have been provided for excipients. ABP 959 (in contrast to the reference product) contains sorbitol. The use of the specific excipient is acceptable from a quality point of view. However due to safety considerations in relation to patients with hereditary fructose intolerance

(HFI) the CHMP recommended that the applicant should explore the possibility of developing a new sorbitol-free formulation (REC). The safety issue related to sorbitol-content and especially the paediatric population is discussed in the Clinical safety section.

Three formulations were used during product development, these include a phosphate buffered saline (PBS) formulation, a sorbitol formulation and the commercial sorbitol+EDTA formulation. The FP is produced by dilution of the 90 mg/ml AS to 10 mg/ml with a formulation buffer consisting of acetate, EDTA , sorbitol, and polysorbate 80 at pH 5.2.

PBS and sorbitol formulations have been used in Phase 1 clinical study, the non-clinical and phase 3 clinical study was conducted using the sorbitol formulation.

The commercial Sorbitol+EDTA formulation used in development, process validation and stability studies, but not in clinical studies. Adequate comparability studies have been performed between sorbitol and sorbitol+EDTA formulations. The studies have included batch analytical data, additional characterisation and forced degradation studies of four pre- and two post-change lots manufactured at ATO. Based on the presented results the FP formulated with sorbitol+EDTA has a similar or improved stability profile compared to the sorbitol only formulation.

Comprehensive process characterisation studies have been conducted to evaluate the robustness of the manufacturing process. The studies demonstrate that the manufacturing process is under control and can deliver the required product quality and process consistency when operated within acceptable ranges.

The presented studies of batch analytical results, additional characterisation and forced degradation study data are considered sufficient to support comparability of the FP sorbitol and sorbitol+EDTA formulations.

A process design approach has been used to develop the FP manufacturing process. This was based on prior knowledge, data of reference product including other mAb manufacturing processes experience, ABP 959 process development studies and the results of process risk assessments. The FP manufacturing process is controlled by process parameters, in-process controls (IPCs), release specifications, and periodic testing controls of the AS and FP (e.g. validation, comparability and stability). The control strategy is based on knowledge of product quality attributes (PQAs), quality risk management used to identify potential risks to patients and a subset of PQAs identified as critical quality attributes (CQA).

The development manufacturing process of FP, selected formulation and container closure system has been justified and sufficiently described.

The compatibility of the ABP 959 FP with commonly used PVC and polyolefin IV bags, infusion systems and solutions (0.9% sodium chloride, 5% dextrose and Ringer's solution) has been studied at different temperatures (room temperature +5°C and +30°C). ABP 959 FP remained stable, however, more particles (>10 µm) were detected in PVC IV bag of ABP 959 FP stored in 0.9% sodium chloride and in Ringer's solution in comparison to polyolefin IV bag at room temperature and +30°C. ABP 959 in 5% dextrose showed similar particulation in both PVC and polyolefin IV bags. ABP 959 in 5% dextrose showed similar low particulation in both PVC and polyolefin IV bags. The detected particle increase, related to infusion solutions used for dilution, infusion bags and catheters remain at acceptable levels in accordance with USP and Ph. Eur. limits.

The FP is supplied in a 30 cc Type I glass vial, elastomeric stopper, and aluminium seal with flip-off cap. A full description of the container closure components including representative drawings are presented in the dossier. The vial and stoppers are in compliant with the Ph. Eur. Inorganic and organic extractables have been analysed against acceptable exposure level, the presented results for the leachables and extractables

meet the specifications. Container closure integrity has been demonstrated by vacuum decay method. From the quality point of view the container closure is considered suitable.

2.3.3.2. Manufacture of the product and process controls

The FP is manufactured by Amgen Ireland (ADL). The same site performs, packaging, labelling and batch release testing, with the exception of Belgium and Luxembourg markets where the release testing is performed by Amgen Belgium (NV). During the procedure a major objection was raised concerning the GMP status of ASM which was resolved by provision of a valid GMP certificate; valid GMP certificates have been presented for all other FP manufacturing and testing facilities.

The FP manufacturing process includes preparation of formulation buffer, AS thaw, FP formulation, bioburden reduction filtration, filtered formulated FP hold, sterile filtration, filling and stoppering, capping, inspection, and storage. The process steps have been described with sufficient detail and the batch formula has been clearly presented.

The process steps are controlled by process parameters and in-process testing. Process parameters with limits are presented for each step. In-process control testing with action limits is used for monitoring of the manufacturing process to ensure that FP will conform to its specifications. IPCs which should be controlled within a defined range to ensure finished product quality are designated as critical. Critical in-process controls with action limits have been set for formulation, bioburden reduction filtration and sterile filtration with action limits. In addition to IPCs, some in-process tests have been designated as real time release testing (RTRT) i.e. testing performed in-process that is listed on the specification and has an acceptance criterion. Real time release testing and limits are presented for protein concentration, osmolality, pH, polysorbate 80 concentration, volume and appearance. Protein concentration in the FP is analysed by RTRT during formulation step. Down-stream process includes several filtration steps that could indirectly react with active substance and reduce the concentration of FP. The provided studies show that there was no meaningful difference in the protein concentration between the formulation step and the release testing of filled vials. Process parameters and acceptance criteria set are overall adequately justified by validation studies.

The RTRT parameters, methods and limits were presented. The process parameters and acceptance criteria set are overall adequately justified by validation studies.

The FP manufacturing process has been successfully validated at the commercial site. Validation has included steps for formulation, filtration, filling, stoppering, capping, inspection, and storage for the vial presentation. All validation batches met the release results of the proposed commercial specification acceptance criteria. The proposed batch size range has been successfully validated, demonstrating consistency and reliability of the manufacturing process. Sufficient information is provided on filter validation and media fills. Validation has included membrane compatibility, microbial retention, and extractable substance determination.

The microbial control strategy and chemical stability data have been discussed to support the proposed AS post-thaw hold time.

Shipping validation is supported by three studies, shipping container qualification, post-transport verification of maintaining of product quality and monitoring of the transport route, duration and thermal performance. The shipping validation results confirm that the product quality is maintained.

2.3.3.3. Product specification

The finished product release and shelf-life specifications, includes tests for physical characteristics (physical appearance, colour, clarity), identity (immunoassay), purity and impurities (SE-UHPLC, HCP, (AEX-HPLC, rCE-SDS and HIC-HPLC), adventitious agents (bacterial endotoxins, closure integrity, sterility) and potency (bioassay), protein concentration (Ph. Eur.), pH (Ph. Eur.), osmolality(Ph. Eur.), subvisible particles (Ph. Eur.), Polysorbate 80 (UV), EDTA (chromatography) and volume (Ph. Eur.).

A sufficient panel of quality attributes is proposed for release and shelf-life specifications. The specifications of FP include the same parameters, analytical tests and acceptance criteria as AS specifications with additional tests of FP for clarity, purity and impurities, sterility, closure integrity, protein concentration, pH, osmolality, subvisible particles, Polysorbate 80 and volume.

Separate limits are proposed at release and shelf-life for all the purity tests included in the FP specifications document. The proposed limits for the purity tests are found clinically qualified and supported by batch data for ABP 959 and/or by means of Soliris.

As requested, the EDTA concentration has been added to the FP specifications as a real-time release test. The FP specifications have for most parts remained similar for FP batches manufactured at ATO and ADL.

Real time release testing is performed for protein concentration, osmolality, pH, Polysorbate 80 concentration, volume and appearance. EDTA concentration, bioburden and filter integrity and volume are critical in-process controls.

The non-compendial analytical methods for identity (ABP 959 ID ELISA), purity & impurities (AEX-HPLC, SE-UHPLC), rCE-SDS, HIC-HPLC, container closure integrity), potency (inhibition of TCC formation assay), general methods (Polysorbate 80) and EDTA were presented and have been validated in accordance with the ICH Q2 Guideline. Summary of validation of non-compendial analytical methods are presented in the dossier.

The compendial methods have been verified according to the appropriate Ph. Eur. chapters and determined to be suitable for use. The presented batch analysis data show that the FP process does not result in any additional impurities. In addition, AS and FP lots are monitored during shelf life for product-related impurities.

The risk of elemental impurities in the finished product is low and meets the threshold outlined in the ICH Q3D guideline. No further actions or additional controls are required. The conclusions of the applicant are based on the totality of the following evidence and are endorsed.

Risk assessment has been performed to rule out elemental and nitrosamine impurities of FP covering manufacturing process and equipment, excipients (USP, NF, and/or PhEur), container closure system and risk of oxidation. The absence of the masking effect over time for the FP was demonstrated. The principles outlined in the "Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004" (EMA/369136/2020)" were applied in the risk assessment. In conclusion, no significant risk of nitrosamine impurities has been identified for ABP 959 finished product and therefore, no additional control measures are deemed necessary.

Batch analytical data has been provided for lots manufactured. All lots met the acceptance criteria in place at the time of release. The provided results indicate that the manufacturing process is under control and the changes made in the manufacturing processes have not affected on the quality of the FP.

2.3.3.4. Stability of the product

A shelf life of 36 months has been proposed for Bekemv stored at the recommended storage condition of 5°C.

Stability data were presented for FP stored at long-term (5±3°C), accelerated (25±2°C, 30±2°C and 30±2°C/ 60% to 70%) and at stressed conditions (40±2°C) for maximum of 48, 6 and 3 months respectively.

Real-time data of 30 and 24 months at the long-term condition are currently available for Sorbitol+EDTA FP batches. Stability data of 3 months are presented for commercial Sorbitol+EDTA batches. Long-term stability studies show that the FP is stable at the proposed storage conditions. Supporting data of 48 months is presented for Sorbitol formulation. The applicant commits to continue the ongoing stability studies described in 3.2.P.8.1 until completion.

FP stability studies were conducted in accordance with ICH Q5C and Q1A. Adequate stability indicating test methods, acceptance criteria and studies are presented in the dossier. The parameters and test methods of stability studies are a sub-set of the FP specifications.

In addition, forced degradation, photostability (as per ICH Q1B) and transportation studies have been performed. The photostability studies demonstrated that the secondary packaging effectively protects the FP from degradation. No meaningful differences were observed for any of the tested parameters under either ICH or clinical lighting conditions.

Studies were performed to evaluate compatibility during dilution for infusion and storage in polyvinyl chloride and polyolefin IV bags, and a second study was conducted to evaluate compatibility during infusion over the intended duration using common IV administration components and equipment (infusion sets, heparin locks, catheters, and infusion pump). The conclusions of these studies are reflected in section 6.3 of the SmPC.

Formulation robustness and transport studies have been performed to show the effectiveness of polysorbate 80 to prevent the formation of particles during stress and long term stability studies. Visible and subvisible particle results remained within the specification acceptance criteria through the proposed shelf life of 36 months at the recommended (5 °C). In addition, no trend has been observed in the subvisible particles results at the recommended (5 °C), accelerated (25 °C or 30 °C), or stressed (40 °C) storage conditions. Based on these studies "BEKEMV vials in the original package may be removed from refrigerated storage for only one single period of up to 7 days. At the end of this period the product can be put back in the refrigerator" (SmPC 6.4).

Based on available stability data, the proposed shelf-life of 3 years with the storage conditions "*Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light."* as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.3.3.5. Biosimilarity

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. The strength, dosage form, dosing regimens, and route of administration of ABP 959 are the same as for the reference medicinal product. The analytical similarity assessment consists of 3 pairwise comparisons including Bekemv to Soliris-EU, Bekemv to Soliris-US, and Soliris-EU to Soliris-US. The FP material used in the analytical biosimilarity studies is considered

representative of the material used in clinical trials. . The statistical approach chosen by the applicant to analyse similarity assessment is endorsed. Tabular and graphical presentation allows for a clear comparison of Bekemv to Soliris-EU and Soliris-US. In addition, sufficient raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen.

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, and general properties including protein concentration and volume. In addition, stressed and accelerated stability studies as well as photodegradation studies were performed between Bekemv and Soliris-EU.

Similarity between Bekemv, Soliris-EU and Soliris-US has been demonstrated for the following physicochemical and biological properties:

- Primary structure
- high order structure
- Particles and aggregates
- product-related substances and impurities
- Thermal stability and degradation studies (ABP 959 and Soliris-EU)
- General properties including protein concentration and volume
- Inhibition of TCC formation assay (Potency)
- Inhibition of haemolysis bioassay
- Relative binding to C5
- C5 binding kinetics and affinity
- Lack of binding to C3
- Neonatal Fc Receptor (FcRn) Binding by AlphaScreen

The attributes and analytical techniques used in the analytical similarity assessment are shown in Table 1.

Table 1 Attributes and analytical techniques used in the analytical similarity assessment

Molecular parameter	Attribute	Methods	Key findings, conclusions
Primary structure	Intact Mass	ESI-TOF-MS	The mass of LC and HC were similar for the 2 products. Amino acid sequence coverage was confirmed to be 100 %, and the amino acid sequence of ABP 959 was confirmed to be identical to the sequence of EU-approved Soliris Both products have the same post-translational modifications at similar levels Overall, similarity in terms of primary structure was demonstrated.
	Amino acid sequence	Peptide mapping LC-MS/MS	
	Post-translational modifications		
Higher order structure	Secondary and tertiary structure	Far/Near UV CD, DSC	Secondary and tertiary structure appear comparable.
Content	Protein content	OD280	ABP 959 and EU-approved Soliris are similar in their protein concentration.
	Extinction coefficient	Amino acid analysis	
Charged variants	Basic species, acidic species	AEX-HPLC	Minor differences between ABP 959 and EU approved Soliris were noted in the relative proportion of the charge variants. However,

	and main variants	Isolated fractions were further characterised via peptide map, SE-UHPLC, CE-SDS (reduced /nonreduced), HILIC, RP-HPLC, of TCC formation assay (potency) and inhibition of haemolysis bioassay	based on the characterisation results presented, it can be concluded that the slight differences observed in charge variants are clinically insignificant. All variants are biologically active. The applicant has appropriately discussed and justified the differences detected in ABP 959 and EU-approved Soliris to support the similarity.
Glycation and glycosylation	Oligosaccharide profile (afucosylation, high mannose variants, galactosylation, sialylation)	HILIC -HPLC	ABP 959 was shown to have minor differences in afucosylation, galactosylation and sialylation levels compared to EU-approved Soliris, but it has been sufficiently justified that these differences are highly unlikely to be of clinical relevance.

Minor differences in the levels of post-translational modifications, relative proportion of the charge variants, individual glycan species, levels of glycation, and levels of monomer, HMW, LMW, HC+LC and were sufficiently justified to have no clinical impact.

Overall, appropriate analytical methods have been utilised to ensure an understanding of the Soliris-EU and Soliris-US product profiles and the developed Bekemv product. In conclusion, the presented biological and physiochemical data support the claim of biosimilarity for Bekemv.

The applicant informed that six of the 42 subjects in the clinical efficacy/safety trial were enrolled at clinical sites in Great Britain using locally-sourced finished product. Batches were purchased for the study 20150168 UK clinical sites during/after the end of the Brexit period. All but one of these batches were manufactured prior to the end of the transition period. According to the applicant, the origin of the shipment, i.e. the country originating the shipment to the clinical site, is Ireland while the clinical site receiving and dosing the batch is UK. Furthermore, all batches used in the UK clinical sites after 31 December 2020 were labelled with the EMA authorisation number.

The applicant has provided analytical and functional bridging data between EU-Soliris and the batches used at the UK clinical site after the end of the Brexit transition period. Based on the results it can be concluded that analytical and functional bridging between EU-Soliris and the Soliris batches used at the UK clinical site has been demonstrated.

Overall the FP material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials. The approach chosen to analyse similarity assessment is endorsed. ABP 959 is considered to be highly similar to EU-approved and US-approved eculizumab with respect to the presented physicochemical and biological characterisations. In addition, in the context of a global development, acceptable bridging between US-approved eculizumab and the EU reference medicinal product has been presented, supporting the use of both US-approved eculizumab and EU approved eculizumab in the clinical trials. In conclusion, it is considered that biosimilarity of Bekemv to the reference product Soliris has been sufficiently demonstrated.

2.3.3.6. Adventitious agents

None of the materials used in the manufacturing process contain any material human or animal origin. There is no risk form Transmissible Spongiform Encephalopathy (TSE) or viral contamination.

Viral clearance studies have been conducted in accordance with the guidance given in ICH Q5A, as well as in other relevant guidelines. Four model viruses have been chosen for the studies: XMuLV (enveloped RNA retrovirus), MMV (non-enveloped RNA parvovirus), Reo-3 (non-enveloped RNA reovirus) and PrV (enveloped DNA herpesvirus). The selected viruses cover adequate range of properties, including size, genome, and resistance to low pH inactivation. The choice of model viruses is considered appropriate. Four process steps have been assessed using qualified small-scale models operating under worst-case conditions,. The small-scale models have been described in the dossier and are qualified. The feed material used in the small-scale viral clearance studies was obtained from lots that are representative of the AS process at the commercial site (ASM). Lifetime of chromatography resins for viral clearance capacity has been evaluated for new and used resins.

The risk of microbial and mycoplasma contamination is adequately addressed. MCB, WCB, and (limit of *in vitro* cell age) LIVCA are sterile and free of mycoplasma, and tested unprocessed bulk batches showed very low bioburden of zero CFU/mL. Finally, the assessment of TSE risk has been performed on all raw materials used to produce ABP 959, from transfection of the cell line through fill and finish of the FP. The manufacturing process uses no excipients, cell culture media, or purification material of animal origin

Acceptable assessment of TSE risk has been performed on cell line and raw materials used to produce AS and FP. No excipients, cell culture media components, or purification resins containing animal material are used during manufacture.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

In general, the active substance part of the dossier is of good quality. An MO raised concerning the GMP status of a testing site has been resolved by provision of a valid GMP certificate.

Information on development, manufacture and control of the finished product have been presented in an appropriate manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics. Overall, the available quality data support biosimilarity versus EU-approved Soliris. The safety issue related to sorbitol-content is discussed in the Clinical safety section.

At the time of the CHMP opinion, there were a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the sorbitol-content. This point is put forward and agreed as recommendations for future quality development.

2.3.5. 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.

2.3.6. 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 should explore the possibility of developing a new formulation without sorbitol.

2.4. Non-clinical aspects

2.4.1. Introduction

The active substance of ABP 959 and Soliris is eculizumab, a humanised recombinant immunoglobulin isotype class G subclass 2/4 kappa monoclonal antibody (IgG2/4K mAb). Eculizumab binds to human complement component 5 (C5) and prevents its cleavage into C5a and C5b, thereby blocking the generation of the terminal complement complex and cell lysis.

ABP 959 is expressed in a Chinese hamster ovary cells (CHO) and Soliris in a murine myeloma cells.

The demonstration of biosimilarity of ABP 959 to Soliris-EU is based on the totality of evidence data of analytical, nonclinical, and clinical comparative studies to demonstrate structural and functional similarity. A single-dose pharmacokinetic (PK)/pharmacodynamic (PD) similarity study in healthy adult male subjects (Study 20150164) have been conducted as well as a randomised, double-blind, active-controlled, 2-period crossover comparative clinical study in adult subjects with PNH (Study 20150168).

The nonclinical data package consisted of *in vitro* biofunctional assays,– Biological Activity, and *ex vivo* pharmacology characterisation studies in human serum to support a demonstration of similar inhibition of the complement pathway (relevant to the mechanism of action) by ABP 959 and the Soliris-US and Soliris-EU.

No comparative *in vivo* pharmacology, PK/toxicokinetic, or toxicology studies were conducted. There were no residual uncertainties identified that needed to be resolved by additional nonclinical pharmacology, PK/TK, or toxicology studies.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The biological activities of ABP 959 and Soliris-EU were evaluated with *in vitro* and *ex vivo* assays relevant to MoA of eculizumab. The similarity assessment consisted of 3 pairwise comparisons ABP 959, Soliris-EU and Soliris-US.

In vitro studies

Fab-mediated biological activity analyses included inhibition of terminal complement complex (TCC) formation, inhibition of haemolysis, binding affinity and kinetics to component 5 (C5). Binding specificity i.e., lack of binding to other complement factors, was demonstrated to component 3 (C3) and to first subcomponent of the C1-complex of the classical pathway of complement activation (C1q).

Eculizumab is an IgG2/4, therefore lacks or has low level of binding to FcγRs and thus a lack of effector functions is expected. Binding (or lack of) to FcγR type Ia, IIa, IIb, IIIa and IIIb, and to FcRn was similar with

APB 959 and Soliris-EU. No ADCC, CDC or ADCP assays were conducted, and are not required. Fc-mediated functions in general are not considered to mediate the pharmacological action of eculizumab.

In general, the functional data indicate that the ABP 959 and Soliris-EU (and US-sourced) are similar. Biological activities relevant to the primary mechanism of action including inhibition of TCC formation, inhibition of haemolysis, C5 binding -, binding kinetics and affinity to human C5, and binding specificity are similar. To conclude, Fab-mediated biological activity analyses indicated similar inhibition of TCC formation and haemolysis, and relative binding activity to C5 for ABP 959 and Soliris-EU. Binding specificity, i.e., lack of binding to C3 was demonstrated, and to first subcomponent of the C1-complex of the classical pathway of complement activation (C1q). Binding to FcRn was similar for ABP 959 and Soliris-EU.

Ex vivo haemolytic studies

Comparative pharmacology *ex vivo* haemolytic studies included evaluation of the classical pathway (CH) and alternative pathway (AH) using ABP 959 or Soliris-EU or Soliris-US. Studies were conducted to evaluate the ability of ABP 959 and Soliris (EU and US) to inhibit complement pathways in models of various physiological and pathophysiological conditions in clinically relevant assays.

Comparative *ex vivo* haemolytic studies evaluating the inhibition of classical and alternative pathways in human serum indicated similar inhibition potency of ABP 959, Soliris-US and Soliris-EU.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed.

2.4.2.3. 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.

2.4.2.4. 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.

2.4.3. Pharmacokinetics

Comparative i*n vivo* pharmacokinetic (PK)/toxicokinetic studies with ABP 959 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.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single-dose toxicity studies were not conducted given the lack of a pharmacologically relevant species and is also in alignment with regulatory guidance for biosimilar development.

2.4.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were not conducted (same ground applies as stated under 2.4.4.1).

2.4.4.3. Genotoxicity

Genotoxicity studies were not conducted in alignment with regulatory guidance for biosimilar and biotechnology-derived pharmaceutical development.

2.4.4.4. Carcinogenicity

Carcinogenicity studies were not conducted in alignment with regulatory guidance for biosimilar and biotechnology-derived pharmaceutical development.

2.4.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies were not conducted in alignment with regulatory guidance for biosimilar development Eculizumab has same mode of action in children and in adults, and no studies are required for this biosimilar MAA in addition to already existing data on approved Soliris-EU.

2.4.4.6. Toxicokinetic data

Not applicable.

2.4.4.7. Local tolerance

Local tolerance studies were not conducted in alignment with regulatory guidance for biosimilar development.

2.4.4.8. Other toxicity studies

Toxicology Assessment of Excipients in the ABP 959 Commercial Drug Formulation

ABP 959 has the same dosage form, route of administration and product strength as the reference product, Soliris-EU; it is formulated with different compendial excipients that include acetate, sorbitol and disodium edetate. Both the ABP 959 commercial formulation and Soliris-EU contain polysorbate 80, but at different concentrations. The differences in excipients between ABP 959 and Soliris do not represent a safety concern or raise uncertainties regarding similarity. None of the ABP 959 formulation excipients are novel. ABP 959 is formulated with well-known, compendial excipients that have been administered by the same route of

administration (IV) at higher dose levels in other drugs approved for use in adult and paediatric populations in the EU (and US).

2.4.5. Ecotoxicity/environmental risk assessment

The active substance (ABP 959, eculizumab) is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ABP 959 is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

The nonclinical data package was focused on comprehensive *in vitro* and *ex vivo* functional activity analyses relevant for eculizumab MoA. No *in vivo* pharmacology, PK/TK, or toxicology studies were conducted and are not generally required for a biosimilar for the approval of the marketing authorisation within EU. This approach was also agreed by CHMP Scientific Advice (given during 2015, Procedure No. EMEA/H/SA/3164/ 1/2015/III).

The *in vitro* data is only shortly summarised under nonclinical aspects. ABP 959 differs from Soliris-EU regarding the formulation and cell-line, in which the DS is produced (CHO in ABP 959, NS0 in Soliris-EU). The functional comparative data demonstrated that inhibition of TCC formation and haemolysis, binding kinetics and affinity to human C5, binding specificity (i.e., lack of binding to other complement factors C3, C1q) and binding to FcRn are similar for ABP 959 and Soliris. Furthermore, binding (or lack of) to Fc-R type Ia, IIa, IIb, IIIa and IIIb was similar. Similar inhibition potency for alternative pathway and classical pathway was demonstrated for ABP 959 and Soliris-EU *ex vivo*.

ABP 959 three formulations PBS, sorbitol, and sorbitol with EDTA (which is intended formulation for registration) have all been included in the *in vitro* functional comparative programme. *Ex vivo* studies were done in sorbitol formulation. The formulation changes are not expected to impact the clinical performance of ABP 959. ABP 959 contains following changes in the formulation in excipients in comparison to Soliris-EU; sorbitol, PS80, EDTA and acetate. None of these excipients are novel and have been used in other registered products in EU, administered same route (IV) and are not exceeding the amounts in medicinal products approved for IV-treatment of adult and paediatric patients. The safety of EDTA and sorbitol was adequately clarified. Due to the high sorbitol content of the product, a contraindication was added for subjects with hereditary fructose intolerance.

The active substance (ABP 959, eculizumab) is a natural substance (protein), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ABP 959 is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The nonclinical *in vitro* and *ex vivo* functional activity data support the biosimilarity of ABP 959 versus the Soliris-EU (and Soliris-US).

2.5. Clinical aspects

2.5.1. 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**

Clinical studies supporting this MAA for ABP 959 include a completed randomised, double-blind, 3-arm, parallel group, single-dose PK/PD similarity study in healthy adult male subjects (Study 20150164) and a completed randomised, double-blind, active-controlled, 2-period crossover comparative clinical study in adult subjects with PNH (Study 20150168).

Table 2 Listing of clinical studies

Type of Study	Study Identifier Protocol No.	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	Number of Subjects Randomized/ Number of Subjects Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Study Duration[b]	Study Status; Type of Report/Location
Study Reports of Healthy Subject Pharmacokinetic and Initial Tolerability								
PK/PD similarity	20150164	Primary: PK similarity of ABP 959 relative to eculizumab (US) and to eculizumab (EU); PK similarity of eculizumab (US) relative to eculizumab (EU); PD similarity of ABP 959 relative to eculizumab (US) and to eculizumab (EU) Secondary: Safety, tolerability, and immunogenicity	Randomized, double-blind, single-dose, 3-arm, parallel group, stratified by CPU and ethnicity (Japanese vs non-Japanese)	ABP 959, eculizumab (US), eculizumab (EU); 300 mg IV infusion, single dose	219/217[a]	Healthy subjects, 18 to 45 yrs of age; BMI 18.0 to 30.0 kg/m^2 for non-Japanese subjects; BMI 18.0 to 25.0 kg/m^2 for Japanese subjects	57 days	Complete; CSR/Module 5.3.3.1 (20150164)

Type of Study	Study Identifier Protocol No.	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	Number of Subjects Randomized/ Number of Subjects Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Study Duration[b]	Study Status; Type of Report/Location
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indications								
Clinical similarity	20150168	Primary: Efficacy of ABP 959 compared with eculizumab Secondary: Safety, PK, PD and immunogenicity of ABP 959 compared with eculizumab	Randomized, multicenter, double-blind, active-controlled, 2-period crossover, multiple-dose study	ABP 959, eculizumab (US), eculizumab (EU); 900 mg IV infusion once Q14day until wk 52; at wk 53, subjects initially administered ABP 959 crossed over to eculizumab for 26 wks and subjects initially administered eculizumab crossed over to ABP 959 for 26 wks[c]	42/42	• Adult men and women 18 years of age and older with historical diagnosis of PNH by documented flow cytometry • Administration of eculizumab for ≥ 6 months and currently receiving 900 mg of eculizumab every 14±2 days • Hemoglobin ≥ 9.0 g/dL for at least 6 weeks before randomization • LDH < 1.5 x ULN at screening	79 weeks	Complete; CSR/Module 5.3.5.1 (20150168)

BMI = body mass index; CPU = clinical pharmacology unit; CSR = clinical study report; EOS = end-of-study; EU = European Union; IV = intravenous; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal haemoglobinuria; Q14day = every 14 days; US = United States: ULN = upper limit of normal; wk(s) = week(s)

a In total, there were 219 subjects (210 subjects were randomised to treatment plus 9 additional subjects enrolled as replacements). Of the 219 subjects, 2 subjects discontinued the study before infusion, thus, 217 subjects were treated with investigational product and completed the infusion.

b Does not include screening period.

c Due to restricted distribution of eculizumab, some clinical sites used locally sourced eculizumab and some clinical sites used eculizumab centrally sourced by Amgen. In either case, only US-licensed or European Economic Area-authorised reference medicinal product was used in the study. The utilisation of eculizumab (US) or eculizumab (EU) was supported by data from analytical and functional similarity studies in addition to PK/PD data from Study 20150164, which establish the requisite scientific bridge between eculizumab (US) and eculizumab (EU) to justify the relevance of data generated with each product and support the requirements for a marketing application.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

ABP 959 is developed by Amgen Inc. as a biosimilar product to both Soliris-EU and Soliris-US.

The pharmacokinetic (PK) similarity of ABP 959 has been investigated in two clinical studies (i.e. phase I study 20150164 in healthy male subjects and phase III study 20150168 in subjects with paroxysmal nocturnal haemoglobinuria [PNH]).

Analytical methods

Pharmacokinetics

Two electrochemiluminescence (ECL) assay methods were developed and used to determine total (eluted) and unbound (free) serum concentrations of ABP 959 and eculizumab (US and EU) in serum samples from PK/PD similarity study 20150164 and from comparative clinical study 20150168. Both methods were validated according to ICH guidance including accuracy, precision, robustness, ruggedness, selectivity, specificity, parallelism, Hook effect and stability. Validation reports and bioanalytical reports including ISR were provided. In the pivotal PK study 20150164 the original method validation was performed. Those results are using a validated method. The result of study 20150168 is considered supportive but not confirmatory of similar efficacy, therefore it is not required to perform cross validation with drug substance batches used in all the clinical studies.

Pharmacodynamics

Commercially available Wako Autokit CH50 was used in PK study 20150164 and CH50 haemolytic assay was used in the comparative clinical study 20150168. Plasma lactate dehydrogenase assay was also used to assess lysis as a primary endpoint.

Wako Autokit CH50 is an automated homogenous liposome-based assay for total complement activity in human serum. The method was validated according to ICH guidance and manufacturer's instructions as appropriate.

The haemolytic assay CH50 is measured based on lysis of antibody-coated sheep red blood cells (EA) due to the activation of complement on the cell's surface. Patients with PNH are known to have higher than normal levels of haemolysis and higher than normal circulating haemoglobin levels. Therefore, a control for endogenous haemoglobin levels was run in parallel with the haemolytic assay and subtracted from the CH50 assay to obtain the final CH50 result. The method was validated for precision, accuracy, sensitivity, specificity and stability. The results below the LLOQ were included in the similarity assessment of the two treatment groups and taking into account the low CH50 values; this is considered appropriate.

Immunogenicity

For Study 20150164 and Study 20150168, samples were evaluated for binding ADAs using a 2-tiered immunoassay that consisted of a screening assay and a confirmatory assay. A validated ECL bridging immunoassay was used to detect anti-drug antibodies. All samples positive for binding ADAs were assessed for neutralizing antibodies using a target binding assay.

Clinical PK/PD study 20150164 in healthy male subjects

The study was conducted at two centres in Australia between 10 May 2016 and 26 Mar 2017.

Free and total serum concentrations of eculizumab were determined using a single validated electrochemiluminescent assay. Eluted eculizumab samples were analysed between 26 July 2016 and 04 Apr 2017 and free eculizumab samples were analysed between 21 Sept 2016 and 05 Apr 2017.

The study was a phase I, randomised, double-blind, single-dose, 3-arm, parallel group study in healthy male subjects. Demographic and baseline characteristics were well-balanced between the 3 treatment groups. The study aimed to recruit a minimum of 16% (i.e. n = 12/treatment group) first- or second-generation Japanese subjects in order to meet Japan PMDA requirements.

Each subject received either a single 300 mg (one vial of 30 ml contained 300 mg of eculizumab [10 mg/ml]) IV infusion (35 ± 5 minute) of ABP959, Soliris-EU, or Soliris-US (in a ratio of 1:1:1 stratified by clinical pharmacology unit [CPU] and ethnicity [Japanese vs non-Japanese]) in the morning on Day 1 after a light low-fat breakfast.

PK blood samples were collected at pre-dose, at scheduled time points during the study, and at the end of the study.

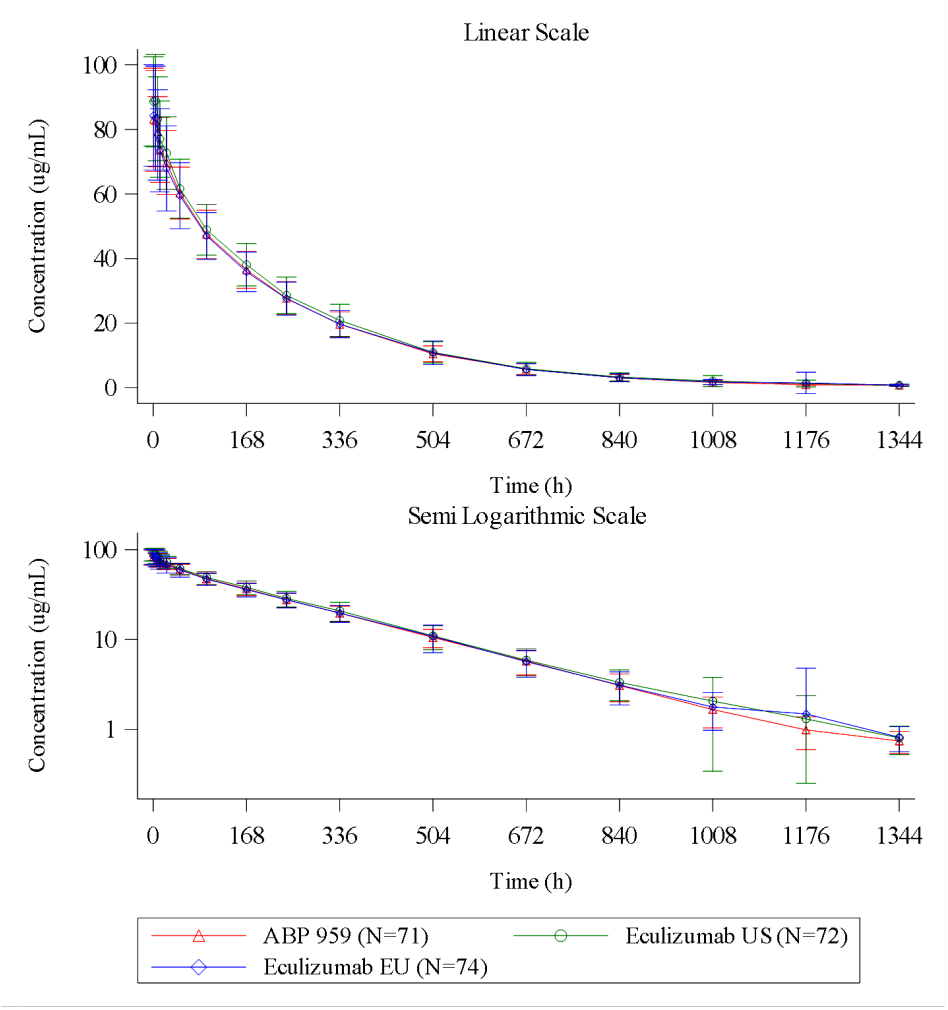
- The primary PK endpoint: AUC_{inf}.
- The secondary PK endpoints: AUC_{last}, C_{max}, $t_{1/2}$, t_{max}

PK results

All 217 subjects, who received study drug, were included in all PK analysis populations (PK parameter population was as the primary analysis population); 71 (100%) subjects in the ABP 959 treatment group, 72 (100%) subjects in the Soliris-US treatment group, and 74 (100%) subjects in the Soliris-EU treatment group.

The mean serum **total** concentration-time profiles following a single 300-mg IV infusion were similar and overlapped for all 3 treatments over the entire course of sampling (see Figure 2).

Figure 2 Mean (±SD) ABP 959, Soliris-US, and Soliris-EU serum total concentration-time profiles (Study 20150164 PK concentration population)



EU = European Union; PK = pharmacokinetic; US = United States

The results of the study demonstrated PK similarity between ABP 959 and Soliris-EU/Soliris-US (table 3). The 90% CIs of the LS GMR of both the primary PK parameter AUC_{inf} and the secondary parameters of C_{max} and AUC_{last}, for the comparisons of ABP 959 to Soliris-US and ABP 959 to Soliris-EU were fully contained within the pre-specified equivalence criteria of 0.80 to 1.25. Additionally, PK similarity was demonstrated between Soliris-US and Soliris-EU, thus establishing the PK component of the scientific bridge between Soliris-US and Soliris-EU.

Table 3 Summary of statistical assessment of total ABP 959, Soliris-EU, and Soliris-US PK parameters (Study 20150164 PK parameter population)

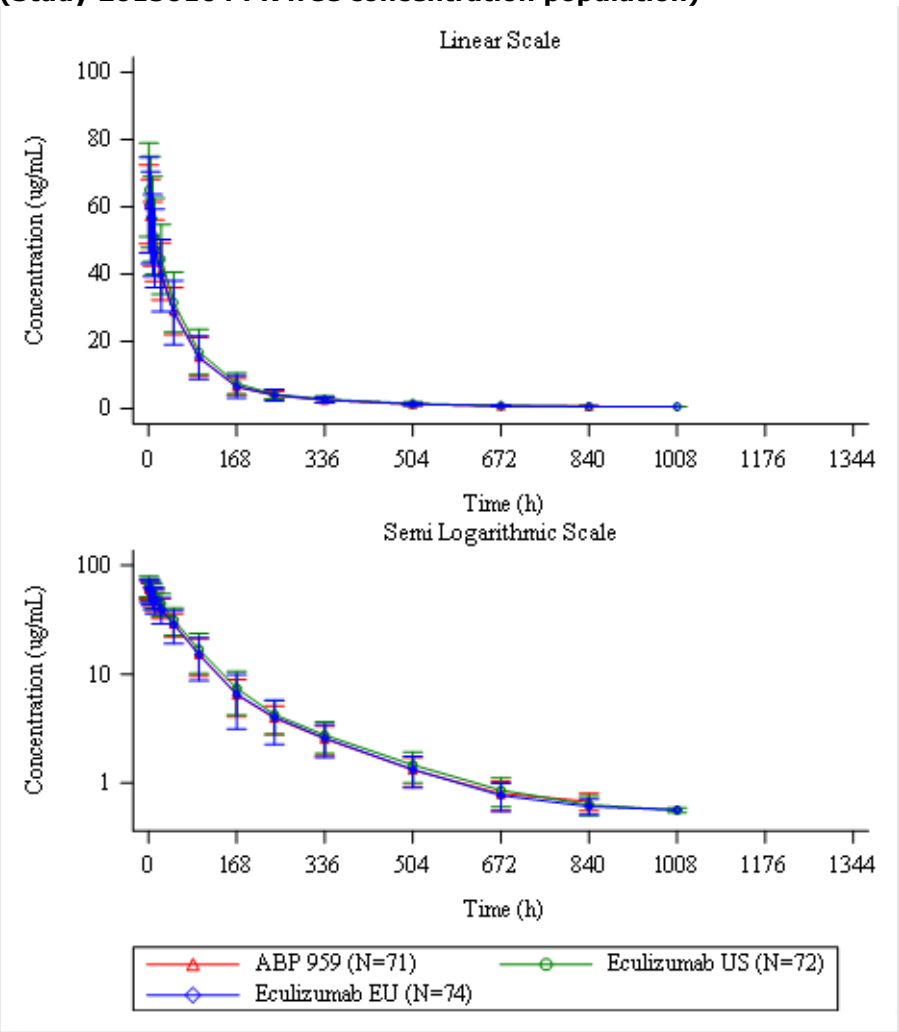
Treatment and Comparison	AUC_{inf}(μg•hr/mL) LS Geometric Mean [n]	C_{max} (μg/mL) LS Geometric Mean [n]	AUC_{last} (μg•hr/mL) LS Geometric Mean [n]
ABP 959	19981.2 [70]	89.592 [71]	19902.5 [70]
Soliris-US	20840.2 [68]	94.414 [72]	20711.7 [70]
Soliris-EU	19937.8 [71]	89.370 [74]	19913.1 [72]
Ratio of LS geometric means (90% CI)			
ABP 959 vs Soliris-US	0.9588 (0.9129, 1.0070)	0.9489 (0.9096, 0.9899)	0.9609 (0.9154, 1.0087)
ABP 959 vs Soliris-EU	1.0022 (0.9547, 1.0520)	1.0025 (0.9613, 1.0455)	0.9995 (0.9525, 1.0488)
Soliris-US vs Soliris-EU	1.0453 (0.9954, 1.0976)	1.0564 (1.0131, 1.1016)	1.0401 (0.9912, 1.0914)

AUC_{inf} = area under the serum drug concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the serum drug concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed serum drug concentration; EU = European Union; LS = least squares; PK = pharmacokinetic; US = United States

The terminal $t_{1/2}$ was estimated to be, on average, 8 days. For all of the subjects in each treatment group, AUC_{last} accounted for at least 89% of the total AUC. 56% of the subjects had the t_{max} at the end of the infusion (i.e. at timepoint 35 minutes) and 40% of the subjects had the t_{max} at 4 hours after the infusion. Seven subjects (2 subjects in ABP 959 group and 5 subjects in Soliris-EU group) had the t_{max} at 8 hours after the infusion and in the Soliris-EU group, one subject had the t_{max} at 12 hours and another subject had the t_{max} ~ at 96 hours.

The mean serum **free** concentration-time profiles following a single IV infusion of all 3 treatments were similar and overlapped over the entire course of sampling (see Figure 3).

Figure 3 Mean (±SD) ABP 959, Soliris-US, and Soliris-EU serum free concentration-time profiles (Study 20150164 PK free concentration population)



EU = European Union; PK = pharmacokinetic; US = United States

For each of the treatment comparisons, the 90% CIs of the LS GMR were fully contained within the bioequivalence (BE) criteria of 0.80 to 1.25 for the primary (AUC_{inf}) and secondary PK endpoints (C_{max} and AUC_{last}), confirming PK similarity between ABP 959 and Soliris-US, ABP 959 and Soliris-EU, and Soliris-US and Soliris-EU, based on **free** drug concentrations (see Table 4).

Table 4 Summary of statistical assessment of free ABP 959, Soliris-US, and Soliris-EU PK parameters (Study 20150164 PK parameter population)

Treatment and Comparison	AUC_{inf} (µg•hr/mL) LS Geometric Mean [n]	C_{max} (µg/mL) LS Geometric Mean [n]	AUC_{last} (µg•hr/mL) LS Geometric Mean [n]
ABP 959	5718.3 [69]	65.712 [71]	5535.0 [70]
Soliris-US	6233.8 [70]	70.319 [72]	6054.0 [70]
Soliris-EU	5718.2 [70]	64.593 [74]	5534.5 [72]
Ratio of LS geometric means (90% CI)			
ABP 959 vs Soliris-US	0.9173 (0.8477, 0.9926)	0.9345 (0.8751, 0.9979)	0.9143 (0.8434, 0.9911)
ABP 959 vs Soliris-EU	1.0000 (0.9241, 1.0821)	1.0173 (0.9531, 1.0858)	1.0001 (0.9231, 1.0835)
Soliris-US vs Soliris-EU	1.0902 (1.0077, 1.1794)	1.0887 (1.0202, 1.1617)	1.0939 (1.0097, 1.1851)

AUC_{inf} = area under the serum drug concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the serum drug concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed serum drug concentration; EU = European Union; LS = least squares; PK = pharmacokinetic; US = United States
Source: Modified from Table 14-9.5.1.1 in CSR 20150164

Clinical comparative efficacy and safety study 20150168 in adult subjects with PNH

To assess PK was the secondary objective.

PK endpoints: eculizumab (total and free) AUC from week 13 to week 15, and trough concentrations.

PK sampling timepoints: at baseline on day 1/visit 1/ week 1, pre-dose (trough) at scheduled time points during the study, and at the end of the study.

Bioanalytical site was the same as in the study 20150164. Total and free eculizumab concentrations were measured by the electrochemiluminescent methods.

PK results

PK concentration analysis set included 42 subjects and PK parameter analysis set contained 37 subjects (ABP 959/Soliris n = 18 and Soliris/ABP 959 n = 19). The reason for the exclusion of 5 subjects from the PK parameter analysis set was that none of these subjects had evaluable serum concentration profile from weeks 13 to 15.

AUC from week 13 to week 15

The GMR (90% CI) for the **total** PK AUC from week 13 to week 15 was 0.9122 (0.7586, 1.0968), which demonstrates comparable PK between the treatment groups in subjects with PNH (see Table 5).

Table 5 Summary of statistical assessment of total PK concentration AUC (µg*day/ml) from week13 to week 15 (study 20150168 PK parameter analysis set)

Statistic	ABP 959 (N = 18)	Soliris (N = 19)
n	18	19
Mean (SD)	4146.48 (1513.940)	4455.39 (1311.303)
Median	4108.31	4335.13
%CV	36.5	29.4
Minimum, maximum	2012.4, 7854.6	2449.5, 6892.5
Geometric mean	3898.05	4273.28
Geometric CV	37.5	30.6
Geometric LS mean[a]	3898.05	4273.28
GMR (ABP 959/Soliris)[a]	0.9122	
90% CI of GMR[a]	(0.7586, 1.0968)	

AUC = area under the curve; CSR = clinical study report; CV = coefficient of variation; GMR = geometric mean ratio; LS = least squares; PK = pharmacokinetic
[a] Estimated from an analysis of variance model

The GMR (90% CI) for the **free** PK AUC from week 13 to week 15 was 0.9508 (0.7454, 1.2130), which confirms comparable PK between the treatment groups in subjects with PNH (see Table 6).

Table 6 Summary of statistical assessment of free PK concentration AUC (µg*day/ml) from week 13 to week 15 (study 20150168 PK parameter analysis set)

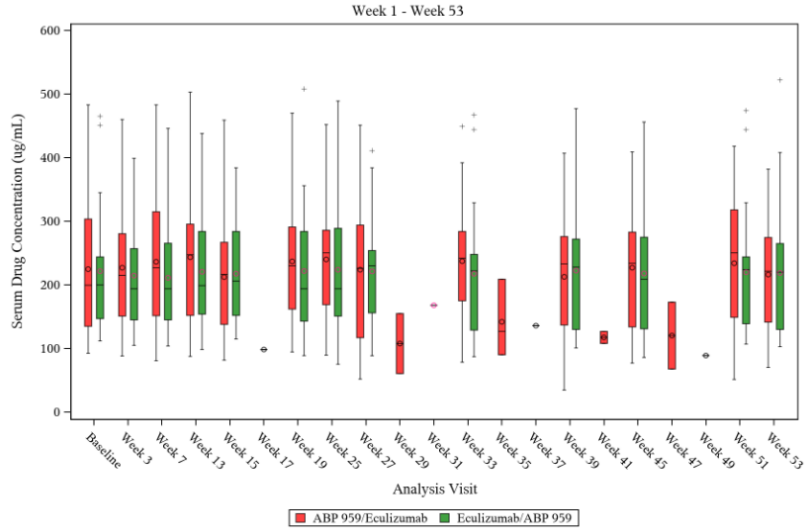
Statistic	ABP 959 (N = 18)	Soliris (N = 19)
n	18	19
Mean (SD)	3054.38 (1315.023)	3138.15 (1372.653)
Median	3136.12	2622.54
%CV	43.1	43.7
Minimum, maximum	1036.5, 5419.9	1774.0, 6541.5
Geometric mean	2761.19	2903.93
Geometric CV	51.3	40.6
Geometric LS mean[a]	2761.19	2903.93
GMR (ABP 959/Soliris)[a]	0.9508	
90% CI of GMR[a]	(0.7454, 1.2130)	

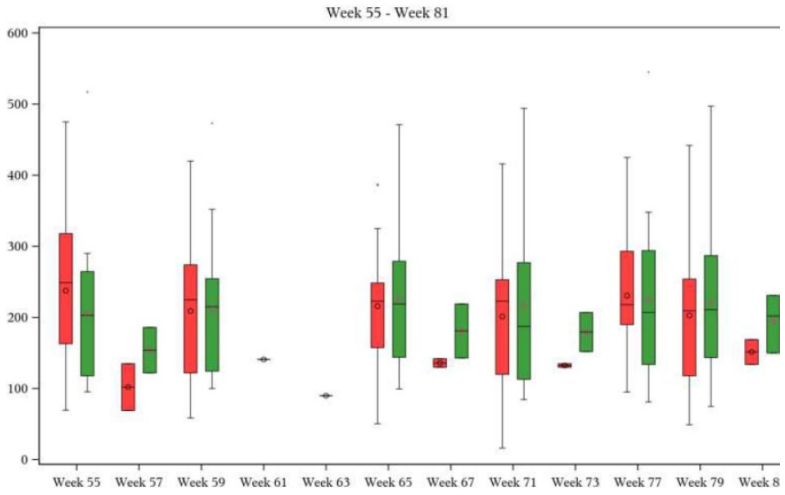
AUC = area under the curve; CSR = clinical study report; CV = coefficient of variation; GMR = geometric mean ratio; LS = least squares; PK = pharmacokinetic
[a] Estimated from an analysis of variance model

Trough concentrations

Geometric mean values for trough **total** concentrations of ABP 959 and Soliris were similar between the 2 treatment groups at all time points tested over the entire study (see Figure 4).

Figure 4 Boxplot of trough serum total concentrations (Study 20150168 PK concentration analysis set)

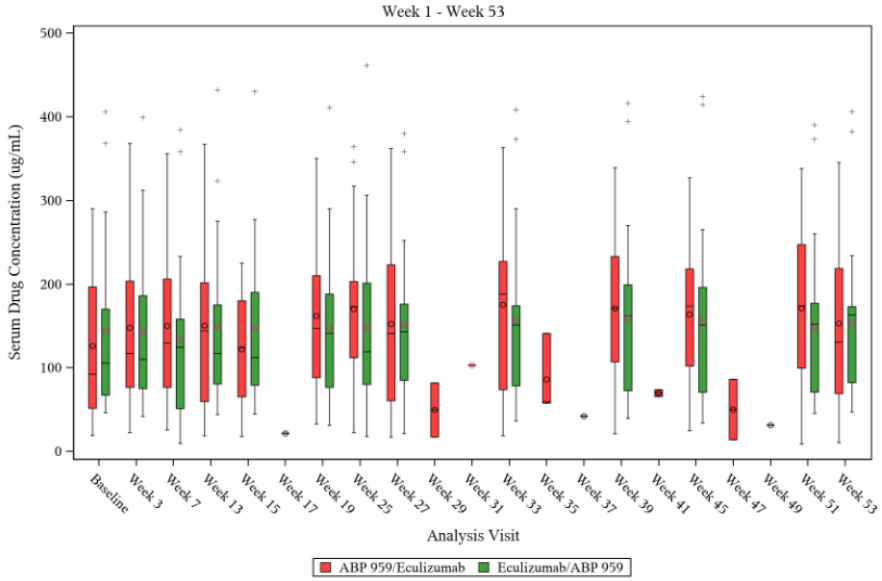


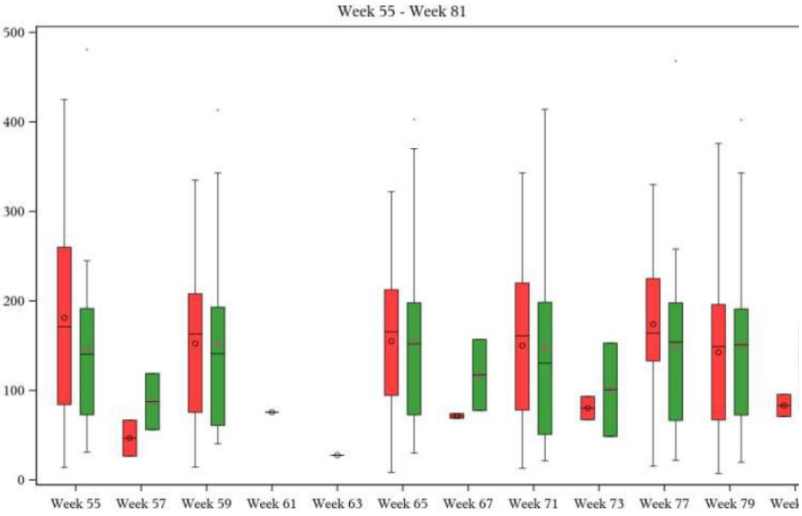


IQR = inter-quartile range; PK = pharmacokinetic
Note: At Week 77 the result for subject 16833001001 was excluded due to predose sample time was after start of infusion. Circle =mean; '-' = median; box lower margin = 1st quartile (Q1); box upper margin = 3rd quartile (Q3); whisker to the highest value below upper fence (1.5 x IQR)+Q3, whisker to the lowest value above the lower fence Q1-(1.5 x IQR); + = outlier.

Geometric mean values for trough **free** concentrations of ABP 959 and Soliris were similar between the 2 treatment groups at all time points tested over the entire study (see Figure 5).

Figure 5 Boxplot of trough serum free concentrations (Study 20150168 PK concentration analysis set)





IQR = inter-quartile range; PK = pharmacokinetic
Note: At Week 77 the result for subject 16833001001 was excluded due to predose sample time was after start of infusion. Circle = mean; '-' = median; box lower margin = 1st quartile (Q1); box upper margin = 3rd quartile (Q3); whisker to the highest value below upper fence (1.5 x IQR)+Q3, whisker to the lowest value above the lower fence Q1-(1.5 x IQR); + = outlier.

Modelling and Simulation to Confirm the Appropriateness of a 300 mg IV Dose of Eculizumab Originator and Biosimilar ABP 959 to Detect Differences in PD Response as Measured by CH50

The primary objectives of ABP 959 population pharmacokinetic analysis in healthy subjects were:

1. To estimate the PK/PD properties of ecu-US and ecu-EU ("originator") and ABP 959 ("biosimilar"), with a focus on the concentration-response relationship with CH50 (total complement activity) of each compound.

2. To simulate PK/PD profiles for hypothetical trials of originator and biosimilar at different dose levels, with a focus on CH50 profiles and variability.

3. To evaluate if dose levels other than 300 mg have equivalent or worse ability to detect difference in CH50 response.

Source data collected in Study 20150164 included demographics, dosing information, PK sampling information, clinical laboratory values, and other covariate information. Nonlinear mixed-effects modelling software (NONMEM) was used for population PK and PK-PD modelling.

A one-compartment model with the quasi-equilibrium approximation to the full target-mediated drug disposition model was selected for the Base PK model. Covariates for the population PK and PK/PD model included baseline body weight, baseline CH50, baseline C5, age and race. The following covariates were found to satisfy the inclusion criteria with forward addition and backward elimination significance levels of 0.01 and 0.001, respectively: Baseline C5 predicted baseline free target concentrations and the half-life of free target; bodyweight predicted eculizumab volume of distribution and the half-life of free target; and race (white or non-white) predicted eculizumab volume of distribution.

For the CH50 PD model, no hysteresis was noted between free or total drug concentration, free and total ligand and drug:ligand complex, and CH50. As such, a direct-effect model was implemented for CH50. Free and total drug, free and total ligand, and drug:ligand complex were assessed as drivers for changes in CH50. Free eculizumab was implemented as a predictor of CH50 response. Subject baseline weight, baseline age, baseline C5 concentration, race and treatment (ecu-US, ecu-EU or ABP 959) were tested as covariates by forward addition (p=0.01) and backward subtraction (p=0.001). The only parameter-covariate relationship included was baseline C5 on IC50.

Simulations of 100, 200, 300 and 600 mg doses of Soliris-US, Soliris-EU and ABP 959 were performed using the PK/PD model and estimates gained from these analyses. Final parameter estimates from the full PK and full PD model were used to simulate individual-level model parameters that included between-subject and within-subject variability. Bioequivalence testing per protocol was performed on these simulated CH50 activity data and the percent of simulated trials where bioequivalence was correctly declared was calculated for each dose level.

The point estimate and 90% CI of each of the three-hundred (300) replicate trials for each of the four (4) simulated dose levels are pooled for each of the three (3) treatment arms. Generally, the variation in mean and 90% CI values increased with decreasing dose, and the majority of 90% CI’s lied outside the [80, 125] boundary for the 100 mg cases.

2.5.2.2. 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.

Primary and secondary pharmacology

Clinical PK/PD study 20150164 in healthy male subjects

The co-primary endpoint of the PK/PD study 20150164 was to demonstrate PD similarity as assessed by area between the effect curve (ABEC) of 50% total haemolytic complement activity (CH50) of ABP 959 compared with FDA-licensed eculizumab (Soliris-US) and EU-authorised eculizumab (Soliris-EU). The residual functional activity of C5 can be screened using a CH50 assay. The CH50 parameter relates to the amount of test serum required to cause 50% haemolysis; therefore, a decrease in CH50 is a sensitive measure of reduced C5 functional activity.

CH50 in serum collected from healthy subjects was evaluated by a liposome immunoassay using the commercially available Wako Autokit CH50. The method was validated according to ICH guidance and manufacturer's instructions as appropriate. The assay range was 10-60 U/ml and the sensitivity was sufficient for healthy subject population.

The sampling times, derivation of ABEC of CH50 and its statistical analysis methods are considered adequate.

A total of 217 subjects were included in the PD analysis population (all subjects who received any amount of investigational product and who had at least 1 reported CH50 value); 71 (100%) subjects in the ABP 959 treatment group, 72 (100%) subjects in the Soliris-US treatment group, and 74 (100%) subjects in the Soliris-EU treatment group. Four subjects terminated the study too soon for their CH50 data to have returned to baseline (although the maximal reduction in CH50 levels was captured for these subjects). Therefore, the CH50 profiles for these subjects could not be fully characterised and these 4 subjects were excluded from the PD Parameter (n=213), Per Protocol PD Parameter (n=213), and PK/PD (n=213) Populations.

The results of the study demonstrated PD similarity between ABP 959 and Soliris-US and Soliris-EU (Table 7). The 90% and 95% CIs of the least squares geometric mean ratio (LS GMR) of the ABEC of CH50 for the comparisons of ABP 959 to Soliris-US and ABP 959 to Soliris-EU were contained within the prespecified margin of 0.80 to 1.25, indicating similar inhibition of C5 activity.

Table 7 Summary of statistical assessment of ABEC of CH50 for ABP 959, Soliris-US and Soliris-EU, study 20150164

Treatment and Comparison	ABEC of CH50 (%*h) LS Geometric Mean [n]	
ABP 959	17724.5 [70]	
Eculizumab (US)	16549.4 [70]	
Eculizumab (EU)	16361.1 [73]	
	Ratio of LS geometric means (90% CI)	Ratio of LS geometric means (95% CI)
ABP 959 vs eculizumab (US)	1.0710 (0.9634, 1.1906)	1.0710 (0.9439, 1.2152)
ABP 959 vs eculizumab (EU)	1.0824 (0.9747, 1.2020)	1.0824 (0.9552, 1.2266)
Eculizumab (US) vs eculizumab (EU)	1.0106 (0.9101, 1.1223)	1.0106 (0.8919, 1.1452)

ABEC = area between the effect curve; CH50 = 50% total hemolytic complement activity; CSR = clinical study report; EU = European Union; LS = least squares; PD= pharmacodynamic; US = United States

Similar results were observed for the Japanese and the non-Japanese subgroups (data not shown).

The applicant has not performed studies on dose-response or dose finding, or effects of age or genetic polymorphism on PK/PD relationships. Since this is a biosimilar development, this is acceptable and studies in these aspects are not required.

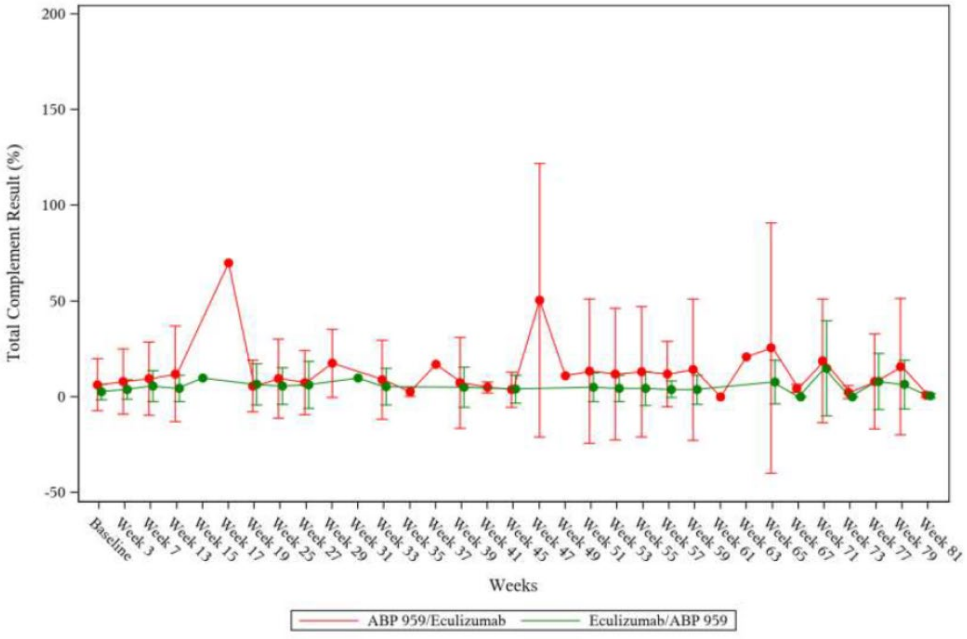
Clinical comparative efficacy and safety study 20150168 in adult subjects with PNH

CH50 was a secondary endpoint in the phase 3 study 20150168. Given that most PNH patients, during stable maintenance treatment, would be expected to have CH50 levels below the detection limits of the assay used to evaluate CH50 in serum from healthy subjects in the PK/PD similarity study 20140164, a CH50 haemolytic assay was developed for use in Study 20150168 in order to address previous EMA feedback concerning CH50 detection limits in PNH subjects enrolled in the study.

Total Complement (%) is calculated as the percent of the lower limit of human reference range (LLN) for all CH50 values, including those under the lower limit of quantification (LLOQ) The mean values were below the LLOQ at baseline in both groups, but thereafter the mean value increased above LLOQ in the ABP959/eculizumab group. Nevertheless, values below LLOQ were frequent in both treatment groups.

At baseline, 4 subjects in the ABP 959/Soliris treatment group had higher total complement (CH50) values prior to ABP 959 dosing that remained high throughout the treatment period, which resulted in slightly higher mean values for the ABP 959/Soliris treatment group vs. Soliris/ABP 959 group through the crossover in treatment at week 53. Of note, CH50 values for these subjects remained high following the switch to Soliris at week 53. Hence, the noted difference might not reflect a difference between medications but could be due to a difference between individual subjects. Time course of CH50 is given in Figure 6.

Figure 6 Mean (±SD) of total complement (%) through end of study (FAS)



CH50 = 50% total haemolytic complement activity. Total Complement (%) is calculated as the percent of the lower limit of human reference range of 58 U/mL for all CH50 values, including those under the lower limit of quantification of 10.72 U/mL. The limit of detection for the assay is 0 U/mL.

Additional boxplots were generated in order to further characterise the PK trough concentration-CH50 response relationship using data from Study 20150168. The figures support a correlation between CH50 and trough PK levels, with higher trough PK levels (both unbound and total) correlating with lower CH50 values for both treatment groups. As shown in the boxplots, the majority of subjects maintained low CH50 values throughout the study. However, there were several subjects with higher CH50 values (figure not shown). Lower trough unbound concentrations were observed in the subjects with higher CH50 values (figure not shown).

Upon request, the applicant further generated line plots for the four individual subjects with high CH50 value through end of study (EOS) in the ABP 959/Soliris treatment group. The line plots demonstrate inverse correlation of CH50 levels with unbound (data not shown) and total trough eculizumab concentrations. In three subjects, there was no clear pattern of different concentrations of eculizumab during treatment with ABP 959 vs. Soliris. However, in one subject, there was a change during the study. Most of the duration of Period 1, i.e., during treatment with ABP 959, concentrations of eculizumab are high and CH50 is suppressed. However, during Period 2 of the study (starting prior to the switch and during treatment with Soliris), the eculizumab concentrations are lower and CH50 higher. This subject also suffered from serious adverse events during the study: chronic heart failure with acute exacerbations requiring hospitalisation and cholecystitis that could not be surgically treated due to patient's general condition and persisted causing recurrent need for hospital treatment.

The applicant also generated scatter plots showing inverse relation of CH50 with unbound and total eculizumab concentration (figures not shown).

Further, the applicant was requested to analyse CH50 results using the same methodology as was used for the primary lactate dehydrogenase (LDH) endpoint for controlling confounders, although the analysis is for the parallel Period 1 of one year instead of Weeks 13 to 27. Baseline (week 1) total complement (CH50) was included as a covariate and proved to be a significant predictor of CH50 results over Period 1 (although the model assumption of baseline CH50 being equally predictive of all post-baseline CH50 values through Week 53 may not be appropriate). Based on the treatment main effect, the baseline adjusted CH50 values at the beginning of Period 1 were, on average, approximately 20% higher in patients using ABP 959 as compared with those using Soliris, but this difference was somewhat reduced over time.

Table 8 Repeated measure analysis of log-transformed total complement (%) in Period 1

	Estimate (SE)	95% CI	p-value
Fixed Effects			
Treatment: ABP 959 vs. Eculizumab	0.179 (0.345)	(-0.529, 0.887)	0.6082
Stratification factor (RBC transfusion received within the last 12 months before randomization): Yes vs. No	0.999 (0.477)	(-0.027, 2.025)	0.0554
Week 1 Total Complement	0.966 (0.148)	(0.649, 1.282)	<.0001
Time	0.000 (0.001)	(-0.001, 0.002)	0.6236
Treatment by Time interaction	-0.001 (0.001)	(-0.003, 0.001)	0.1865
Random Effect			
Subject	0.352 (0.153)	(0.052, 0.651)	0.0215

CH50 = 50% total hemolytic complement activity; EOS = end-of-study; max = maximum; min = minimum
The point estimate and corresponding confidence limits for the log-transformed total complement were estimated from a linear mixed effects model with treatment, stratification factor, week 1 total complement, time (as a continuous variable) and treatment by time interaction term as fixed effects, and subject as a random effect. A within subject variance-covariance structure of compound symmetry was used. Degree of freedom method was Kenward-Roger. Total complement from all assessed time points from week 3 to week 53 were included in the mixed model. Total Complement with a value of 0 was excluded from the analysis.

The applicant provided a listing of trough serum concentration of eculizumab, CH50 and LDH (data not shown). However, the association of eculizumab trough concentration with LDH levels did not seem to be as clear as the relation of eculizumab trough concentration with CH50 values.

2.5.3. Discussion on clinical pharmacology

The pharmacokinetics of ABP 959 was investigated in two clinical studies (i.e. a pivotal phase I PK/PD study in adult, healthy male subjects [study 20150164] and a comparative clinical study in adult subjects with PNH [study 20150168]). In study 20150164, eculizumab was administered as a single IV infusion of 300 mg subtherapeutic dose (the choice of dose has been supported by CHMP in scientific advice). In study 20150168, the dose of 900 mg (the dose used for the treatment of PNH) was administered as IV infusion every 14 days. Period 1 was 52 weeks (parallel treatment) and period 2 was 26 weeks starting at week 53 (crossover treatment). In the pivotal PK/PD study (i.e. study 20150164) and in the comparative clinical efficacy and safety study (20150168), different formulations of the test ABP 959 product have been used. Consequently, the applicant was asked to discuss the impact of formulation differences on the administration of ABP 959 and on the PK of eculizumab. In the response, the applicant provided data on different analytical comparability assessments and the functional similarity studies between 3 different ABP 959 formulations (PBS, sorbitol, and sorbitol + EDTA) and it can be concluded that the formulation changes have had no impact on the PK of eculizumab.

Analytical methods

Pharmacokinetics

Two ECL assay methods were developed and used to determine serum concentrations of ABP 959 and eculizumab (US and EU) in serum samples from PK/PD similarity study 20150164 and from comparative clinical study 20150168. Both methods were validated according to ICH guidance including accuracy, precision, robustness, ruggedness, selectivity, specificity, parallelism, Hook effect and stability. Validation reports and bioanalytical reports including ISR were provided.

Pharmacodynamics

Commercially available Wako Autokit CH50 was used in PK study 20150164 and CH50 haemolytic assay was used in the comparative clinical study 20150168. Plasma lactate dehydrogenase assay was also used to assess lysis as a primary endpoint. LDH was determined with a photometric method by Medpace Refence Laboratories.

Wako Autokit CH50 is an automated homogenous liposome-based assay for total complement activity in human serum. The method was validated according to ICH guidance and manufacturer's instructions as appropriate.

In the haemolytic assay CH50 is measured based on lysis of antibody-coated sheep red blood cells (EA) due to the activation of complement on the cell's surface. Patients with PNH are known to have higher than normal levels of haemolysis and higher than normal circulating haemoglobin levels. Therefore, a control for endogenous haemoglobin levels was run in parallel with the haemolytic assay and subtracted from the CH50 assay to obtain the final CH50 result. The method was validated for precision, accuracy, sensitivity, specificity and stability. However, most patient samples were below the quantitation limit, and these values were included in the similarity analysis between the treatment groups. Although the applicant has used an unconventional approach in the analysis, it can be concluded that the similarity of the treatment groups has been demonstrated.

Immunogenicity

For Study 20150164 and Study 20150168, samples were evaluated for binding ADAs using a 2-tiered immunoassay that consisted of a screening assay and a confirmatory assay. A validated ECL bridging immunoassay was used to detect anti-drug antibodies. All samples positive for binding ADAs were assessed for neutralizing antibodies using a target binding assay.

Upon request the applicant generated additional validation data to support the drug tolerance. Based on these new validation data, ADA could be detected in majority (38/42) of the subjects in study 20150168. Thus, the previously drawn conclusion on ADA is considered supported in these subjects. 4 subjects had trough total drug concentrations above the drug tolerance threshold at all time points, resulting in inconclusive data. However, these 4 subjects were distributed equally across the treatment groups. The immunological similarity between the RMP and Bekemv has been demonstrated. This is supported with similar quality attributes potentially related to immunogenicity (like protein aggregates, impurities), and lack of eculizumab induced immunogenicity that would affect efficacy and safety.

Pivotal clinical PK/PD study in healthy, adult male subjects (20150164)

The primary PK endpoint AUC_{inf} was based on PK samples collected up to day 57. The 57-days covered more than 5 times the reported mean $t_{1/2}$ of eculizumab (~ 11 days) and was long enough to characterise the whole PK profile of eculizumab. All subjects' AUC_{last} covered over 80% of AUC_{inf}.

No subjects had pre-dose eculizumab concentrations.

On the basis of the provided PK data for total eculizumab in PK parameter population, the primary (i.e. AUC_{inf}) and secondary PK endpoints (i.e. AUC_{last} and C_{max}) seemed to be quite similar between ABP 959, Soliris-EU and Soliris-US. The 90% CIs of the geometric mean ratios were within the criteria of 0.80 to 1.25 in all comparisons of Soliris-EU versus ABP 959 based on total eculizumab concentrations. Some differences could be seen in C_{max} in where the geometric LS mean of Soliris-US was slightly higher than that of ABP 959 and Soliris-EU with the 90% CI of the respective comparisons excluding unity. As per the CHMP Clinical

pharmacology and pharmacokinetics: Q&A document "7.1 What are the key pharmacokinetic considerations in the assessment of biosimilarity (updated May 2020)", instances where the 90% CI excludes unity would require further discussion. In this case, however, the instance is not considered to raise concerns: The exclusion of unity by the 90% CI can plausibly be associated with lower variability than anticipated (e.g. CV of the AUC_{inf} 16-19% vs. assumed 40%) and, consequently, an indication of nominally statistically significant PK difference between the products that is unlikely clinically relevant. The 90% CIs were well within the pre-specified acceptable criteria of 80-125%.

The proposed approach to evaluate the possible type I error inflation by simulation is endorsed. The simulations should be performed such that the maximal possible type I error inflation can be identified in a reliable way. In the analysis of equivalence, the confidence intervals should be adjusted accordingly. However, adjustment of the confidence intervals is not requested, as 90% confidence intervals are well within the acceptance criteria.

Assessment of free eculizumab concentrations was strongly encouraged by the CHMP (EMA/CHMP/SAWP/674462/2015/III) and the applicant has followed the advice.

The 90% CIs of the geometric mean ratios were also within the BE criteria of 0.80 to 1.25 in all comparisons of Soliris-EU versus ABP 959 based on free eculizumab concentrations. The 90% CI of free eculizumab AUC_{inf}, C_{max} and AUC_{last} of Soliris-US versus other products excluded unity, similar to the finding of total eculizumab Soliris-US C_{max} being higher than the C_{max} of Soliris-EU and ABP 959.

In addition to the C_{max} and AUC_{last}, $t_{1/2}$ and t_{max} were the secondary PK parameters. The $t_{1/2}$ was on average 8 days and 96% of the subjects had the t_{max} at the end-of-infusion (i.e. at 35 minutes) or at 4 hours after the end-of-infusion.

The applicant performed several sensitivity/subgroup secondary statistical analyses in PK parameter population. The PK results of these sensitivity/subgroup analyses were quite similar as the primary PK results.

The co-primary endpoint of the PK/PD study 20150164 was to demonstrate PD similarity as assessed by area between the effect curve (ABEC) of 50% total haemolytic complement activity (CH50) of ABP 959 compared with FDA-licensed eculizumab (Soliris-US) and EU-authorised eculizumab (Soliris-EU).

PD similarity between ABP 959 and Soliris-US and Soliris-EU was demonstrated. The 90% and 95% CIs of the least squares geometric mean ratio (LS GMR) of the ABEC of CH50 for the comparisons of ABP 959 to Soliris-US and ABP 959 to Soliris-EU were contained within the prespecified margin of 0.80 to 1.25, indicating similar inhibition of C5 activity.

Clinical comparative efficacy and safety study 20150168 in adult subjects with PNH

The GMR (90% CI) for the total PK AUC from week 13 to week 15 was 0.9122 (0.7586, 1.0968) and for the free PK AUC it was 0.9508 (0.7454, 1.2130). Consequently, the AUC from week 13 to week 15 was slightly greater to Soliris than to ABP 959 both for total and free eculizumab. The number of subjects was small (n = 20 in ABP 959/Soliris group and n = 22 in Soliris/ABP 959 group) in the treatment groups and 90% CIs include 1.00, so the differences in the AUCs are not of concern.

Both total and free eculizumab trough concentrations at different timepoints seemed to be quite same level and although the lower and upper 90% CI limits of the GMRs were not exactly within the bioequivalence range (i.e. 0.80-1.25), all 90% CIs included 1.00. The trough concentrations varied so that at some

timepoints they were higher in the ABP group and at some other timepoints they were higher in the Soliris group.

At baseline, 4 subjects in the ABP 959/Soliris treatment group had higher CH50 values prior to ABP 959 dosing that remained high throughout the treatment period, which resulted in slightly higher mean values for the ABP 959/Soliris treatment group vs. Soliris/ABP 959 group through the crossover in treatment at week 53. Upon CHMP request, the applicant provided further analyses on the outliers. Consistent with the MoA of eculizumab, unbound and total serum concentrations of eculizumab showed a clear inverse correlation with CH50 values. Line plots of the four outliers did not show any clear pattern of different response during treatment with ABP 959 or Soliris. The applicant did not discuss potential reasons for low trough concentrations of eculizumab and high CH50 results in these subjects, e.g., if the subjects have high synthesis of C5 that would lead to high C5 concentrations that bind eculizumab and therefore cause low free eculizumab concentrations; or if the subjects have higher clearance of eculizumab causing low eculizumab concentrations and consequent lesser effect on CH50. One subject had higher concentration of eculizumab and better CH50 suppression during most of Period 1, but lower eculizumab concentration and higher CH50 values from week 48 onwards (starting before switch to Soliris) through end of study. Since the subject had serious illnesses potentially affecting eculizumab kinetics and complement activation (unstable heart failure, subchronic cholecystitis), no firm conclusions can be drawn from these results. Overall, the provided analyses did not indicate any study drug related different response during treatment with ABP 959 or Soliris.

Upon CHMP request, the applicant analysed CH50 results using the same methodology as was used for the primary LDH endpoint for controlling confounders, but for the entire parallel Period 1 instead of the period from week 13 to 27. The baseline adjusted CH50 values at the beginning of Period 1 were, on average, approximately 20% higher in patients using ABP 959 as compared with those using Soliris, but this difference was somewhat reduced over time. Neither the initial level of CH50 nor the trajectory over time differed between the treatments to the extent that could indicate statistical or clinical significance.

Total complement (%) was calculated as the percent of the lower limit of human reference range (LLN) for all CH50 values, including those under the lower limit of quantification (LLOQ). Values below LLOQ were frequent in both treatment groups. These values were included in the similarity analysis between the treatment groups. Although the applicant used an unconventional approach in the analysis, it is concluded that the similarity of the treatment groups has been demonstrated.

PKPD modelling and simulation

The applicant has developed a PK model of total and free eculizumab, and a PD model of eculizumab direct (non-delayed) effect on CH50 response. The PK model is considered acceptable, but the PD model uses free eculizumab concentrations to predict CH50 response. This approach is problematic because it assumes the same free eculizumab concentration to always result in the same CH50 response. However, CH50 response measures the functioning of the complement system in body; therefore, mechanistic reasoning suggests that it should be free C5, and not free eculizumab, that is used to predict CH50 response. Moreover, eculizumab dosing leads to a build-up of C5 because the eculizumab-C5 complex is eliminated more slowly than free C5. Because of the build-up of C5, the same free eculizumab concentration will not necessarily lead to the same CH50 response at each given timepoint. As such, it is uncertain whether the PK-PD model generalises to other dose levels; thus, the specific numbers from the applicant's simulation of biosimilarity pass rates as a function of dose are not considered reliable. However, this does not invalidate the general conclusion that lower doses would have a reduced power to detect biosimilarity because of poorer ratio of signal to noise. As such, it is not considered necessary to request further PK/PD analyses with a modified PD model structure.

No clinical studies in special populations and no *in vitro* or *in-vivo* drug-drug interaction studies were conducted with the ABP 959 and this is acceptable.

ABP 959 is indicated in adults and children only for the treatment of PNH. Consequently, the proposed SmPC for the ABP 959 the Section "5.2 Pharmacokinetic properties" is otherwise similar as in the Soliris SmPC; however, including only the data for PNH indication and this is acceptable.

2.5.4. Conclusions on clinical pharmacology

The pivotal PK/PD study (20150164) for the ABP 959 group with the Soliris-EU and Soliris-US treatment groups demonstrated bioequivalence of ABP 959 with Soliris-EU and Soliris-US. Further data on different analytical comparability assessments and the functional similarity studies between 3 different ABP 959 formulations (PBS, sorbitol, and sorbitol + EDTA) confirmed that the formulation changes had no impact on the PK of eculizumab.

Consistent with the mode of action of eculizumab, CH50 correlated inversely with eculizumab concentrations. In the phase 3 clinical study 20150168, a great majority of subjects reached good suppression of CH50.

2.5.5. Clinical efficacy

The clinical evidence supporting the similarity of ABP 959 to Soliris (eculizumab) includes one completed randomised, double-blind, 3-arm, parallel-group, single-dose PK/PD similarity study in healthy adult male subjects (Study 20150164) and one completed randomised, double-blind, active-controlled, 2-period crossover comparative clinical study in adult subjects with PNH (Study 20150168).

2.5.5.1. Dose response study

No clinical dose-response studies were conducted, and none are required for a biosimilar development. The applicant performed modelling and simulation to confirm the appropriateness of a 300mg IV dose of eculizumab to detect differences in PD response as measured by CH50 in the PK/PD study 20150164.

2.5.5.2. Main study

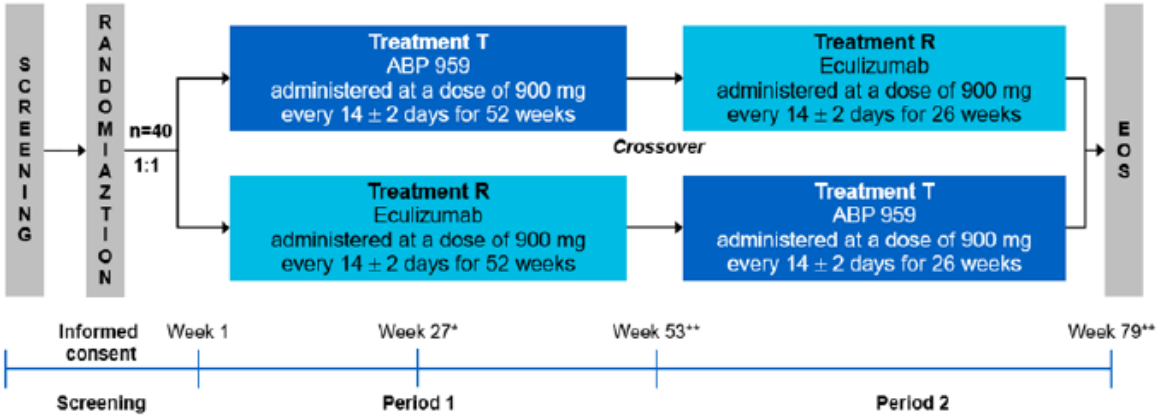
Study 20150168: A Randomized, Double-blind, Active-controlled, Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared with Eculizumab in Adult Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Methods

The study design is provided in Figure 7 Subjects were randomised in a 1:1 ratio to receive each investigational product (ABP 959 or Soliris) in 1 of 2 treatment sequences, either treatment T (test) followed by treatment R (reference) (Sequence TR) or treatment R followed by treatment T (Sequence RT). Treatments were administered over 2 periods. Period 1 was 52 weeks in duration; Period 2 started at week 53 with a crossover in treatment and was 26 weeks in duration.

The end-of-study (EOS) visit occurred 2 weeks (± 2 days) after the last dose of investigational product in Period 2.

Figure 7 Study design, study 20150168



AUEC = area under the effect curve; EOS = end-of-study; LDH = lactate dehydrogenase; R = reference; T = test
*Parallel LDH endpoint at week 27
**Crossover AUEC of LDH endpoint at week 13 to week 27, week 39 to week 53, and week 65 to week 79.

The study was conducted at specialised hospital clinics in Czechia, Finland, France, Ireland, Italy, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Turkey, the United Kingdom and the US.

Central facilities were utilised for 1) clinical laboratory tests performed during all visits after screening, 2) total complement (CH50) sample analysis, 3) PK sample analysis, and 4) antidrug antibody (ADA) sample analysis.

- **Study Participants**

Eligible subjects were men and women 18 years of age and older with a historical diagnosis of PNH by documented flow cytometry (e.g., type III erythrocyte cells of ≥ 10%) who were stable on eculizumab treatment, i.e., administration of eculizumab for ≥6 months and currently receiving 900 mg of eculizumab every 14 ± 2 days. Subjects were to have all the following: haemoglobin ≥ 9.0 g/dL for at least 6 weeks before randomisation and LDH <1.5 x the upper limit of normal (ULN) at screening, platelet count ≥ 50 x 109/L, and absolute neutrophil count ≥ 0.5 x 10^9/L (500 µL). Subjects were to have been vaccinated against *Neisseria meningitidis*. Subjects were excluded from participation if they had a history of known or suspected hereditary complement deficiency, had clinically significant cardiovascular disease, had evidence of acute thrombosis, or had experienced ≥2 breakthrough events (i.e., signs and symptoms of intravascular haemolysis that required dose and/or schedule adjustments of eculizumab) in the previous 12 months before screening.

- **Treatments**

Subjects received either:

- Sequence TR: ABP 959 900 mg administered intravenously (IV) every 14 ± 2 days for 52 weeks in Period 1 followed by Soliris 900 mg administered IV every 14 ± 2 days for 26 weeks in Period 2, or
- Sequence RT: Soliris 900 mg administered IV every 14 ± 2 days for 52 weeks in Period 1 followed by ABP 959 900 mg administered IV every 14 ± 2 days for 26 weeks in Period 2

Soliris sourced from both the US and the EU were utilised in this study. Due to restricted distribution of eculizumab, some clinical sites used locally sourced eculizumab and some clinical sites used eculizumab centrally sourced by Amgen. For each site, only Soliris-US or Soliris-EU were used in the study.

No rescue treatment is defined in the protocol.

- **Objectives**

The primary objective of the study is to evaluate the efficacy of ABP 959 compared with that of Soliris based on control of intravascular haemolysis.

The secondary objective is to assess the safety, PK, and immunogenicity of ABP 959 compared with that of Soliris.

- **Outcomes/endpoints**

Primary endpoints

In order to satisfy global regulatory requirements, the primary efficacy analyses for this study are based on a parallel comparison and on a crossover comparison between treatment groups, each with their own primary endpoint.

The primary efficacy endpoint for the parallel comparison is haemolysis, as measured by lactate dehydrogenase (LDH) at week 27. Week 27 was chosen for the analysis of LDH in the parallel comparison by the applicant, because at the week 27 time point, patients will have reached steady-state of LDH following the change of treatment from Soliris to ABP 959 eliminating the possibility of carryover effects of drug exposure from prior Soliris treatment in subjects with stable PNH given the 11-day half-life of Soliris and also allows sufficient time for LDH response to ABP 959 for those subjects randomised to ABP 959 in Period 1.

The primary efficacy endpoint for the crossover comparison is haemolysis, as measured by the time-adjusted area under the effect curve (AUEC) of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79.

Results from the primary analysis for the parallel comparison are summarised within the currently submitted interim analysis clinical study report (CSR).

To address concerns regarding the non-specificity of lactate dehydrogenase (LDH) (i.e., high values caused by other conditions than haemolysis, which interfere with results of the study), an **LDH Review Committee** external to sponsor was established for this study. The LDH Review Committee consisted of 3 qualified members (2 independent reviewers and 1 adjudicator reviewer) who were experts in the field of PNH. The objective of the LDH Review Committee was to review blinded LDH data and to identify those values

impacted by confounding events (acute infection, trauma, surgery) unrelated to efficacy of investigational product for exclusion in the primary analysis of LDH and AUEC of LDH. If the 2 independent reviewers agreed that a value should be excluded, the rationale from both reviewers was followed. If the 2 independent reviewers did not agree and a final review by the adjudicator (per LDH committee charter) was needed, the rationale from the adjudicator was followed. In general, LDH results flagged to be excluded were excluded from all derivations and analysis models.

Secondary endpoints

Efficacy endpoints

- Total complement (CH50), total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, degree of haemoglobinuria, and type III erythrocytes at week 27, week 39, week 53, and post-crossover week 65 and week 79
- Crossover comparison of haemolysis as measured by LDH at week 53 and week 79
- Lactate dehydrogenase-time profile
- Red blood cell transfusion
- Pharmacokinetic area under the curve (AUC) of ABP 959 and Soliris from week 13 to 15, and trough PK

Safety Endpoints:

- Treatment-emergent adverse events (TEAE)
- Treatment-emergent serious adverse events
- Treatment-emergent events of interest (EOIs)
- Incidence of anti-drug antibodies (ADAs)

A Data Monitoring Committee (DMC) external to sponsor was formed with members consisting of individuals chosen for their expertise in PNH. The primary role of the DMC was to monitor safety data. Independent safety reviews of unblinded safety data were performed by the DMC approximately every 6 months throughout the study.

- **Sample size**

The sample size of 40 subjects was chosen to provide approximately 87% power to demonstrate non-inferiority (NI) at a 1-sided significance level of 0.025 on the primary endpoint of week 27 LDH for the parallel comparison, assuming an inter-subject coefficient of variation (CV) of 130% for ABP 959 and eculizumab, a true geometric mean ratio (GMR) of 1 between ABP 959 and eculizumab, a NI margin of 2.873, and a 10% dropout rate.

The sample size of 40 was anticipated also to provide greater than 95% power to demonstrate similarity at a 2-sided significance level of 0.05 on the primary endpoint of time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79 for the crossover comparison, assuming an intra-subject CV of 34%, a true GMR of 1 between ABP 959 and eculizumab, a similarity margin of (0.77, 1.30), and a 10% dropout rate.

- **Randomisation and Blinding (masking)**

Randomisation was to occur within 8 days before the first dose of investigational product administration (defined as day 1) and was stratified by red blood cell (RBC) transfusion received within the last 12 months before randomisation (yes vs no). An interactive voice/web response system (IXRS) was used to randomise the subject centrally to receive either ABP 959/Soliris or Soliris/ABP 959.

Since the investigational product (IP) containers are different for ABP 959 and eculizumab, IP (ABP 959 or eculizumab) is prepared by an unblinded pharmacist, or designee, into a common IV preparation for administration to the subject. Subjects, sponsor, designated PRA, and other clinical site staff are blinded to the IP allocation for each subject. Select PRA staff (e.g. clinical research associate), not involved in the monitoring or the daily operations of the study, are unblinded to subject IP allocation in order to perform IP accountability.

- **Statistical methods**

The clinical similarity of the week 27 LDH between treatments was assessed by comparing the 1-sided 97.5% upper CI limit for the GMR of LDH at week 27 between ABP 959 treatment and Soliris treatment with a NI margin of 2.873. The point estimate of the mean difference in the log transformed LDH and the corresponding 1-sided 97.5% upper CI limit was estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable), and treatment by time interaction term as fixed effects, compound symmetry covariance structure was applied to address repeat LDH measurements. The point estimate and the upper CI limit for the GMR were then calculated by transforming back to the original scale. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 (ie, study day 78 to study day 189) were included in the mixed model. Lactate dehydrogenase values impacted by confounding events unrelated to efficacy of investigational product, as determined by the LDH Review Committee (see Section 8.2.6), were excluded from the analysis. Only observed values were used in the model, missing LDH values were not imputed.

Two interim blinded assessments were planned and completed. No change was made to the analysis plan.

The primary endpoint for the crossover comparison was haemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79. The primary analysis for the crossover comparison (ie, the final analysis) was conducted after all subjects completed the EOS visit. The primary analysis for the crossover comparison was conducted using the modified FAS (mFAS), which consisted of all randomised subjects with an LDH-time profile evaluable for the time-adjusted AUEC for at least one of the three assessment periods. Time-adjusted AUECs were calculated using trapezoidal rule on linear scale and standardised to a 7-day interval. The point estimates and confidence limits for the log-transformed time-adjusted AUEC were estimated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and subject as a random effect. A within subject variance-covariance structure of unstructured was used. Degree of freedom method was Kenward-Roger. Point estimates and corresponding confidence limits for the geometric LS means and the ratio of geometric LS means were calculated by transforming back to the original scale.

Results

- **Participant flow**

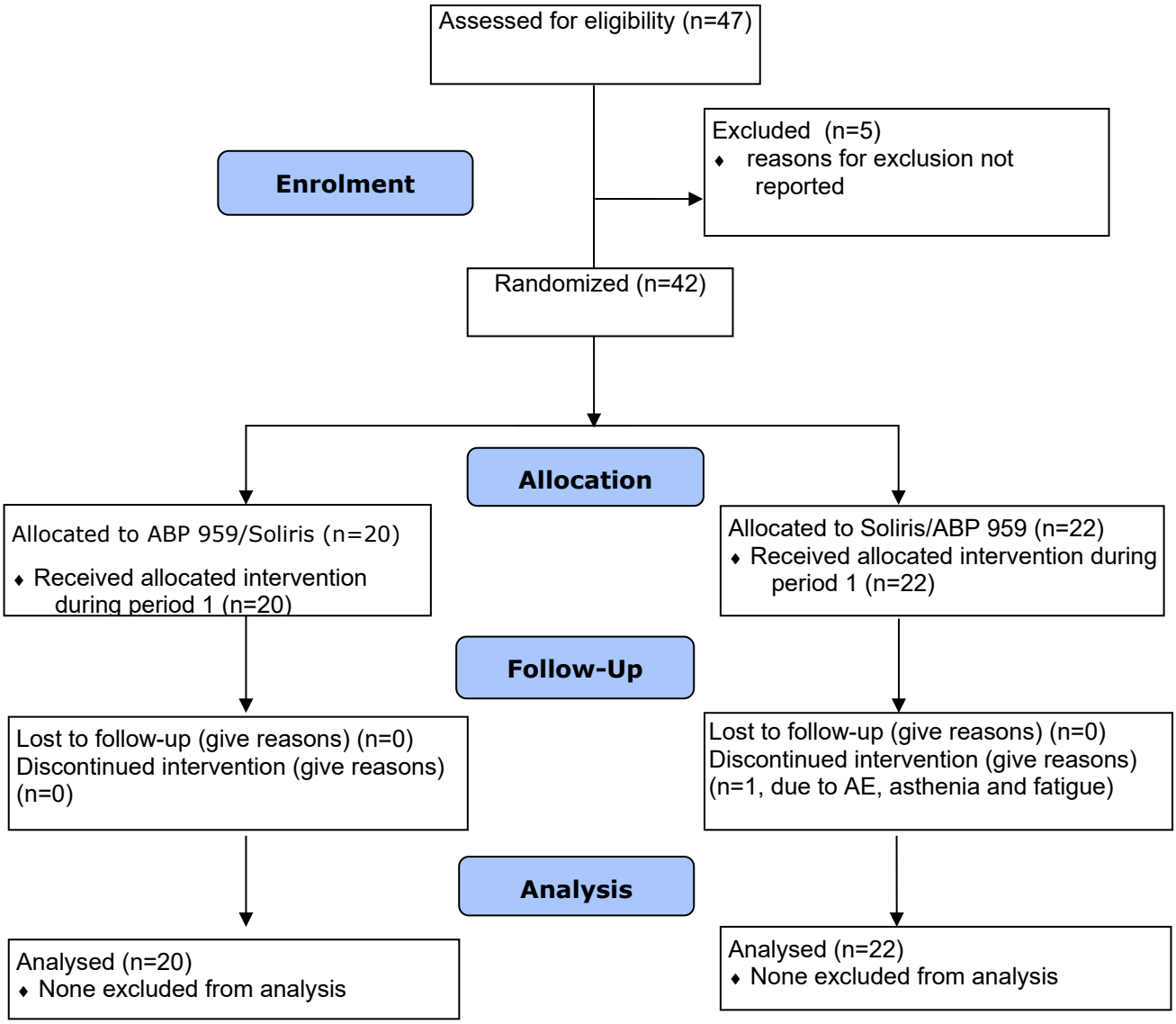
A total of 47 subjects were screened and 42 subjects (20 in the ABP 959/Soliris treatment group and 22 in the Soliris/ABP 959 treatment group) were randomised.

Figure 8 gives the participant flow for Periods 1 and 2 of the study. Of the 42 subjects who were initially randomised, 39 (92.9%) completed the study and 3 (7.1%) subjects discontinued the study. Reasons for discontinuing the study were consent withdrawn (1 [5.0%] subject in the ABP 959/eculizumab treatment group), adverse event (1 [4.5%] subject in the eculizumab/ABP 959 treatment group), and other (identified as patient's personal needs) (1 [4.5%] subject in the eculizumab/ABP 959 treatment group). No subjects discontinued the study due to COVID-19-related reasons.

In general, subject incidence of study completion and discontinuation was comparable between the 2 treatment groups.

Figure 8 Disposition of subjects (Period 1 of study 20150168)

Period 1 of study 20150168



Period 2 of study 20150168

Subjects treated with IP (n=20)	Subjects treated with IP (n=21)
Discontinued IP during Period 2 (n=1) • Consent withdrawal for treatment	Discontinued IP during Period 2 (n=1) • Other reason (personal needs)

- **Recruitment**

The study initiation date was 22 Jan 2019. Data cut-off date for primary analysis of parallel comparison was 10 Jan 2022. Study completion date was 12 July 2022. Dates defining the period of recruitment are not given in the CSR.

- **Conduct of the study**

Amendments to the study plan were based on advice from CHMP SA or from national agencies or related to practical or linguistic aspects.

After the data cut-off for the primary analysis was performed, unblinded data and results from the primary analysis were made available to pre-identified personnel from the applicant and the contract research organisation, who were involved in development of the interim CSR or regulatory submissions and who were not involved in any remaining blinded study conduct or data cleaning processes. All subjects and investigators remained blinded throughout the study and until the final study database lock.

- **Baseline data**

Demographic and baseline physical characteristics are given in table 9 and baseline disease characteristics in table 10.

Table 9 Demographic and baseline physical characteristics (full analysis set)

Characteristic	ABP 959/Eculizumab (N = 20) n (%)	Eculizumab/ABP 959 (N = 22) n (%)	Total (N = 42) n (%)
Sex [n (%)]			
Female	11 (55.0)	11 (50.0)	22 (52.4)
Male	9 (45.0)	11 (50.0)	20 (47.6)
Race [n (%)]			
White	16 (80.0)	17 (77.3)	33 (78.6)
Asian	0 (0.0)	1 (4.5)	1 (2.4)
Not allowed to collect	4 (20.0)	4 (18.2)	8 (19.0)
Ethnicity [n (%)]			
Hispanic or Latino	0 (0.0)	1 (4.5)	1 (2.4)
Not Hispanic or Latino	14 (70.0)	13 (59.1)	27 (64.3)
Not allowed to collect	4 (20.0)	4 (18.2)	8 (19.0)
Not reported	1 (5.0)	4 (18.2)	5 (11.9)
Unknown	1 (5.0)	0 (0.0)	1 (2.4)
Age at enrollment (years)			
n	20	22	42
Mean (SD)	50.2 (16.73)	50.2 (16.90)	50.2 (16.61)
Median	48.5	51.5	49.5
Min, Max	21, 78	21, 77	21, 78
Age group at enrollment [n (%)]			
≤ 54 years	13 (65.0)	12 (54.5)	25 (59.5)
> 54 years	7 (35.0)	10 (45.5)	17 (40.5)
Weight (kg)			
n	19	22	41
Mean (SD)	73.65 (15.944)	77.29 (15.894)	75.60 (15.824)
Median	73.30	77.00	77.00
Min, Max	41.0, 107.9	52.0, 114.7	41.0, 114.7
Height (cm)			
n	20	22	42
Mean (SD)	168.93 (11.471)	170.11 (12.874)	169.55 (12.093)
Median	168.50	169.00	168.50
Min, Max	153.0, 196.0	153.0, 207.0	153.0, 207.0

Table 10 Baseline disease characteristics (full analysis set)

Characteristic	ABP 959/Eculizumab (N = 20) n (%)	Eculizumab/ABP 959 (N = 22) n (%)	Total (N = 42) n (%)
Age at PNH diagnosis (years)			
n	20	22	42
Mean (SD)	40.4 (18.53)	41.0 (18.42)	40.7 (18.25)
Median	34.5	37.0	36.5
Min, Max	17, 72	8, 74	8, 74
Time since original diagnosis (months)			
n	20	22	42
Mean (SD)	131.35 (88.745)	125.43 (138.488)	128.25 (116.112)
Median	108.02	64.99	84.87
Min, Max	20.0, 372.0	16.8, 480.0	16.8, 480.0
Time (duration) on eculizumab treatment prior to study enrollment (months)			
n	20	22	42
Mean (SD)	77.80 (40.159)	59.87 (38.354)	68.41 (39.786)
Median	91.47	53.04	60.14
Min, Max	7.5, 158.7	10.8, 150.0	7.5, 158.7
LDH at study baseline (U/L)			
n	20	22	42
Mean (SD)	199.7 (61.06)	193.9 (45.09)	196.6 (52.70)
Median	191.0	187.5	188.5
Min, Max	116, 430	124, 287	116, 430
RBC transfusion within 12 months before randomization per eCRF – n (%)			
Yes	2 (10.0)	3 (13.6)	5 (11.9)
No	18 (90.0)	19 (86.4)	37 (88.1)
Number of packed RBC units received in last 12 months			
n	2	3	5
Mean (SD)	1.5 (0.71)	1.7 (1.15)	1.6 (0.89)
Median	1.5	1.0	1.0
Min, Max	1, 2	1, 3	1, 3
Hemoglobin at study baseline (mg/dL)			
n	20	21	41
Mean (SD)	113.0 (15.03)	113.8 (16.09)	113.4 (15.39)
Median	109.0	115.0	111.0
Min, Max	89, 146	83, 137	83, 146

The subjects were required to be stable on eculizumab treatment. The mean (196.6 U/L) and median (188.5 U/L) LDH values were normal at baseline. No violation of the inclusion criterion of LDH <1.5 x the upper limit of normal (ULN) at screening is reported in the listing of protocol violations; however, some elevated LDH

values up to 430 U/L were seen already at baseline. The mean (113.4 g/L) and median (111 g/L) haemoglobin (Hb) levels at baseline were slightly below normal. Only 5 subjects had received RBC units during the prior year. Even though the inclusion criteria required Hb ≥9.0 g/dL (in SI units, 90 g/L) for at least 6 weeks before randomisation, the range of Hb at baseline started from 83 g/L.

- **Numbers analysed**

A total of 47 subjects were screened and 42 subjects (20 in the ABP 959/eculizumab treatment group and 22 in the eculizumab/ABP 959 treatment group) were randomised. All 42 randomised subjects were included in the full analysis set (FAS), the per-protocol population set (PPP), the safety analysis set, and the PK concentration analysis set. Five subjects (2 in the ABP 959/Soliris group and 3 in the Soliris/ABP 95 group) were excluded from the PK parameter analysis set due to one or more PK samples not valid or missing from weeks 13 to 15.

- **Outcomes and estimation**

The primary efficacy endpoint for the parallel comparison

Results for analysis of the primary efficacy endpoint for the parallel comparison of haemolysis are provided in Table 11. The 1-sided 97.5% upper CI was contained within the NI margin of 2.873, thus establishing similarity in clinical efficacy between ABP 959 and Soliris in the parallel comparison. Furthermore, the small difference in the point estimates is not clinically relevant.

Table 11 Primary analysis of LDH (U/L) at week 27 – parallel comparison (FAS)

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Number of subjects (n)	20	22
Week 27 geometric LS mean[a]	205.69	193.53
95% CI	(191.23, 221.24)	(180.80, 207.17)
Ratio of week 27 geometric LS mean (ABP 959/eculizumab)[a]	1.0628	
97.5% upper CI limit	1.1576	
95% CI	(0.9758, 1.1576)	

LDH = lactate dehydrogenase; LS = least squares; eculizumab = Soliris; n = number of subjects included in the mixed model
LDH values impacted by confounding events determined by the blinded independent LDH Review Committee were excluded.
[a] The point estimate and corresponding confidence limits for the log-transformed LDH values were estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable), and treatment by time interaction term as fixed effects, and with subject as a random effect. A within subject variance-covariance structure of compound symmetry was used. Degree of freedom method was Kenward-Roger. The geometric LS means and point estimate and corresponding confidence limits for the ratio of geometric LS means were calculated by transforming back to the original scale. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 were included in the mixed model.

Additional analyses were conducted upon CHMP request on the primary efficacy endpoint for the parallel comparison (LDH at week 27) using a weighted population based on prior red blood cell (RBC) transfusion

stratification factor as observed in the current study data (i.e., using number of subjects as observed in the study for prior transfusion and no prior transfusion strata). Since the FAS and PPP populations were identical, only the table for the FAS is included in this AR (Table 16). The applicant clarified that Table 15 provides the geometric LS means over a balanced population (i.e., assuming equal number of subjects in the prior transfusion and no-prior transfusion strata) and Table 16 below uses the observed weight.

Table 12 Ad hoc analysis of LDH (U/L) at week 27 with observed weights for prior transfusion from the study - parallel comparison (full analysis set)

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Number of Subjects (n)	20	22
Week 27 geometric LS mean[a]	198.41	186.68
95% confidence interval	(186.50, 211.08)	(176.04, 197.97)
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a]	1.0628	
97.5% upper confidence interval limit	1.1576	
95% confidence interval	(0.9758, 1.1576)	

Note: LS= Least squares.
n = Number of subjects included in the mixed model.
LDH values impacted by confounding events determined by the blinded independent LDH review committee were excluded.
a The point estimate and corresponding confidence limits for the log-transformed LDH values are estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable) and treatment by time interaction term as fixed effects, and subject as a random effect.
A within subject variance-covariance structure of compound symmetry is used. Degree of freedom method is Kenward-Roger. Point estimates and corresponding confidence limits for the geometric LS means and the ratio of geometric LS means are calculated by transforming back to the original scale. The observed weights of the stratification factor were used in estimating of the geometric LS means. LDH values from all assessed time points from week 13 to week 27 are included in the mixed model.

Upon request, the applicant presented the number of LDH observations missing per treatment group for each time point included in the primary analysis model, i.e. week 13 to week 27 (table 17).

Table 13 Number of missing LDH values from week 13 to 27

Time Point	Number of Missing LDH Values in ABP 959/Eculizumab Treatment Group	Number of Missing LDH Values in Eculizumab/ABP 959 Treatment Group
Week 13	2	1
Week 15	3	0
Week 19	1	1
Week 25	2	1
Week 27	2	2

LDH = lactate dehydrogenase
Source: Table 14-4.5 in Study 20150168 primary analysis clinical study report

- **Ancillary analyses**

Subgroup analyses of the primary efficacy endpoint for the parallel comparison of haemolysis at week 27 were conducted for the subgroup of subjects who received RBC transfusion within 12 months prior to randomisation, age group, and gender.

Table 14 Subgroup analysis of LDH (U/L) at week 27 (FAS)

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Red blood cell transfusion received within 12 months of randomization = Yes (N1)	2	3
Number of Subjects (n)	2	3
Week 27 geometric LS mean[a]	205.13	221.34
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a]	0.9267	
97.5% upper confidence interval limit	1.4827	
95% confidence interval	(0.5792, 1.4827)	

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Red blood cell transfusion received within 12 months of randomization = No (N1)	18	19
Number of Subjects (n)	18	19
Week 27 geometric LS mean[a]	197.31	181.85
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a]	1.0851	
97.5% upper confidence interval limit	1.1819	
95% confidence interval	(0.9961, 1.1819)	

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Age Group: <= 54 Years (N1)	13	12
Number of Subjects (n)	13	12
Week 27 geometric LS mean[a]	194.79	176.55
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a]	1.1033	
97.5% upper confidence interval limit	1.2190	
95% confidence interval	(0.9986, 1.2190)	

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Age Group: > 54 Years (N1)	7	10
Number of Subjects (n)	7	10
Week 27 geometric LS mean[a]	200.25	201.86
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a]	0.9920	
97.5% upper confidence interval limit	1.1849	
95% confidence interval	(0.8306, 1.1849)	

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Sex: Male (N1)	9	11
Number of Subjects (n)	9	11
Week 27 geometric LS mean[a]	213.04	194.12
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a] 97.5% upper confidence interval limit 95% confidence interval	1.0975 1.2592 (0.9565, 1.2592)	

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Sex: Female (N1)	11	11
Number of Subjects (n)	11	11
Week 27 geometric LS mean[a]	185.13	180.56
Ratio of Week 27 geometric LS mean (ABP 959/Eculizumab)[a] 97.5% upper confidence interval limit 95% confidence interval	1.0253 1.1406 (0.9217, 1.1406)	

Analysis using a Bayesian elastic meta-analytic-predictive (EMAP) prior method, which leverages rich historical data available on eculizumab to improve study power, was conducted as a supplemental analysis for the primary endpoint of LDH at week 27. The methods and results of this analysis are covered by Section 2.6.5.5. "Analysis performed across trials (pooled analyses AND meta-analysis)".

The primary efficacy endpoint for the crossover comparison

Results for analysis of the primary efficacy endpoint for the crossover comparison of haemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79, are provided in Table 15. The 90% CI was contained within a similarity margin of (0.77, 1.30), thus establishing similarity in clinical efficacy between ABP 959 and eculizumab.

Table 15 Primary analysis of time-adjusted AUEC (U*day/L/week) of LDH - crossover comparison (modified full analysis set)

Statistics	ABP 959 (N = 41)	Eculizumab (N = 41)
Number of Subjects (n)	40	40
Geometric LS mean[a]	1445.76	1473.44
Ratio of geometric LS mean (ABP 959/Eculizumab)[a] 90% confidence interval	0.9812 (0.9403, 1.0239)	

Note: LS = Least squares; AUEC = Area under the effect curve.
n = Number of subjects included in the mixed model.
The time-adjusted area under the effect curve of LDH is calculated for week 13 to week 27, week 39 to week 53 and week 65 to week 79.
LDH values impacted by confounding events determined by the blinded independent LDH review committee were excluded.
[a] The point estimate and corresponding confidence limits for the log-transformed time-adjusted AUEC are estimated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and subject as a random effect. A within subject variance-covariance structure of unstructured is used. Degree of freedom method is Kenward-Roger. The geometric LS means and point estimate and corresponding confidence limits for the ratio of geometirc LS means are calculated by transforming back to the original scale.

Since all subjects from the mFAS were included in the PPC analysis set, results from the sensitivity analysis on PPC analysis set were identical with results from the primary efficacy analysis for the crossover comparison.

Ancillary analyses/cross-over comparison

Results for subgroup analyses of the primary efficacy endpoint for the crossover comparison of haemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79, are provided in the CSR for the following subgroups: RBC transfusion received within 12 months of randomisation [yes/no], age group [<=54 years/>54 years], and gender. In general, results for all subgroups were consistent with results from the primary efficacy analyses for the crossover comparison (data not shown).

Secondary efficacy endpoints

The secondary efficacy≥ endpoints were:

- Total complement (CH50), total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, degree of haemoglobinuria, and type III erythrocytes at week 27, week 39, week 53, and post-crossover week 65 and week 79
- Crossover comparison of haemolysis as measured by LDH at week 53 and week 79
- RBC transfusion
- LDH-time profile
- Pharmacokinetic area under the curve (AUC) of ABP 959 and eculizumab from week 13 to week 15, and trough PK

The PD results (CH50) are assessed in Section 3.3.1.2 Pharmacodynamics and discussed in Section 3.3.2 of this AR.

Mean values for the continuous efficacy laboratory endpoints at week 27, week 39, weeks 53, 65 and 79 are provided in Table 16. Results on haemoglobinuria are given in Table 17.

Table 16 Continuous efficacy lab endpoints by visit (Study 20150168 FAS)

Efficacy Lab Endpoint Time Point	ABP 959/Eculizumab (N = 20)	Eculizumab/ABP 959 (N = 22)
Total complement (%)		
Baseline		
n	20	22
Mean (SD)	6.4 (13.48)	2.6 (4.11)
Min, max	0, 56	0, 17
Week 27		
n	19	21
Mean (SD)	7.5 (16.68)	6.3 (12.25)
Min, max	0, 50	0, 50
Week 39		
n	17	21
Mean (SD)	7.4 (23.80)	5.1 (10.36)
Min, max	0, 98	0, 37
Week 53		
n	20	21
Mean (SD)	12.0 (34.29)	4.6 (6.84)
Min, max	0, 144	0, 20
Week 65		
n	16	18
Mean (SD)	25.6 (65.27)	7.8 (11.37)
Min, max	0, 222	0, 37
Week 79 (EOS)		
n	18	20
Mean (SD)	15.8 (35.65)	6.5 (12.67)
Min, max	0, 132	0, 55
Hemoglobin (g/L)		
Baseline		
n	20	21
Mean (SD)	113.0 (15.03)	113.8 (16.09)
Min, max	89, 146	83, 137
Week 27		
n	18	20
Mean (SD)	110.6 (15.19)	116.1 (16.08)
Min, max	91, 141	88, 141
Week 39		
n	16	20
Mean (SD)	114.6 (14.12)	115.0 (15.39)
Min, max	99, 145	84, 141
Week 53		
n	19	21
Mean (SD)	109.8 (15.17)	115.8 (15.20)
Min, max	90, 142	82, 136
Week 65		
n	15	18
Mean (SD)	106.9 (17.74)	115.7 (18.36)
Min, max	68, 139	87, 145
Week 79 (EOS)		
n	19	20
Mean (SD)	113.0 (16.78)	115.7 (16.75)
Min, max	90, 151	82, 142

Table 17 Continuous efficacy lab endpoints by visit (Study 20150168 FAS) continued

Efficacy Lab Endpoint Time Point	ABP 959/Eculizumab (N = 20) n (%)	Eculizumab/ABP 959 (N = 22) n (%)
Hemoglobin, free (mg/dL)		
Baseline		
n	20	22
Mean (SD)	9.30 (26.960)	3.76 (2.758)
Min, max	0.6, 123.2	0.5, 10.3
Week 27		
n	17	21
Mean (SD)	5.38 (14.839)	3.10 (2.920)
Min, max	0.6, 62.8	0.2, 11.1
Week 39		
n	17	21
Mean (SD)	3.74 (5.093)	10.25 (27.926)
Min, max	0.6, 18.9	0.5, 129.4
Week 53		
n	18	21
Mean (SD)	13.60 (33.793)	3.08 (2.529)
Min, max	0.7, 128.7	0.5, 9.6
Week 65		
n	16	18
Mean (SD)	3.22 (2.249)	2.75 (2.077)
Min, max	0.5, 8.4	0.4, 8.1
Week 79 (EOS)		
n	17	15
Mean (SD)	6.59 (10.232)	13.89 (41.634)
Min, max	0.7, 36.1	0.1, 164.0
Haptoglobin (g/L)		
Baseline		
n	20	22
Mean (SD)	0.200 (0.2562)	0.286 (0.3714)
Min, max	0.07, 1.01	0.07, 1.43
Week 27		
n	19	21
Mean (SD)	0.201 (0.2809)	0.300 (0.4153)
Min, max	0.07, 1.20	0.07, 1.74
Week 39		
n	18	21
Mean (SD)	0.196 (0.3085)	0.301 (0.4266)
Min, max	0.07, 1.32	0.07, 1.80
Week 53		
n	20	21
Mean (SD)	0.196 (0.2571)	0.383 (0.6550)
Min, max	0.07, 0.85	0.07, 2.98
Week 65		
n	16	18
Mean (SD)	0.201 (0.2521)	0.466 (0.5624)
Min, max	0.07, 0.91	0.07, 2.10
Week 79 (EOS)		
n	19	20
Mean (SD)	0.201 (0.2473)	0.335 (0.4744)
Min, max	0.07, 0.95	0.08, 1.91

Table 17 Continuous efficacy lab endpoints by visit (Study 20150168 FAS) continued

Efficacy Lab Endpoint Time Point	ABP 959/Eculizumab (N = 20) n (%)	Eculizumab/ABP 959 (N = 22) n (%)
Bilirubin (µmol/L)		
Baseline		
n	20	22
Mean (SD)	23.63 (12.537)	21.12 (13.872)
Min, max	10.3, 48.7	7.2, 65.3
Week 27		
n	19	21
Mean (SD)	28.69 (22.529)	24.30 (19.209)
Min, max	12.1, 92.3	6.0, 77.8
Week 39		
n	18	21
Mean (SD)	24.08 (14.258)	24.15 (16.655)
Min, max	8.0, 65.2	7.9, 81.9
Week 53		
n	20	21
Mean (SD)	25.76 (17.156)	21.32 (14.036)
Min, max	4.4, 77.3	9.1, 64.3
Week 65		
n	16	18
Mean (SD)	24.51 (16.736)	20.02 (13.808)
Min, max	9.1, 75.1	8.0, 67.7
Week 79 (EOS)		
n	19	20
Mean (SD)	23.73 (16.161)	23.15 (17.286)
Min, max	10.1, 72.5	7.4, 73.5
Type III erythrocytes (%)		
Baseline		
n	18	21
Mean (SD)	39.9197 (25.36275)	36.7478 (29.93810)
Min, max	6.322, 79.012	0.042, 82.720
Week 27		
n	17	21
Mean (SD)	40.9121 (23.17684)	40.1304 (30.01551)
Min, max	6.824, 77.264	0.024, 96.295
Week 39		
n	16	20
Mean (SD)	41.2158 (24.81071)	43.3663 (29.65777)
Min, max	6.540, 79.488	0.026, 85.399
Week 53		
n	19	21
Mean (SD)	41.8196 (23.23819)	40.4676 (31.14150)
Min, max	5.660, 75.795	0.021, 95.810
Week 65		
n	15	17
Mean (SD)	39.1192 (22.20104)	37.5379 (28.76642)
Min, max	4.519, 79.187	0.025, 81.743
Week 79 (EOS)		
n	15	16
Mean (SD)	43.7609 (21.51712)	42.5501 (30.20582)
Min, max	5.100, 76.218	0.042, 82.803

CH50 = 50% total haemolytic complement activity; EOS = end-of-study; max = maximum; min = minimum
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of investigational product. Total complement (%) was calculated as the percent of the lower limit of human reference range of 58 U/mL for all CH50 values, including those under the lower limit of quantification of 10.72 U/mL. The limit of detection for the assay was 0 U/mL

Table 18 Summary of haemoglobinuria by visit (FAS)

Time Point	ABP 959/Eculizumab (N = 20) n (%)	Eculizumab/ABP 959 (N = 22) n (%)
Baseline		
Number of samples	20	21
Negative	17 (85.0)	21 (100.0)
Trace	0	0
Small	2 (10.0)	0
Moderate	0	0
Large	1 (5.0)	0
Week 27		
Number of samples	19	21
Negative	17 (89.5)	20 (95.2)
Trace	0	1 (4.8)
Small	1 (5.3)	0
Moderate	0	0
Large	1 (5.3)	0
Week 39		
Number of samples	17	21
Negative	16 (94.1)	20 (95.2)
Trace	1 (5.9)	1 (4.8)
Small	0	0
Moderate	0	0
Large	0	0
Week 53		
Number of samples	19	20
Negative	16 (84.2)	19 (95.0)
Trace	1 (5.3)	1 (5.0)
Small	1 (5.3)	0
Moderate	1 (5.3)	0
Large	0	0
Week 65		
Number of samples	16	18
Negative	15 (93.8)	17 (94.4)
Trace	0	1 (5.6)
Small	0	0
Moderate	0	0
Large	1 (6.3)	0
Week 79/EOS		
Number of samples	18	20
Negative	16 (88.9)	19 (95.0)
Trace	0	1 (5.0)
Small	1 (5.6)	0
Moderate	0	0
Large	1 (5.6)	0

EOS = end-of-study
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of investigational product.

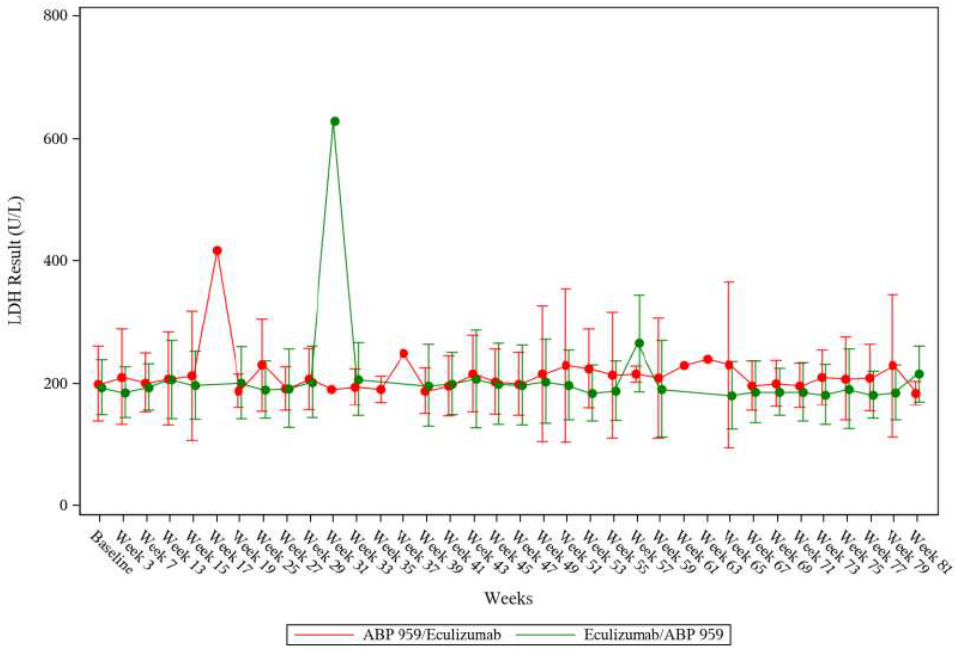
Results for analysis of the secondary efficacy endpoint for the crossover comparison of haemolysis, as measured by LDH at week 53 and week 79 are provided in Table 19. LDH time profile is given in Figure 9. LDH values were stable over time. The results were comparable between the 2 treatment groups.

Table 19 Analysis of LDH (U/L) at week 53 and week 79 – crossover comparison (FAS)

Statistics	ABP 959 (N = 42)	Eculizumab (N = 42)
Number of subjects (n)	39	40
Geometric LS mean[a]	209.95	203.56
Ratio of geometric LS mean (ABP 959/eculizumab)[a]	1.0314	
97.5% upper CI limit	1.1201	
95% CI	(0.9497, 1.1201)	

LDH = lactate dehydrogenase; LS = least squares; FAS = full analysis set
n = number of subjects included in the mixed model
Note: Lactate dehydrogenase values impacted by confounding events determined by the blinded independent LDH Review Committee were excluded.
a The point estimate and corresponding confidence limits for the log-transformed LDH values were estimated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and with subject as a random effect. A within subject variance-covariance structure of unstructured was used. Degree of freedom method was Kenward-Roger. The geometric LS means and point estimate and corresponding confidence limit for the ratio of geometric LS means were calculated by transforming back to the original scale.

Figure 9 Mean (± SD) LDH values (U/L) through end of study (FAS)



Note: LDH values impacted by confounding events determined by the blinded independent LDH Review Committee were excluded.

Notably, the week 17, week 37, week 61, and week 63 LDH values for the ABP 959/Soliris treatment group and the week 31 LDH values for both the ABP 959/Soliris treatment group and the Soliris/ABP 959 treatment group in CSR Figure 10-2 contain results from 1 subject each at the particular visit.

Summaries of red blood cell (RBC) transfusions in Periods 1 and 2 are given in Table 20.

Table 20 Summary of red blood cell transfusions (FAS)

Period 1

Statistics	ABP 959 (N = 20)	Eculizumab (N = 22)
Number of Packed Red Blood Cell Units transfused per month for Period 1		
n	2	5
Mean (std)	0.210 (0.1838)	0.220 (0.1155)
Median	0.210	0.170
Q1, Q3	0.080, 0.340	0.170, 0.340
Min, Max	0.08, 0.34	0.08, 0.34
Number of Packed Red Blood Cell Units transfused per month from week 13 to the end of Period 1		
n	2	5
Mean (std)	0.270 (0.2263)	0.278 (0.1446)
Median	0.270	0.210
Q1, Q3	0.110, 0.430	0.210, 0.430
Min, Max	0.11, 0.43	0.11, 0.43

Period 2

Statistics	ABP 959 (N = 21)[a]	Eculizumab (N = 20)[a]
Number of Packed Red Blood Cell Units transfused per month for Period 2		
n	3	1
Mean (std)	0.610 (0.4850)	0.330 (-)
Median	0.330	0.330
Q1, Q3	0.330, 1.170	0.330, 0.330
Min, Max	0.33, 1.17	0.33, 0.33
Number of Packed Red Blood Cell Units transfused per month from week 65 to end of study		
n	2	1
Mean (std)	0.725 (0.2051)	0.570 (-)
Median	0.725	0.570
Q1, Q3	0.580, 0.870	0.570, 0.570
Min, Max	0.58, 0.87	0.57, 0.57

[a] N is the number of subjects in the full analysis set who were treated with IP in period 2.

Over the entire study through the EOS, the mean (SD) number of packed RBC units transfused per month was 0.200 (0.1980) for 2 subjects in the ABP 959/eculizumab treatment group and 0.238 (0.2078) for 6 subjects in the eculizumab/ABP 959 treatment group (Table 21).

Table 21 Summary of red blood cell transfusions through EOS (FAS)

Statistics	ABP 959/Eculizumab (N = 20)	Eculizumab/ABP 959 (N = 22)
Number of packed RBC units transfused per month		
n	2	6
Mean (SD)	0.200 (0.1980)	0.238 (0.2078)

EOS = end-of-study; RBC = red blood cell
Note: All RBC units transfused are included in this summary.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 22 Summary of efficacy for trial 20150168

Title: A Randomized, Double-blind, Active-controlled, Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)		
Study identifier	Study 20150168 EudraCT Number: 2017-001418-27 NCT Number: NCT03818607	
Design	This is a multi-centre, randomised, double-blind, active-controlled, 2-period, crossover study to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of ABP 959 compared with Soliris in subjects with PNH.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks N/A N/A The total duration of study treatment is up to 79 weeks. Study participation consists of a screening period of up to 4 weeks, Period 1 is 52 weeks in duration (parallel treatment); Period 2 starts at week 53 with a crossover in treatment and is 26 weeks in duration; an End-Of-Study visit occurs 2 weeks (± 2 days) after the last dose of investigational product in Period 2.
Hypothesis	Clinical similarity, non-inferiority	
Treatments groups	ABP 959 (Test [T]) / Soliris (Reference [R]) treatment group	In treatment T, subjects receive a 900-mg IV dose of ABP 959 administered every 14 ± 2 days for 52 weeks (Period 1). At week 53, subjects crossover to receive treatment R, a 900-mg IV dose of Soliris (US or EU) administered every 14 ± 2 days for 26 weeks (Period 2). 20 subjects randomized
	Soliris (R)/ ABP 959 (T) treatment group	In treatment R, subjects receive a 900-mg IV dose of Soliris (US or EU) administered every 14 ± 2 days for 52 weeks (Period 1). At week 53, subjects crossover to receive treatment T, a 900-mg IV dose of ABP 959 administered every 14 ± 2 days for 26 weeks (Period 2). 22 subjects randomised

Title: A Randomized, Double-blind, Active-controlled, Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)			
Endpoints and definitions	Primary Endpoint (parallel comparison)	Haemolysis, as measured by LDH at week 27	The primary efficacy endpoint for the parallel comparison is haemolysis, as measured by lactate dehydrogenase (LDH) at week 27.
	Primary Endpoint (crossover comparison)	Haemolysis, as measured by AUEC of LDH from wk 13 to wk 27, from wk 39 to wk 53, and from wk 65 to wk 79.	The primary efficacy endpoint for the crossover comparison is haemolysis, as measured by the time-adjusted area under the effect curve (AUEC of LDH) from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79.
	Secondary endpoints	N/A - see next column	Total complement (50% total haemolytic complement activity [CH50]), total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, degree of haemoglobinuria, and type III erythrocytes at week 27, week 39, week 53, and post-crossover week 65 and week 79
	Secondary endpoint	LDH at wk 53 and wk 79	Crossover comparison of haemolysis as measured by LDH at week 53 and week 79
	Secondary endpoint	LDH-time profile	LDH-time profile
	Secondary endpoint	RBC transfusion	RBC transfusion
Database lock for Primary Analysis (Parallel Comparison)	10 January 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis for the parallel comparison was performed when all subjects completed or had the chance to complete the week 53 visit or had completed the EOS visit prior to week 53. Clinical similarity of the primary efficacy endpoint for the parallel comparison was evaluated using the full analysis set (FAS), which consisted of all randomised subjects. The clinical similarity of the primary endpoint of week 27 LDH between ABP 959 and Soliris was assessed by comparing the 1-sided 97.5% upper CI limit for the geometric mean ratios (GMR) of the LDH at week 27 between ABP 959 treatment and Soliris treatment with a non-inferiority (NI) margin of 2.873. To assess the robustness of the primary parallel comparison, the parallel comparison was also conducted using the per-protocol analysis set for the primary endpoint of LDH at week 27 for the parallel comparison (PPP analysis set), which was a subset of the FAS consisting of subjects who did not experience an important protocol deviation between week 13 and week 27 affecting their primary efficacy evaluation for the parallel comparison. All subjects from the FAS were included in the PPP analysis		

Title: A Randomized, Double-blind, Active-controlled, Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)			
	set; thus, results from the sensitivity analysis were identical with results from the primary efficacy analysis for the parallel comparison. The primary efficacy endpoint for the crossover comparison of haemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79, was evaluated using the full analysis set (FAS), which consisted of all randomised subjects. A sensitivity analysis was conducted using the PPC analysis set identical to the FAS. The secondary endpoints of total complement (CH50), total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, degree of haemoglobinuria, and type III erythrocytes (%) were summarised descriptively at week 27, week 39, week 53, week 65 and week 79 using the FAS and are included in Module 2.7.3 of the application and Study 20150168 Clinical Study Report (CSR) in Module 5.3.5.1.		
Descriptive statistics and estimate variability for LDH at wk 27 (FAS analysis set)	Treatment group	ABP 959	Soliris
	Number of subjects	20	22
	Week 27 Geometric LS mean Ratio of week 27 geometric LS mean (ABP 959/ Soliris)	205.69 1.0628	193.53
	97.5% Upper CI Limit 95% CI	1.1576 (0.9758, 1.1576)	
Notes	The point estimate and corresponding confidence limits for the log-transformed LDH values were estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable), and treatment by time interaction term as fixed effects. Compound symmetry covariance structure was applied to address repeat LDH measurement within subject. Degrees of freedom method was Kenward-Roger. The geometric LS means and point estimate and corresponding confidence limits for the ratio of geometric LS means were calculated by transforming back to the original scale. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 were included in the mixed model.		
Time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79 (FAS analysis set)	Treatment group	ABP 959	Soliris
	Number of subjects	40	40
	Geometric LS mean 95% CI	1445.76 (1295.63, 1613.28)	1473.44 (1321.86, 1642.41)
	Ratio of geometric LS mean (ABP 959/eculizumab) 90% CI	0.9812 (0.9403, 1.0239)	

Title: A Randomized, Double-blind, Active-controlled, Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)	
Notes	The point estimate and corresponding confidence limits for the log-transformed time-adjusted AUEC were estimated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects. Unstructured covariance structure was applied to address repeat AUEC assessments within subject. Degrees of freedom method was Kenward-Roger. Point estimates and corresponding confidence limits for the geometric LS means and the ratio of geometric LS means were calculated by transforming back to the original scale.

2.5.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

A supplemental analysis for the primary endpoint of LDH at week 27 was pre-planned in order to use prior information from historical eculizumab clinical studies. The method and results are summarised in this section.

Estimates of mean and SD for week 27 LDH were extracted from five relevant historical eculizumab studies and combined via Bayesian normal-normal hierarchical model to provide a meta-analytic-predictive (MAP) prior distribution for the true mean LDH in the Soliris arm in the current 20150168 study. The prior information contained by the MAP prior was equivalent to the data from 23.13 subjects. This prior information was further discounted adaptively according to the congruence between the historical eculizumab data and the Study 20150168 Soliris arm data to establish the elastic MAP (EMAP) prior. The particular discounting function was chosen to induce strong information borrowing when Study 20150168 Soliris arm data are congruent to historical eculizumab data (i.e. use MAP worth of 23.13 subjects as the prior) or discard the historical data altogether when a discrepancy exists between the two, leading an adoption of a non-informative prior for mean LDH in Soliris.

Based on prespecified criteria and LDH data at week 27, the EMAP prior for mean natural log(LDH) at week 27 for the Soliris arm was derived as being is normally distributed with mean value 5.53 and infinite variance, equivalent to a non-informative prior with no borrowing from historical data. Consequently, posterior week 27 GMR of ABP 959 vs. Soliris is 1.022 with respective 97.5% upper credible interval 1.205. The posterior probability of GMR < NI margin 2.873 is approximately 1, which is greater than the prespecified cutoff of 0.972, the critical value found via simulation to control the frequentist type I error at 0.025 under the null hypothesis that ABP959 is inferior to eculizumab with $\mu_t - \mu_r$ =1.06 (the NI margin on natural logarithm scale). Therefore, similarity was concluded by the applicant.

2.5.5.6. Supportive study

Not applicable.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design
The included patients were stable on Soliris treatment. This was discussed in scientific advice (EMA/CHMP/SAWP/674462/2015 and EMA/114622/2023) and not considered to be an ideal population, as subjects already stable on eculizumab therapy are a relatively insensitive population for detecting differences between treatments. But it was recognised to be the most feasible population. CHMP concluded that provided stringent similarity could be shown in healthy volunteers, ideally supported by data well within the standard acceptance ranges, the phase 3 population might be acceptable.. As a conclusion, the lack of a naïve group of PNH subjects is considered a weakness. The study design was, however, discussed and accepted by the CHMP during scientific advice, taking in account the rarity of PNH and consequent constraints in recruitment.

The primary objective of the single pivotal study 20150168 has not been specified within the estimand framework as per ICH E9(R1). This is not considered a problem *per se*, but it is noted that the use of LDH Review Committee - to review and identify LDH values impacted by confounding events (e.g., acute infection, or trauma including surgery) and potentially exclude these data from the analysis - effectively considers these confounding effects as intercurrent events. The analysis with some of the data excluded represents a hypothetical scenario where these confounding effects did not happen. The acceptability of this approach rests heavily on the assumption that the confounding effects leading to exclusion of data are indeed unrelated to the randomised treatment (not only to its efficacy). The applicant clarified in their response that the reviewers and adjudicator received both LDH values, laboratory data (inclusive of comments documenting tube haemolysis observed in the specimen) in the laboratory and clinical information of every subject. In a trial aiming to demonstrate equivalence, no data should be excluded from the analysis based on the outcome alone per CHMP GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE.

In the current study, exclusion of LDH measurements was impacted by the measured values themselves, which is not acceptable in principle. The reviewers also considered the laboratory notes indicating tube haemolysis; however, no information was provided as to whether tube haemolysis in the specimen was detected by the lab prior to bioanalysis or otherwise independently of the result. Furthermore, there are instances where a reviewer flagged an LDH measurement for exclusion due to tube haemolysis while the other reviewer did not. This suggests that the comments from the laboratory did not clearly indicate that the specimen was found invalid due to tube haemolysis. For these reasons the LDH review procedure leading to exclusion of LDH values from the analysis aiming to demonstrate equivalence is unacceptable in principle. Missing LDH values were not imputed in the analysis. The applicant was requested to present number of observations missing per treatment group for each time point included in the primary analysis model, i.e., week 13 to week 27. The numbers of missing values were negligible (1–3 values/sampling time point/study group) and are deemed to be missing at random.

The sample size calculation was based on power to demonstrate 1) non-inferiority (NI) of ABP 959 vs. Soliris at a 1-sided significance level of 0.025 in the primary endpoint of week 27 LDH for the parallel comparison (for EMA), and 2) similarity of ABP 959 vs. Soliris at a 2-sided significance level of 0.05 on the primary endpoint of time-adjusted AUEC of LDH for the crossover comparison from week 13 to week 27, from week

39 to week 53, and from week 65 to week 79 (for FDA). Usually, equivalent efficacy is required to be demonstrated for biosimilars. In this case, however, the NI approach for the primary parallel comparison endpoint can be agreed. In a study population already stabilised on eculizumab treatment, it would be unlikely that superiority would be found in maintenance of efficacy.

The proposed NI margin corresponding to 2.873-fold increase in average LDH level at week 27 in ABP 959 as compared with Soliris is found not acceptable clinically since this would consider "acceptable" LDH values of up to four times of what is usually referred to as upper limit of normal range. From a methodological point of view, the derivation of the NI appears to make some questionable assumptions, e.g., equating clinical relevance of 1.5xULN increase of LDH individual PNH patient with 1.5-fold increase in average LDH levels attained with the comparative treatments. However, the actual observed point estimate for LDH is close to 1 (1.0628) and the 95% CI for the primary analysis of LDH at Week 27 was narrow [0.9758, 1.1576]. The observed difference in LDH is deemed to be not clinically relevant.

Two interim analyses were performed on blinded variability. The second interim analysis allowed for a switch of primary analysis from parallel comparison to crossover comparison, had the inter-subject CV of LDH been large. This adaptive design has not been shown to preserve the type I error rate in all situations. However, it is agreed with the "Type I error report" presented by the applicant that the impact is probably reasonably small in the present situation and hence accepted.

A one-year parallel comparison is considered sufficient for assessment of efficacy and safety of ABP 959 vs. originator. Analysis of the primary endpoint at week 27 instead of Week 52 can be followed with the following justification: usually the recommendation would be to test at a time point with the highest 'effect dynamic' based on the comparison of the originator vs. placebo. This does not similarly apply in the present case where efficacy in eculizumab-pre-treated and stable patients is compared, investigating the ability to maintain treatment effect from baseline onwards. It is difficult to concur on the most sensitive assessment time point without making assumptions about the nature of such potential differences that need to be ruled out (e.g., rapidity of response onset vs. maximum achievable effect).

There are uncertainties if biosimilarity compared to the reference product can be supported by study 20150168. Considering that the included patients were stable on the reference product and not treatment-naïve, the study may not have been sensitive enough to detect potential differences between the substances in a population with high disease activity. Additional quality data as well as data from the study in healthy volunteers (PK, PD, ADA) were requested to be considered and discussed by the applicant in line with the scientific advice EMA/CHMP/SAWP/425900/2017. The efficacy data from the cross-over phase in study 20150168 positively support the application**.** It is however to be noted that final data from period 2 of the trial also represent a population already treated with eculizumab**,** similar to period 1, and as such is not a sensitive population for demonstration of difference between efficacy of ABP 959 and Soliris. In light of the results on other parts of the biosimilarity exercise, rarity of PNH, and the overall approach, a study in treatment-naïve subjects is not deemed to be required.

The primary and secondary endpoints of the study are deemed to yield an overall sufficient assessment of the degree of haemolysis in the study subjects and the therapeutic effect of eculizumab. Regarding PD, the method for determination of CH50 was changed between studies 20150164 and 20150168 since most PNH patients, during stable maintenance treatment, are expected to have CH50 levels below the detection limits of the commercially available Wako Autokit CH50 used in PK study 20150164. In study 20150168, the haemolytic assay CH50 was measured based on lysis of antibody-coated sheep red blood cells (EA) due to the activation of complement on the cell's surface. Patients with PNH are known to have higher than normal levels of haemolysis and higher than normal circulating haemoglobin levels. Therefore, a control for

endogenous haemoglobin levels was run in parallel with the haemolytic assay and subtracted from the CH50 assay to obtain the final CH50 result. Nevertheless, the observed CH50 values in study 20150168 were mostly below detection limit even with this method. The results below the LLOQ were included in the similarity analysis of the treatment groups and the applicant considers that these values were meaningful although the variability at such low levels is significant. Although the applicant has used an unconventional approach in the analysis, it can be concluded that the similarity of the treatment groups has been demonstrated.

The sample size estimation was based on the cross-sectional variability approximated from the TRIUMPH study results (Hillmen P et.al. The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Haemoglobinuria. The New England Journal of Medicine. 2006;355:1233-1243) where mean (SE) LHD at week 27 was 327.3 (67.6). The CV of 130% has been deduced from these figures and used, in part, as the justification of the proposed NI margin. As stated previously , the NI margin is considered wide and, formally, sufficient power for demonstrating the postulated NI was achieved with the total sample size of 40. The planned statistical analysis is actually able to considerably reduce random variability by adjusting for baseline LDH and using multiple time points' data for estimating average LDH at week 27. In conclusion, the study is able to provide results more precise than anticipated based on the initial, overly simplistic statistical analysis plans. Subjects were randomised to continue Soliris or switch to ABP 959 in 1:1 ratio within strata determined by whether or not RBC transfusion was received within the last 12 months. The randomisation scheme is considered appropriate. The study was double-blind which is considered ideal considering the study objectives.

The primary model-based estimates of mean ("LS mean") LDH values at week 27 are produced by a statistical model in which mean LDH value of a treatment group is linear trajectory from week 13 to week 27. The individual LDH values are modelled to also depend on subjects' baseline (week 1) LDH and stratification factor (RBC transfusion within 12 months before baseline). Given that subjects were stable on Soliris prior to randomisation and have been on randomised treatment for at least 13 weeks, the statistical model is considered appropriate in the sense that the LDH values from week 13 through 27 can be anticipated to estimate the same quantity.

Time-adjusted AUECs of LDH for the primary efficacy endpoint for the crossover comparison (from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79) were calculated using trapezoidal rule and standardised to describe LDH during a 7-day interval. Despite the linear interpolation, AUECs were statistically modelled as log-linear. Interpretation of results is further challenged by the fact that the AUEC are based on "trough" LDH measured approximately 14 days from previous dose, not on a real intervals of 7 days. While complicating the interpretation of estimates at patient and group level, these considerations do not prevent evaluation of similarity.

Conduct of the study

The amendments to the study are not considered to have compromised integrity of the study, even though the three latest protocol versions were implemented when the trial was already ongoing. All amendments occurred prior to data cut-off date (10 Jan 2022). Reported protocol deviations are deemed to not have affected assessment of the primary endpoints.

Efficacy data and additional analyses

Baseline

Of 47 screened,42 subjects (20 in the ABP 959/eculizumab treatment group and 22 in the eculizumab/ABP 959 treatment group) were randomised. All 42 randomised subjects are included in the clinical efficacy analyses.

The subjects represent a wide age range (21 to 78 years, median 36,5 years) of adult patients with PNH, with an equal gender distribution (22 female, 20 male). Regardless of the small size of the study, the baseline and disease characteristics are overall comparable. Most subjects are white, which is not considered a problem in the EU. At baseline, the mean duration from diagnosis was 5.7 years with a range from 1.4 years to 40 years. Overall, the subjects are representative of a wide range of adult PNH patients; except that subjects not tolerating eculizumab or not achieving stabilisation of PNH with eculizumab are not included, since subjects were required to be stable on eculizumab for enrolment.

Mean LDH values were normal; however, LDH values up to 430 U/L were seen at baseline, which exceeds the inclusion criterion of <1.5 x ULN at screening. Similarly, Hb values as low as 83 g/l at baseline, below the required 90 g/L, are reported. No violations of these inclusion criteria are reported in the CSR. Since the mean and median values and ranges of LDH and Hb are comparable between study arms, the presence of some subjects with Hb and LDH values outside of the inclusion criteria is not deemed to have compromised efficacy results. These/this subject(s) may have experienced haemolysis between screening and baseline samples. No further information was therefore requested on this matter.

Clinical efficacy

The week 27 mean LDH was estimated assuming a linear trajectory from week 13 through 27 that, at subject level, also depends on subject's baseline LDH and whether RBC transfusion was needed within 12 months before baseline. Any systematic trends in LDH level from week 13 to week 27 were negligible and, therefore, the LS means reflect the average LDH values during this time frame. The between-subject variability was negligible - probably due to the adjustment for baseline LDH. Overall, the primary statistical model is considered to use the data adequately and efficiently to address the primary objective.

The estimates of geometric LS means ratio of 1.0628 and the upper bound of the 95% CI (1.1576) are well below 2.873. Hence, a noninferior therapeutic effect was successfully demonstrated using the NI margin pre-specified by the applicant. Furthermore, the noted small difference in LDH at Week 27 is not considered clinically relevant. Additional analyses conducted upon CHMP request on the primary efficacy endpoint for the parallel comparison (LDH at week 27) using a weighted population based on prior red blood cell (RBC) transfusion stratification factor as observed in the current study data (i.e., using number of subjects as observed in the study for prior transfusion and no prior transfusion strata) demonstrated similar results in both study groups.

Results for analysis of the primary efficacy endpoint for the crossover comparison of haemolysis, as measured by the time-adjusted AUEC of LDH from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79, were suggestive of similar clinical efficacy between ABP 959 and eculizumab, since the 90% CI was contained within a similarity margin of (0.77, 1.30).

The applicant had pre-planned a supplementary analysis where available historical data from eculizumab clinical trials are used to give more precise estimate of mean LDH at week 27 in Soliris treatment. The five studies used by the applicant appeared comparable with study 20150168. Ultimately the applicant's pre-specified algorithm resulted in no use of historical data sources. While the data and methodology used for

this supplementary analysis leave some questions open, these are not considered critical because study 20150168 is considered, in principle, to provide supportive data only. Regarding efficient use of available data, an appropriate statistical model was used for the primary comparison of mean LDH levels between ABP 959 and Soliris and likely resulted considerable efficiency gains as compared with the potential gains by the use of historical data sources.

The secondary endpoints are given descriptively, without statistical comparison. In general, the values of total haemoglobin (Hb), serum-free haemoglobin, haptoglobin, bilirubin, degree of haemoglobinuria, and type III erythrocytes were stable over time and results were comparable between the groups administered ABP 959 and Soliris during the entire trial. Due to the small size of the study, some differences are seen in the mean levels of the measures of haemolysis at different sampling points; however, the direction of these differences varies, and there is no indication of increased haemolysis or disease activity in either study arm.

Over the entire study through the EOS, the mean (SD) number of packed red blood cell (RBC) units transfused per month was 0.200 (0.1980) for 2 subjects in the ABP 959/Soliris treatment group and 0.238 (0.2078) for 6 subjects in the Soliris/ABP 959 treatment group. For the time period of week 13 to the end of Period 1, the mean (SD) number of packed RBC units transfused per month was 0.160 (0.0707) for 2 subjects in the ABP 959 treatment group and 0.278 (0.1446) for 5 subjects in the Soliris treatment group. In Period 2 (through the primary analysis data cut-off), the mean (SD) number of packed RBC units transfused per month was 1.155 (0.1061) for 2 subjects in the ABP 959 treatment group. For the time period of week 65 to EOS, the mean (SD) number of packed RBC units transfused per month was 0.950 for 1 subject in the ABP 959 treatment group. No subjects in the Soliris treatment group were transfused in Period 2. Overall, there was no relevant difference between occurrence of RBC transfusions during the compared treatments over the study. The planned subgroups by RBC transfusion history, age, and gender were very small, therefore, no firm conclusions can be drawn from subgroup analyses. However, the results in the subgroups are overall consistent with the primary analysis.

2.5.7. Conclusions on the clinical efficacy

The maintenance design of Period 1 of the single pivotal phase 3 study is considered insensitive for demonstration of potential differences in efficacy and safety; even with the additional data obtained after cross-over for the 6-month Period 2 of the study. Furthermore, the study is small, with only 42 participants. Therefore, the currently available data are considered supportive but not confirmatory of similar efficacy.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

A total of 259 subjects received any amount of ABP 959 or Soliris IV, either as healthy subjects or subjects with PNH. Of the 259 subjects who received investigational product, 112 received ABP 959.

Table 23 Overall extent of exposure to investigational product (all clinical studies)

Study Type / Study Number	Number of Subjects Receiving any Amount of Investigational Product			
	ABP 959	Eculizumab (US)	Eculizumab (EU)	Total
PK/PD similarity study in healthy male subjects				
Study 20150164	71	72	74	217
Comparative clinical study in PNH patients (crossover in treatment)				
Study 20150168 (Period 1)	20		22[a]	42
Study 20150168 (Period 2)	21		20[a]	41
All clinical studies				
Total	112		188[b]	259

CSR = clinical study report; EU = European Union; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal haemoglobinuria; US = United States

[a] Both eculizumab (EU) and eculizumab (US) are being used in Study 20150168.

[b] Includes subjects receiving eculizumab (US) or eculizumab (EU) in Study 20150164 plus subjects receiving eculizumab (US or EU) in Study 20150168.

In Study 20150164, 217 healthy male subjects received a single 300-mg IV dose of ABP 959, FDA-licensed eculizumab (Soliris-US), or EU-authorised eculizumab (Soliris-EU).

In Study 20150168, 42 subjects (20 in the ABP 959/Soliris treatment group and 22 in the Soliris/ABP 959 treatment group) received 900 mg US or EU Soliris or ABP 959 (administered as an IV infusion every 14 days) for 52 weeks in Period 1 followed by the switch treatment for 26 weeks in Period 2.

Exposure in the Comparative Clinical Study – Study 20150168

Period 1

In period 1 the number of doses administered to subjects, the mean total dose of investigational product received, and the total investigational product exposure duration were similar between the ABP 959 and Soliris treatment groups.

41 (97.6%) subjects completed Period 1 dosing and 1 (4.5%) subject discontinued during Period 1. The reason for discontinuing investigational product for the subject in the Soliris/ABP 959 treatment group in Period 1 was adverse event (asthenia and fatigue).

Table 24 Investigational product exposure summary in period 1 (Study 20150168 safety analysis set)

Variable	ABP 959 (N = 20)	Eculizumab (N = 22)
Subjects receiving at least 1 dose	20	22
Total number of doses administered		
n	20	22
Mean (SD)	26.3 (1.16)	25.2 (4.07)
Total dose received (mg)		
n	20	22
Mean (SD)	23642.8 (1059.56)	22663.6 (3659.89)
Duration of investigational product exposure (weeks)		
n	20	22
Mean (SD)	52.249 (0.3813)	50.368 (8.3155)
Subjects who missed at least 1 dose of investigational product due to COVID-19-related reasons – n (%)	0	0
Number of subjects with at least 1 dose delay/not administered – n (%)	4 (20.0)	0
Related to COVID-19	1 (5.0)	0
Not related to COVID-19	3 (15.0)	0
Reasons for dose delay/not administered – n (%)[a]		
Adverse event – related to COVID-19	0	0
Adverse event – not related to COVID-19	3 (15.0)	0
Other – related to COVID-19 control measures	1 (5.0)	0
Other – not related to COVID-19 control measures	0	0
Number of subjects with at least 1 dose interruption – n (%)	2 (10.0)	1 (4.5)
Related to COVID-19	0	0
Not related to COVID-19	2 (10.0)	1 (4.5)
Reasons for dose interruption – n (%)[a]		
Adverse event – related to COVID-19	0	0
Adverse event – not related to COVID-19	0	1 (4.5)
Other – related to COVID-19 control measures	0	0
Other – not related to COVID-19 control measures	2 (10.0)	0
Number of subjects with at least 1 increase in dose and/or frequency – n (%)	1 (5.0)	1 (4.5)

COVID-19 = coronavirus disease 2019; CSR = clinical study report

[a] Subjects could have more than one reason for dose interruption and dose delay/not administered.

Period 2

A total of 41 (97.6%) subjects received treatment with IP in Period 2: (20 [100.0%] subjects in the ABP 959/Soliris treatment group and 21 [95.5%] subjects in the Soliris/ABP 959 treatment group), and 39 (92.9%) subjects (19 [95.0%] and 20 [90.9%] subjects, respectively) completed Period 2 IP dosing. One subject in both study groups discontinued IP during Period 2. Reasons for discontinuing IP in Period 2 were consent withdrawal for treatment (1 [5.0%] subject in the ABP 959/ Soliris treatment group) and other (i,e., identified as patient's personal needs) (1 [4.5%] subject in the Soliris/ABP 959 treatment group).

The number of doses administered to subjects, the mean total dose of investigational product received, and the total investigational product exposure duration in Period 2 were similar between the ABP 959 and eculizumab treatment groups.

2.5.8.2. Adverse events

PK/PD Similarity Study – Study 20150164

Adverse events were graded according to the National Cancer Institute (US) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

In Study 20150164, 69.6% of subjects overall reported at least 1 adverse event. Most adverse events were assessed as grade 1 or grade 2 in severity; 133 (61.3%) and 56 (25.8%) subjects, respectively. The number of subjects who experienced grade 3 events in any treatment group was 1 (1.4%) each in the ABP 959, Soliris (US), and Soliris (EU) treatment groups. There were no grade 4 or grade 5 events (no deaths) and no adverse events leading to study or study drug discontinuation.

Table 25 Overall summary of treatment-emergent adverse events (Study 20150164 safety population)

	Number (%) of Subjects[a] and [Number of Events]			
	Treatment			
AE Category	ABP 959 (N = 71)	FDA-licensed Eculizumab (N = 72)	EU-authorized Eculizumab (N = 74)	Overall (N = 217)
Any TEAE	54 (76.1) [128]	46 (63.9) [108]	51 (68.9) [143]	151 (69.6) [379]
Any Grade 1 TEAE	47 (66.2) [97]	39 (54.2) [88]	47 (63.5) [109]	133 (61.3) [294]
Any Grade 2 TEAE	22 (31.0) [30]	13 (18.1) [16]	21 (28.4) [33]	56 (25.8) [79]
Any Grade 3 TEAE	1 (1.4) [1]	1 (1.4) [4]	1 (1.4) [1]	3 (1.4) [6]
Any Grade 4 TEAE	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any Grade 5 TEAE	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any TEAE leading to discontinuation from study	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any TEAE leading to discontinuation of study drug	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any SAE	1 (1.4) [1]	2 (2.8) [5]	2 (2.7) [2]	5 (2.3) [8]
Any drug-related SAE	0 (0.0) [0]	0 (0.0) [0]	1 (1.4) [1]	1 (0.5) [1]
Any life-threatening SAE	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any SAE resulting in death	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any event of interest	23 (32.4) [30]	25 (34.7) [30]	33 (44.6) [43]	81 (37.3) [103]

[a] Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than 1 category were counted once in each of those categories.
Note: A TEAE was defined as an AE that was not present prior to treatment with study drug, but appeared following treatment or was present at treatment initiation but worsened during treatment.
Grade 1 - Mild; Grade 2 - Moderate; Grade 3 - Severe; Grade 4 - Life-threatening; Grade 5 - Death.

The Grade 3 events (severe) were viral infection, epistaxis, facial bones fractures and headache. The events of viral infection, epistaxis, facial bones fractures were considered not related to study drug. The event of headache was considered probably related to the Soliris-EU treatment.

Common adverse events

The most common TEAEs by preferred term (PT) (reported in more than 5% of subjects) were headache, upper respiratory tract infection, back pain and rhinitis.

Table 26 Summary of treatment-emergent adverse events reported in five or more subjects in any treatment group by preferred term in descending order of frequency and by treatment (Study 20150164 safety population)

	Number (%) of Subjects[a] and [Number of Events]			
	Treatment			
MedDRA Preferred Term	ABP 959 (N = 71)	FDA-licensed Eculizumab (N = 72)	EU-authorized Eculizumab (N = 74)	Overall (N = 217)
Subjects with any TEAE	54 (76.1) [128]	46 (63.9) [108]	51 (68.9) [143]	151 (69.6) [379]
Headache	19 (26.8) [27]	18 (25.0) [23]	17 (23.0) [26]	54 (24.9) [76]
Upper respiratory tract infection	14 (19.7) [15]	13 (18.1) [14]	22 (29.7) [23]	49 (22.6) [52]
Back pain	4 (5.6) [4]	1 (1.4) [1]	6 (8.1) [6]	11 (5.1) [11]
Rhinitis	5 (7.0) [5]	3 (4.2) [3]	3 (4.1) [3]	11 (5.1) [11]
Abdominal pain	5 (7.0) [5]	1 (1.4) [1]	3 (4.1) [3]	9 (4.1) [9]
Catheter site pain	4 (5.6) [4]	0 (0.0) [0]	4 (5.4) [5]	8 (3.7) [9]
Fatigue	3 (4.2) [3]	2 (2.8) [2]	2 (2.7) [2]	7 (3.2) [7]
Diarrhoea	2 (2.8) [2]	3 (4.2) [4]	1 (1.4) [1]	6 (2.8) [7]
Oropharyngeal pain	2 (2.8) [2]	0 (0.0) [0]	4 (5.4) [5]	6 (2.8) [7]
Rhinorrhoea	1 (1.4) [1]	4 (5.6) [5]	1 (1.4) [2]	6 (2.8) [8]
Nausea	3 (4.2) [3]	1 (1.4) [1]	1 (1.4) [1]	5 (2.3) [5]
Neck pain	2 (2.8) [2]	1 (1.4) [1]	2 (2.7) [2]	5 (2.3) [5]
Pharyngitis	1 (1.4) [1]	2 (2.8) [2]	2 (2.7) [2]	5 (2.3) [5]
Skin abrasion	1 (1.4) [1]	3 (4.2) [4]	1 (1.4) [1]	5 (2.3) [6]

[a] Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than 1 category were counted once in each of those categories.
Note: AEs were coded using MedDRA Version 19.0.

Events of special interest

The EOIs included infections, infusion reactions, meningococcal infection, sepsis and haematologic abnormalities. There were 70 Grade 1 EOIs, 23 Grade 2 EOIs and one Grade 3 EOI.

Table 27 Overall summary of treatment-emergent adverse events of interest of any grade (Study 20150164 safety population)

Event of Interest[a]	ABP 959 (N = 71)	Eculizumab (US) (N = 72)	Eculizumab (EU) (N = 74)	Overall (N = 217)
	Number of Subjects (%)[b] and [Number of Events][c]			
Any event of interest	23 (32.4) [30]	25 (34.7) [30]	33 (44.6) [43]	81 (37.3) [103]
Infections	20 (28.2) [26]	19 (26.4) [21]	29 (39.2) [36]	68 (31.3) [83]
Infusion reaction	4 (5.6) [4]	8 (11.1) [9]	6 (8.1) [7]	18 (8.3) [20]
Infusion reaction with onset day coincident with IP infusion or the day after IP infusion	3 (4.2) [3]	0 (0.0) [0]	1 (1.4) [1]	4 (1.8) [4]
Hemolytic	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hematologic	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hematopoietic	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Meningococcal infection	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Sepsis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

CSR = clinical study report; EU = European Union; MedDRA = Medical dictionary for Regulatory Activities; US = United States

[a] Identified using the search strategies presented in Section 8.1 of this summary

[b] For each event of interest, subjects were included only once, in the maximum severity, for that event of interest.

[c] For each event of interest, events are counted in the maximum severity.

Grade 1 and 2 infections included upper respiratory tract infection (49 subjects [52 events]); rhinitis (11 subjects [11 events]); pharyngitis (5 subjects [5 events]); oral herpes (3 subjects [3 events]); gastroenteritis viral and viral upper respiratory tract infection; and Campylobacter gastroenteritis, Helicobacter infection, Herpes simplex, Epstein-Barr virus infection, gastroenteritis, and gonorrhoea. The one Grade 3 infection was a viral infection (1 subject [2 events]) in the ABP 959 group.

Infusion reactions were split into 2 categories of infusion reaction with onset day coinciding with study drug infusion or the day after study drug infusion, and infusion reactions with onset any time post dose. The first category included 4 subjects (4 events) with Grade 1 or 2 events of cough, pyrexia, skin reaction, and infusion-related reaction (each 1 subject [1 event]). The second category included 18 subjects (20 events) with Grade 1 or 2 events of cough and pyrexia (each 3 subjects [3 events]); blister and dermatitis (each 2 subjects [2 events]); and skin reaction, erythema, flushing, mouth ulceration, myalgia, nasal obstruction, rhinitis allergic, stomatitis, infusion related reaction and photosensitivity reaction (each 1 subject [1 event]).

No meningococcal infection, sepsis, haematologic, haemolytic, or haematopoetic TEAEs were reported.

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An overall summary of adverse events in Period 1 is presented in Table 28. Most adverse events in Period 1 were CTCAE grade 1 or 2 in severity. Two (10.0%) subjects in the ABP 959 treatment group and 8 (36.4%) subjects in the Soliris treatment group experienced CTCAE grade ≥ 3 adverse events. No subjects in either treatment group experienced CTCAE grade 4 or 5 adverse events.

Period 1

Table 28 Overall summary of adverse events in period 1 (Study 20150168 safety population)

Adverse Event Category	ABP 959 (N = 20) n (%)	Eculizumab (N = 22) n (%)
Any adverse event	15 (75.0)	21 (95.5)
Any grade ≥ 3 adverse event	2 (10.0)	8 (36.4)
Any fatal adverse event	0 (0.0)	0 (0.0)
Any serious adverse event	3 (15.0)	1 (4.5)
Any adverse event leading to discontinuation of IP/study	0 (0.0)	1 (4.5)
Any EOI	9 (45.0)	12 (54.5)
Infusion reaction adverse event[a]	9 (45.0)	12 (54.5)
Serious infection adverse event[b]	1 (5.0)	0 (0.0)

AMQ = Amgen MedDRA Query; EOI = event of interest; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; SOC = system organ class
Note: Only treatment-emergent adverse events were summarised. For each category, subjects were included only once, even if they experienced multiple events in that category.
a Identified using the hypersensitivity SMQ (broad) and infusion reaction AMQ (broad) search strategies
b d) Identified using the infections and infestations SOC (broad) search strategy

Common adverse events in Period 1

In Period 1, the most frequently reported (≥ 20%) adverse events in the ABP 959 treatment group were pyrexia, nasopharyngitis, and anaemia, which were reported in 6 (30.0%), 5 (25.0%), and 4 (20.0%) subjects, respectively; the most frequently reported (≥ 20%) adverse events in the Soliris treatment group were headache, vaccination complication (in most cases a reaction to a COVID-19 vaccination), and hypertension, which were reported in 9 (40.9%), 5 (22.7%), and 5 (22.7%) subjects, respectively.

Table 29. Adverse events experienced by ≥ 10% of subjects in any treatment group by preferred term in period 1 (Study 20150168 safety analysis set)

Preferred Term	ABP 959 (N = 20) n (%)	Eculizumab (N = 22) n (%)
Pyrexia	6 (30.0)	1 (4.5)
Nasopharyngitis	5 (25.0)	2 (9.1)
Anemia	4 (20.0)	4 (18.2)
Diarrhea	3 (15.0)	1 (4.5)
Headache	3 (15.0)	9 (40.9)
Nausea	3 (15.0)	1 (4.5)
Arthralgia	2 (10.0)	1 (4.5)
Back pain	2 (10.0)	1 (4.5)
Cough	2 (10.0)	3 (13.6)
Dizziness	2 (10.0)	2 (9.1)
Fatigue	2 (10.0)	2 (9.1)
Hemolysis	2 (10.0)	2 (9.1)
Hyperbilirubinemia	2 (10.0)	1 (4.5)
Influenza like illness	2 (10.0)	2 (9.1)
Pain in extremity	2 (10.0)	1 (4.5)
Pruritus	2 (10.0)	1 (4.5)
Vaccination complication	1 (5.0)	5 (22.7)
Hypertension	0 (0.0)	5 (22.7)

Events of special interest in Period 1

Table 30 Overall summary of events of interest in period 1 (Study 20150168 safety analysis set)

Adverse Event of Interest	ABP 959 (N = 20) n (%)	Eculizumab (N = 22) n (%)	Risk Difference (%) (95% CI[a])
Number of subjects reporting any adverse event of interest	9 (45.0)	12 (54.5)	-9.5 (-39.3, 21.5)
Infusion reactions[b]	9 (45.0)	12 (54.5)	-9.5 (-39.3, 21.5)
Serious infections[c]	1 (5.0)	0 (0.0)	5.0 (-10.9, 24.9)

AMQ = Amgen MedDRA Query; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; SOC = system organ class

Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarised. For each event of interest, subjects were included only once, even if they experienced multiple events in that event of interest.

[a] Confidence intervals of the risk difference (ABP 959 – eculizumab) were estimated by exact method.

[b] Identified using the hypersensitivity SMQ (broad) and infusion reaction AMQ (broad) search strategies

[c] Identified using the infections and infestations SOC (broad) search strategy

The most frequently reported (≥ 2 subjects in the ABP 959 treatment group) preferred terms mapping to the infusion reaction search strategy were fatigue (2 [10.0%] subjects in the ABP 959 treatment group and 1 [4.5%] subject in the Soliris treatment group), hyperbilirubinemia (2 [10.0%] and 1 [4.5%] subjects, respectively), and pruritus (2 [10.0%] and 1 [4.5%] subjects, respectively. Most infusion reaction EOIs were grade 1 or 2 in severity. No grade ≥ 3 infusion reaction EOIs were experienced by subjects in the ABP 959 treatment group. In Period 1, 1 (5.0%) subject in the ABP 959 treatment group and 0 (0.0%) subjects in the Soliris treatment group experienced events per the serious infection EOI search strategy. The subject in the ABP 959 treatment group experienced a serious infection EOI of grade 2 serious gastroenteritis.

Period 2

Table 31 Overall summary of adverse events in period 2 (Study 20150168 safety population)

Adverse Event Category	ABP 959 (N = 21)[a] n (%)	Eculizumab (N = 20)[a] n (%)
Any adverse event	18 (85.7)	18 (90.0)
Any grade ≥ 3 adverse event	6 (28.6)	4 (20.0)
Any fatal adverse event	0 (0.0)	0 (0.0)
Any serious adverse event	4 (19.0)	1 (5.0)
Any adverse event leading to discontinuation of IP/study	0 (0.0)	0 (0.0)
Any EOI	8 (38.1)	3 (15.0)
Infusion reaction adverse event[b]	6 (28.6)	3 (15.0)
Serious infection adverse event[c]	2 (9.5)	0 (0.0)

Common adverse events in Period 2

Table 32 Adverse events experienced by ≥ 10% of subjects in any treatment group by preferred term in period 2 (safety analysis set)

Preferred Term	ABP 959 (N = 21)[a] n (%)	Eculizumab (N = 20)[a] n (%)
COVID-19	4 (19.0)	5 (25.0)
Nasopharyngitis	4 (19.0)	1 (5.0)
Anemia	3 (14.3)	1 (5.0)
Pyrexia	3 (14.3)	1 (5.0)
Asthenia	2 (9.5)	3 (15.0)
Vaccination complication	2 (9.5)	2 (10.0)
Hemolysis	0 (0.0)	2 (10.0)

Events of special interest in Period 2

Two subjects in the ABP 959 treatment group experienced serious infection EOIs: one serious COVID-19 of grade 2 and one non-serious streptococcal urinary tract infection of grade 3.

Table 33 Overall summary of events of interest in period 2 (study 20150168 safety analysis set)

Adverse Event of Interest	ABP 959 (N = 21)[a] n (%)	Eculizumab (N = 20)[a] n (%)	Risk Difference (%) (95% CI[b])
Number of subjects reporting any adverse event of interest	8 (38.1)	3 (15.0)	23.1 (-6.2, 49.1)
Infusion reactions[c]	6 (28.6)	3 (15.0)	13.6 (-13.5, 39.3)
Serious infections[d]	2 (9.5)	0 (0.0)	9.5 (-7.9, 30.4)

AMQ = Amgen MedDRA Query; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; SOC = system organ class
Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarised. For each event of interest, subjects were included only once, even if they experienced multiple events in that event of interest.

[a] N is the number of subjects in the safety analysis set who were treated with investigational product in Period 2.
[b] Confidence intervals of the risk difference (ABP 959 – eculizumab) were estimated by exact method.
[c] Identified using the hypersensitivity SMQ (broad) and infusion reaction AMQ (broad) search strategies
[d] Identified using the infections and infestations SOC (broad) search

2.5.8.3. Serious adverse event/deaths/other significant events

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There were 8 SAEs that occurred in 5 subjects. There were no life-threatening TEAEs, no deaths, and no TEAEs leading to discontinuation from the study or study drug.

Table 34 Summary of serious treatment-emergent adverse events by preferred term and treatment (study 20150164 safety population)

Preferred Term	ABP 959 (N = 71)	Eculizumab (US) (N = 72)	Eculizumab (EU) (N = 74)	Overall (N = 217)
	Number of Subjects (%) and [Number of Events]			
Subjects with any serious TEAE	1 (1.4) [1]	2 (2.8) [5]	2 (2.7) [2]	5 (2.3) [8]
Epistaxis	0 (0.0) [0]	1 (1.4) [1]	0 (0.0) [0]	1 (0.5) [1]
Facial bones fracture	0 (0.0) [0]	1 (1.4) [3]	0 (0.0) [0]	1 (0.5) [3]
Headache	0 (0.0) [0]	0 (0.0) [0]	1 (1.4) [1]	1 (0.5) [1]
Pericarditis	0 (0.0) [0]	0 (0.0) [0]	1 (1.4) [1]	1 (0.5) [1]
Soft tissue injury	0 (0.0) [0]	1 (1.4) [1]	0 (0.0) [0]	1 (0.5) [1]
Viral infection	1 (1.4) [1]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]

CSR = clinical study report; MedDRA = Medical dictionary for Regulatory Activities; TEAE = treatment- emergent adverse events; EU = European Union; US = United States

Note: Adverse events were coded using MedDRA Version 19.0. For each preferred term, subjects with multiple events in the same category were counted only once in that category. Subjects with events in once in each of those categories.

The serious adverse events were assessed as grade 2 (moderate) or grade 3 (severe), and all but the headache were considered not related to study drug by the applicant.

In the ABP 959 treatment arm, one serious adverse event was reported for one subject. Based on the provided narrative the patient was hospitalised for one day due to an unspecified viral infection on day 13 after administration of the study drug. The event was considered not related to the study drug.

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Period 1

In Period 1, 3 (15.0%) subjects in the ABP 959 treatment group experienced a total of 8 serious adverse events, and 1 (4.5%) subject in the Soliris treatment group experienced a serious adverse event. All SAEs were single events and review of the individual events did not identify any new safety concerns or new pattern of serious adverse events.

Table 35 Serious adverse events by system organ class and preferred term in period 1 (safety analysis set)

System Organ Class Preferred Term	ABP 959 (N = 20) n (%)	Eculizumab (N = 22) n (%)
Number of subjects reporting serious treatment-emergent adverse events	3 (15.0)	1 (4.5)
Cardiac disorders	1 (5.0)	0 (0.0)
Cardiac failure	1 (5.0)	0 (0.0)
Hepatobiliary disorders	1 (5.0)	0 (0.0)
Cholecystitis	1 (5.0)	0 (0.0)
Infections and infestations	1 (5.0)	0 (0.0)
Gastroenteritis	1 (5.0)	0 (0.0)
Nervous system disorders	1 (5.0)	0 (0.0)
Vertigo CNS origin	1 (5.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (4.5)
Anemia	0 (0.0)	1 (4.5)

MedDRA = Medical Dictionary for Regulatory Activities
Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarised. For each system organ class and preferred term, subjects were included only once, even if they experienced multiple events in that system organ class or preferred term.

Period 2

In Period 2, 4 (19.0%) subjects in the ABP 959 treatment group experienced a total of 6 serious adverse events and 1 (5.0%) subject in the Soliris treatment group experienced a total of 4 serious adverse events.

Table 36 Serious adverse events by system organ class and preferred term in period 2 (safety analysis set)

System Organ Class Preferred Term	ABP 959 (N = 21)[a]	Eculizumab (N = 20)[a]
Number of subjects reporting serious treatment-emergent adverse events	4 (19.0)	1 (5.0)
Blood and lymphatic system disorders	1 (4.8)	0 (0.0)
Anemia	1 (4.8)	0 (0.0)
Infections and infestations	1 (4.8)	0 (0.0)
COVID-19	1 (4.8)	0 (0.0)
Injury, poisoning and procedural complications	1 (4.8)	0 (0.0)
Meniscus injury	1 (4.8)	0 (0.0)
Psychiatric disorders	1 (4.8)	0 (0.0)
Depression	1 (4.8)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (5.0)
Cardiac failure	0 (0.0)	1 (5.0)
Cardiac failure chronic	0 (0.0)	1 (5.0)

COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities
Note: Adverse events were coded using MedDRA version 24.1. Only treatment-emergent adverse events were summarised. For each system organ class and preferred term, subjects were included only once, even if they experienced multiple events in that system organ class or preferred term.
[a] N is the number of subjects in the safety analysis set who were treated with investigational product in Period 2.

2.5.8.4. Laboratory findings

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There were 6 subjects with clinically significant laboratory findings, 3 in the Soliris-EU group and 3 in the ABP 959 group. The clinically significant findings included transiently elevated liver function tests and elevated neutrophil and leukocyte values in conjunction with upper respiratory or urinary infections.

No safety signals were identified during the analysis of mean haematology laboratory values over time. No haematologic, haemolytic, or haematopoietic adverse events were reported although sporadic abnormal haematology laboratory values and changes from baseline occurred.

There were no clinically relevant changes in vital signs over the course of the study.

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Haematology Laboratory Results

There were no notable differences between the ABP 959 and Soliris treatment groups in median changes from baseline for white blood cell (WBC) parameters (leukocytes and neutrophils), red blood cell (RBC) parameters (erythrocytes, haemoglobin, and haematocrit), platelets or haemolysis-related parameters (type III cells [erythrocytes, monocytes, and granulocytes] and serum-free haemoglobin) in Period 1 or Period 2.

Based on CTCAE v5.0 grading, postbaseline grade ≥ 3 WBC parameters in Period 1 included neutrophils decreased (5 [25.0%] subjects in the ABP 959 treatment group and 4 [18.2%] subjects in the Soliris treatment group) and WBC count (leukocytes) decreased (3 [15.0%] and 2 [9.1%] subjects, respectively). Postbaseline grade ≥ 3 WBC parameters in Period 2 included neutrophils decreased (5 [23.8%] subjects in the ABP 959 treatment group and 6 [30.0%] subjects in the eculizumab treatment group) and WBC count (leukocytes) decreased (4 [19.0%] and 5 [25.0%] subjects, respectively. Postbaseline grade ≥ 3 RBC parameters in Period 1 included haemoglobin decreased (1 [5.0%] subject in the ABP 959 treatment group and 2 [9.1%] subjects in the Soliris treatment group). Postbaseline grade ≥ 3 RBC parameters in Period 2 included haemoglobin decreased (1 [4.8%] subject in the ABP 959 treatment group and 1 [5.0%] subject in the eculizumab treatment group).

Chemistry Laboratory Results

There were no notable differences between the ABP 959 and Soliris treatment groups in median changes from baseline for hepatobiliary parameters (ALT, AST, bilirubin, ALP, LDH, and haptoglobin) or renal function tests (potassium, creatinine, blood urea nitrogen [BUN], and uric acid) in Period 1 or Period 2.

According to the applicant, one subject in the ABP 959 treatment group had a postbaseline grade ≥ 3 bilirubin with an increase from baseline > 1 x the upper limit of normal to maximum postbaseline grade 3. No subjects experienced postbaseline grade ≥ 3 renal function tests in Period 1 or Period 2. There were no clinically relevant changes in vital signs over the course of the study.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Not applicable.

2.5.8.7. Immunological events

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Blood samples for ADA analysis were collected at pre-dose, at scheduled time points during the study, and at the end of the study.

No subjects were excluded from the ADA Population.

At baseline (day 1, predose), 7 (3.2%) subjects were positive for binding ADAs: 4 (5.6%) subjects, 2 (2.8%) subjects, and 1 (1.4%) subject in the ABP 959, Soliris-US, and Soliris-EU treatment groups, respectively. The signal-to-noise ratios for these 7 subjects were low in magnitude; all samples tested negative for neutralizing ADAs. The applicant comments that these results are expected and demonstrate a suitable assay cut point that can result in a screening assay false positive rate between 2% and 11% (*Devanarayan et al. Recommendations for Systematic Statistical Computation of Immunogenicity Cut Points. The AAPS Journal, Vol. 19, No. 5, September 2017*).

Table 37 presents the results on binding ADA by treatment group for the total ADA population. In the Japanese subgroup (n=12, 4 in each treatment group) no subject had positive ADA results.

Table 37 Summary of binding ADA results by treatment (ADA population)

	Number and Percentage of Subjects with Anti-drug Antibody Positive Results			
Visit	ABP 959 (N=71)	Eculizumab (US) (N=72)	Eculizumab (EU) (N=74)	Overall (N=217)
Day 1, Pre-dose	4/ 71 (5.6%)	2/ 72 (2.8%)	1/ 74 (1.4%)	7/217 (3.2%)
Day 11	5/ 67 (7.5%)	4/ 64 (6.3%)	6/ 67 (9.0%)	15/198 (7.6%)
Day 29	1/ 67 (1.5%)	2/ 69 (2.9%)	0/ 70 (0.0%)	3/206 (1.5%)
Day 57 (EOS)	1/ 70 (1.4%)	2/ 68 (2.9%)	1/ 73 (1.4%)	4/211 (1.9%)
Positive at any time during the study[a]	7/ 71 (9.9%)	5/ 72 (6.9%)	7/ 74 (9.5%)	19/217 (8.8%)
Positive post-baseline with a negative or no result at baseline[b]	3/ 71 (4.2%)	3/ 70 (4.3%)	6/ 73 (8.2%)	12/214 (5.6%)

Data Source: ADIS dataset
Abbreviation: EOS - End of Study.
[a] The denominator includes all subjects with at least one ADA assessment during the study.
[b] The denominator includes all subjects with at least one post-dose ADA assessment during the study.

Sensitivity analysis in the subgroup of subjects with negative binding ADA status confirmed that the 90% CI for the GMR for the parameters AUC_{inf}, AUC_{last}, and C_{max} for all comparisons were within the bioequivalence criteria of 0.80 to 1.25 (ABP 959 versus Soliris-US, ABP 959 versus Soliris-EU, and Soliris-US versus Soliris-EU.

No positive neutralising ADA results were reported in study 20150164.

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Blood samples for ADA analysis were collected at baseline on day 1/visit 1/week 1, pre-dose, at scheduled time points during the study, and at the end of the study.

In Period 1, all 42 subjects had at least one on-study ADA result. No subjects in either treatment group tested positive for pre-existing binding ADAs or neutralizing ADAs at baseline. No subjects in either treatment group tested positive for binding ADAs, neutralising ADAs, or treatment boosted ADAs in Period 1.

In period 2, two subjects (9.1%) in the eculizumab/ABP 959 treatment group tested positive for binding ADAs (for both subjects, the positive binding ADA was observed following the crossover in treatment to ABP 959). Results were transient (i.e., negative results at the subject's last time point tested) for both subjects. Neither subject experienced serious adverse events that were related to the transient ADAs. Of subjects with a postbaseline result through EOS, no subjects in either treatment group tested positive for neutralizing ADAs or treatment boosted ADAs.

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

Not applicable.

2.5.8.9. Discontinuation due to adverse events

There were no events leading to study or study drug discontinuation in Study 20150164.

In Study 20150168 discontinuation of investigational product or study due to 1 or more adverse events occurred in 0 (0.0%) in the ABP 959 and 1 (4.5%) subject, and Soliris treatment groups in Period 1. The subject in the Soliris treatment group discontinued both investigational product and the study due to adverse events of grade 2 non-serious asthenia and grade 2 non-serious fatigue.

In Period 2 (through the primary analysis data cut-off), no subjects in either treatment group discontinued investigational product or study due to 1 or more adverse events.

2.5.8.10. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

The clinical evidence supporting the similarity of ABP 959 to Soliris (eculizumab) includes one single-dose PK/PD-study in healthy adult male subjects (Study 20150164) and one completed comparative clinical efficacy and safety study in adult subjects with paroxysmal nocturnal haematuria (PNH) (Study 20150168).

Safety findings were presented for a total of 259 subjects. In the PK/PD study 217 healthy males were exposed to one single dose of 300mg either Soliris-EU (74 subjects), Soliris-US (72 subjects) or ABP 959 (71 subjects). In the clinical comparative study 42 adult subjects with PNH were treated with 900 mg Soliris or ABP 959 administered as IV infusion every 14 days. Period 1 of the clinical comparative study lasted 52 weeks. Period 2 started at week 53 with a crossover in treatment and was 26 weeks in duration. Thirty-nine subjects (19 [95.0%] and 20 [90.9%] subjects, respectively) completed Period 2.

Due to the small sample size of the Phase 3 study and due to the inevitable carry over effects between study periods as patients entered on a stable Soliris regimen, the clinical studies can only provide limited information on comparability of safety and immunogenicity. In Study 20150168, the risk of experiencing adverse events was inherently low as only patients already on stable Soliris treatment (i.e., subjects with established good tolerance for treatment) were included. Despite these limitations, the development programme is considered acceptable from a safety perspective and was agreed upon via Scientific Advice (SA; EMA/CHMP/SAWP/674462/2015, Procedure No. EMEA/H/SA/3164/1/2015/III).

Exposure to investigational product was similar across the ABP 959 and Soliris treatment groups in both studies. In general, incidence of study completion and discontinuation was comparable between the treatment groups.

PK/PD Similarity Study – Study 20150164

In the PK/PD Similarity Study 69.6% of subjects overall reported at least 1 adverse event. Most adverse events were assessed as grade 1 or grade 2 in severity. The most common TEAEs by PT (reported in more than 5% of subjects) were headache, upper respiratory tract infection, back pain and rhinitis.

There were no life-threatening TEAEs, no deaths, and no TEAEs leading to discontinuation from the study or study drug. There were no serious TEAEs in the ABP 959 treatment arm which were related to the study

drug. No meaningful difference between the groups could be seen in terms of nature, grade or frequency of TEAEs. The safety of all three investigational products was consistent with the known safety profile of Soliris.

Comparative Clinical Study – Study 20150168

In Period 1 of the comparative clinical Study, 15 (75.0%) subjects in the ABP 959 treatment group and 21 (95.5%) subjects in the Soliris treatment group reported at least 1 adverse event. Most adverse events in Period 1 were grade 1 or 2 in severity.

The most common TEAEs by PT (≥ 20%) in the ABP 959 treatment group were pyrexia, nasopharyngitis and anaemia. The most frequently reported adverse events in the Soliris treatment group were headache, vaccination complication, and hypertension. The seemingly large percentual difference between groups regarding some of the preferred terms does not cause concern as the number of subjects is small and the frequency of reported AEs in the ABP 959 group are in line with those reported for Soliris in the SmPC.

Throughout the study (Periods 1 + 2), 7 (17.1%) subjects receiving ABP 959 experienced a total of 14 serious adverse events, and 2 (4.8%) subjects receiving eculizumab experienced a total of 5 serious adverse events. The number of SAEs was higher in the ABP 959 group compared to the Soliris group. However, most SAEs were not considered related to the study drug, all SAEs were single events and review of the individual events did not identify any new safety concerns or new pattern of serious adverse events.

Overall, no meaningful differences between the treatment groups were seen in the nature, seriousness or incidence of adverse events in patients with PNH. The safety of ABP 959 was consistent with the known safety profile of Soliris.

Events of special interest

Based on the mechanism of action, known potential and identified risks, and clinical data available in the product labelling for Soliris the identified EOIs included infections, infusion reactions, meningococcal infection, sepsis and hematologic abnormalities for the PK/PD Similarity Study. For the Comparative Clinical study, only infusion reactions and serious infections were considered EOIs.

In the PK/PD Similarity Study infections were mostly Grade 1 and 2 including upper respiratory tract infection, rhinitis, pharyngitis and oral herpes. No meningococcal infection, sepsis, hematologic, haemolytic, or haematopoietic TEAEs were reported. Infusion reactions on the day of or the day after study drug infusion occurred in 3 subjects in the ABP 959 group and 1 subject in the Soliris-EU group. These infusion reactions were mild events of cough, pyrexia and skin reaction.

In the Comparative Clinical study, the overall subject incidences for infusion reactions were 15 (36.6%) and 15 (35.7%), and for serious infections were 3 (7.3%) and 0 (0.0%) for subjects receiving ABP 959 and Soliris respectively. The small number of serious infections precludes any conclusions on a potential imbalance. No meningococcal infection or sepsis were reported.

Overall, no notable differences between the treatment groups were seen in the incidence of EOIs in healthy subjects or in patients with PNH. The nature, seriousness and incidence of infections and infusion reactions were consistent with the known safety profile of Soliris.

Excipients

ABP959 (in contrast to the reference product) is a sorbitol-containing product. Medicines containing sorbitol/fructose given intravenously may be life-threatening in patients with HFI and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are

available (https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-fructose-sorbitol-used-excipients-medicinal-products-human-use_en.pdf). As Bekemv is a biosimilar product, there is no overwhelming clinical need per definition.

Children below 2 years of age may not yet be diagnosed with HFI. Thus, the obvious difficulties in diagnosing hereditary fructose intolerance (HFI) in children <2 years of age raised concerns on whether ABP959, which (in contrast to the reference product), is a sorbitol-containing product, could be safely used in subjects below this age. Therefore, a contraindication in children below 2 years of age was added for ABP959. The potential risk of serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance was added in the list of safety concerns for Bekemv in the EU RMP v0.5., and in the educational materials as an additional risk minimisation measure. A contraindication was also added for use of Bekemv in subjects with HFI, and further changes were required to other parts of the PI for controlling the risk caused by sorbitol content.

Immunogenicity

In the PK/PD Similarity Study, 7/217 subjects were ADA positive already at baseline. Treatment-emergent ADA (positive post-baseline with a negative of no result at baseline) were seen in 3/71, 3/70 and 6/73 subjects in the ABP 959, Soliris-US and Soliris-EU groups, respectively. No neutralising ADA were detected in the study. No clinically relevant immunogenicity nor differences in immunogenicity between treatment groups were observed in the study.

In the Comparative Clinical study, no subjects were ADA positive at baseline and no subjects developed ADA during the 52 weeks in Period 1. Two subjects became transiently ADA positive after switching from Soliris to ABP 959.

Based on ADA frequencies found in PNH patients in the marketing authorisation studies for Soliris, 1-2 ADA-positive subjects could have been expected among the 42 subjects in study 20150168. The drug tolerance was not optimal and some ADA may have gone undetected. However, the results are not implausible and do not preclude similarity.

Neither of the two studies are optimal for evaluation of immunogenicity. Since the PK/PD study was a single-dose study with a subtherapeutic dose, it does not evaluate potential immunogenicity during long-term treatment. Studies conducted with low doses are however sometimes more sensitive to compare immune responses (please refer to Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies –Non-clinical and Clinical Issues EMA/CHMP/BMWP/403543/2010). The phase 3 study on the other hand is very small and involves a study population already using eculizumab. Hence, any subjects with immune-related allergic reactions or loss of efficacy would have stopped the treatment earlier and would not be eligible for the study.

Nevertheless, eculizumab has a clear, well-known and well-understood mode of action (MoA). The MoA can be thoroughly investigated by binding and functional *in vitro* tests. Efficacy of eculizumab can be seen directly related to the biological events triggered by the binding of eculizumab to its known target; the structure–function relationship is well known; hence, a good correlation between clinical efficacy and pharmacological effect can be derived from comparable binding properties and functional characteristics. Relevant, validated PD markers (LDH, biochemical marker of intravascular haemolysis; and CH50, sensitive biomarker for reduced C5 functional activity), which reflect the MoA of eculizumab are available. They are suitable and sensitive to detect potential differences between the proposed biosimilar and the RMP. Immunogenicity data from prior eculizumab studies and clinical use of eculizumab for 15 years have shown low immunological potential and no clinical consequences by ADA on efficacy and safety.

The degree of analytical and functional similarity between ABP 959 and reference medicinal product is very high. All of the quality attributes potentially related to immunogenicity (like protein aggregates, impurities) are highly similar between the RMP and ABP 959. The comparative PK study demonstrated bioequivalence between ABP 959 and RMP. In the same PK/PD-study similar inhibition of C5 activity was demonstrated. The single-dose PK/PD-study 3/71 and 6/73 healthy volunteers developed treatment-emergent ADAs in the Bekemv and Soliris-EU groups, and no ADAs were developed during the 52 weeks in the ABP 959 group in study 20150168. Mean LDH levels were very similar for ABP 959 and RMP in the phase 3 study 20150168, implicating no loss of efficacy.

2.5.10. Conclusions on the clinical safety

The nature, seriousness and incidence of adverse reactions in healthy subjects were similar between all three treatment groups and consistent with previous findings with Soliris.

No meaningful differences between the treatment groups were seen in the nature, seriousness or incidence of adverse events in patients with PNH. The safety of ABP 959 was consistent with the known safety profile of Soliris.

No clinically relevant immunogenicity nor differences in immunogenicity between treatment groups were observed in either healthy subjects or patients with PNH.

Similar immunogenicity is further supported by the similar PK/PD profile, efficacy and safety, and especially by the structural and functional similarity of ABP 959 and the RMP.

The excipient sorbitol was selected to provide suitable tonicity and maintain product stability. However, when given intravenously, it may cause serious harm in patients with HFI who lack the enzyme needed to break it down. Therefore, a contraindication has been added in patients with hereditary fructose intolerance (HFI) as well as a contraindication in babies and children below 2 years of age since they may not yet be diagnosed with HFI. Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance has been added as an important potential risk in the RMP. Additional risk minimisation measures have also been introduced to mitigate this risk, consisting of the following educational materials: physician’s guide, patient’s/parent’s information brochure, and patient safety card. The target audience and planned distribution path for the controlled distribution and vaccination reminder also include pharmacists dispensing the drug in addition to prescribing physicians. The risk of serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance was added as important potential risk in the list of safety concerns in the RMP.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 38: Summary of safety concerns

Important identified risks	• Meningococcal infections • Serious infections (including sepsis) • *Aspergillus* infection • Infusion reactions
Important potential risks	• Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients • Immunogenicity • Malignancies and hematologic abnormalities in paroxysmal nocturnal hemoglobinuria patients • Serious infections in neonates after maternal exposure to eculizumab • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance
Missing information	• None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Meningococcal infections	Routine risk minimization measures: • SmPC Section 4.3 where a contraindication is included • SmPC Section 4.4 where recommendation for vaccination/antibiotic prophylaxis and monitoring for meningococcal infection is included and where signs and symptoms of meningococcal infections are listed • SmPC Section 4.8 • PL Section 2 where signs and symptoms of meningococcal infections are listed • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Physician's guide • Patient's/parent's information brochure • Patient safety card • Controlled distribution • Vaccination reminder	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Serious infections (including sepsis)	Routine risk minimization measures: • SmPC Section 4.4 where recommendation to inform patients of the signs and symptoms of potential serious infections and to advise patients about gonorrhea prevention is included • SmPC Section 4.8 • PL Sections 2 and 4 • Restricted medical prescription Additional risk minimization measures: • Physician's guide • Patient's/parent's information brochure • Patient safety card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Aspergillus infection	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Physician's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Infusion reactions	Routine risk minimization measures: • SmPC Section 4.2 where a recommendation to monitor patients for 1 hour following infusion is included • SmPC Section 4.4 where a recommendation to interrupt administration of BEKEMV and administer appropriate medical therapy is included • SmPC Section 4.8 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Physician's guide • Patient's/parent's information brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		
Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients	Routine risk minimization measures: • SmPC Section 4.4 and PL Section 3 where a recommendation to monitor PNH patients if treatment with BEKEMV is discontinued is included • Restricted medical prescription Additional risk minimization measures: • Physician's guide • Patient's/parent's information brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Immunogenicity	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Section 2 • Restricted medical prescription Additional risk minimization measures: • Physician's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancies and hematologic abnormalities in paroxysmal nocturnal hemoglobinuria patients	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Serious infections in neonates after maternal exposure to eculizumab	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2 where a recommendation for women of childbearing potential to use adequate contraception to prevent pregnancy during and for at least 5 months after the last dose of treatment with BEKEMV is included • Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaires Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance	Routine risk minimization measures: • SmPC Section 2 • SmPC Section 4.2 where a contraindication in babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included • SmPC Section 4.3 where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included • SmPC Section 4.4 where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included, and where a recommendation to take a detailed history of each patient with regards to HFI symptoms prior to receiving BEKEMV and immediately stop BEKEMV infusion in case of inadvertent administration and suspicion of fructose intolerance, re-establish normal blood glucose levels, and stabilize organ function by means of intensive care, is included • SmPC Section 6.1 • PL Section 2, where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included • PL Section 3 • PL Section 6 • Outer packaging Sections 3 and 7 • Restricted medical prescription Additional risk minimization measures: • Physician's guide • Patient's/parent's information brochure • Patient safety card • Additional national measures in alignment with national requirements for drug prescription, preparation, dispensing, and administration, if deemed necessary	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information		
None		

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

As minor correction, the MAH should replace the product name with the INN in RMP annex 6 like in annex IID of the product information file at the next regulatory opportunity.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. 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.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reason: The proposed package leaflet of ABP 959 300 mg concentrate for solution for infusion has the same content to that of the reference product Soliris 300 mg concentrate for solution for infusion with the exceptions noted on Page 6 of the attached QRD form for submission and assessment of user testing bridging proposals. The applicant considers these differences would not affect the readability and otherwise key information is identical.

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:

> Bekemv 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 generalized 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. The number of batches used in the similarity assessment is very comprehensive.

The statistical approach chosen by the applicant to analyse similarity assessment is endorsed. Tabular and graphical presentation allows for a clear comparison of ABP 959 to Soliris-EU and Soliris-US. In addition, generally sufficient raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen. In conclusion, the overall approaches used for establishment of the biosimilarity assessment criteria are considered acceptable.

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, and general properties including protein concentration and volume. In addition, stressed and accelerated stability studies as well as photodegradation studies were performed between ABP 959 and Soliris-EU.

Summary of nonclinical comparability data

The nonclinical data package included comprehensive *in vitro* and *ex vivo* biological studies relevant for the eculizumab mode of action comparing the functional activity of ABP-959 and Soliris EU (and Soliris-US). In addition, a toxicology assessment of excipients in the ABP-959 commercial drug formulation was included.

The clinical development plan consists of two studies:

1. A pivotal phase I PK/PD study in adult, healthy male subjects [study 20150164]. Study 20150164 was a randomised, double-blind, single-dose, 3-arm, parallel group trial comparing the PK similarity of ABP 959 relative to Soliris-US and to Soliris-EU; PK similarity of Soliris-US relative to Soliris-EU; PD similarity of ABP 959 relative to Soliris-US and to Soliris-EU. Eculizumab was administered as a single IV infusion of 300 mg subtherapeutic dose.
2. Study 20150168, a randomised, multicentre, double-blind, active-controlled, 2-period crossover, multiple-dose efficacy and safety study. Adult men and women with PNH and stable on eculizumab were randomised to continue the reference product Soliris or to switch to Bekemv, both using the approved dose of 900 mg IV infusion every 14 days. The interim one-year analysis of the parallel one-year period 1 of the study is the basis for assessment of clinical similarity of efficacy and safety in this MAA for the EU. The final CSR, also containing the cross-sectional data up to end of study, i.e., the 6-month Period 2 of the study after switch, was received with the response to the LoQ and is additionally assessed as evidence of clinical similarity. The setting was generally agreed upon in scientific advice by the CHMP; though CHMP advice regarding NI margin was not followed. The CHMP would have preferred inclusion of also treatment-naïve PNH subjects but understood the issues with recruitment of study subjects in this orphan disease.

3.2. Results supporting biosimilarity

Quality

Similarity between ABP 959 and Soliris-EU and Soliris-US has been demonstrated for the following physicochemical and biological properties:

- Primary structure
- high order structure
- Particles and aggregates

- product-related substances and impurities
- Thermal stability and degradation studies
- General properties including protein concentration and volume
- Inhibition of TCC formation assay (Potency)
- Inhibition of haemolysis bioassay
- Relative binding to C5
- C5 binding kinetics and affinity
- Lack of binding to C3
- Neonatal Fc Receptor (FcRn) Binding by AlphaScreen

Minor differences in the levels of post-translational modifications, relative proportion of the charge variants, individual glycan species, levels of glycation, and levels of monomer, HMW, LMW, HC+LC and were sufficiently justified to have no clinical impact.

Nonclinical

Similarity between ABP 959 and Soliris-EU and Soliris-US has been demonstrated for biological properties described above under Quality, and *ex vivo* for inhibition potency for the alternative and classical pathways.

Clinical data

Pharmacokinetics

In the comparison of PK data (pivotal PK/PD study 20150164) for the ABP 959 group with the Soliris-EU and Soliris-US treatment groups, the 90% CIs of the geometric LS for the three primary PK parameters (i.e. C_{max}, AUC_{last} and AUC_{inf}) were all within the BE criteria of 80% to 125% based on total and free eculizumab concentrations.

The PK results of the sensitivity/subgroup analyses performed in the study 20150164 were quite similar to the primary PK results.

In the comparative efficacy and safety study (Study 20150168) in PNH subjects no acceptance ranges for PK parameters had been predefined, and PK was a secondary endpoint. The GMR (90% CI) for the total PK AUC from week 13 to week 15 was 0.9122 (0.7586, 1.0968) and for the free PK AUC it was 0.9508 (0.7454, 1.2130), reasonably supporting comparable PK between the treatment groups as demonstrated in the pivotal PK study.

Both total and free eculizumab trough concentrations at different timepoints seemed similar, and although the lower and upper 90% CI limits of the GMRs were not within the traditional bioequivalence range (i.e., 0.80-1.25), all 90% CIs included unity. The trough concentrations varied so that at some timepoints they were higher in the ABP 959 group and at some other timepoints they were higher in the Soliris group. The updated trough free and total concentrations of eculizumab from week 53 to the end of study (i.e., week 79) were also comparable.

Pharmacodynamics

In the phase 1 study 20150164, PD similarity was demonstrated as assessed by area between the effect curve [ABEC] of 50% total haemolytic complement activity [CH50], of ABP 959 vs. Soliris-US, ABP 959 vs.

Soliris-EU and with Soliris (US) vs. Soliris (EU). The ratio of LS geometric means of ABEC of CH50 (95% CI) was 1.0710 (0.9439. 1.2152) for ABP 959 vs. Soliris (US), 1.0824 (0.9552, 1.2266) for ABP 959 vs. Soliris (EU) and 1.0106 (0.8919, 1.1452) for Soliris US) vs. Soliris (EU).

Moreover, it is acknowledged that the currently conducted phase 1 trial did explore both the maximal CH50 response measurable with the bioanalytical method, and the CH50 response at very low eculizumab concentrations. As such, not much additional information would be expected from clinical studies with additional dose levels.

Clinical efficacy

The study population (n=42) of the phase 3 study 20150168 consisted of adult patients with PNH documented by flow cytometry and stable on eculizumab treatment. The primary endpoint was the level of lactate dehydrogenase (LDH), a commonly used measure of intravascular haemolysis. The point estimates of geometric LS means estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time, and treatment by time interaction term as fixed effects, and with subject as a random effect, was 205.6 in the ABP 959 group and 193.5 in the Soliris group. The ratio of the geometric LS mean of LDH at week 27 (ABP 959/Soliris) was 1.0628, with a 1-sided 97.5% upper CI of 1.1576 and a 95% CI of (0.9758, 1.1576). The point estimate of geometric LS means ratio of 1.0628 and the upper bound of the 95% CI (1.1576) are well below the pre-defined NI margin of 2.873. Furthermore, the noted difference in LDH at Week 27 is not considered clinically relevant. Additional analyses conducted on the primary efficacy endpoint for the parallel comparison (LDH at week 27) using a weighted population based on prior red blood cell (RBC) transfusion stratification factor as observed in the current study data (i.e., using number of subjects as observed in the study for prior transfusion and no prior transfusion strata) demonstrated similar results in both study groups.

Results of the secondary endpoint of LDH time profile and other secondary endpoint measures of disease activity overall support similar clinical efficacy by ABP 959 and Soliris. These included laboratory measures of haemolysis (total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, degree of haemoglobinuria), proportion of type III erythrocytes (with absent levels of CD55 and CD59) and red blood cell infusions. Some differences were observed in the levels of the laboratory values, but to both directions, with no consistent trend for better efficacy in either treatment group. Random differences are expectable when the study only includes 42 subjects. Over the entire study through the EOS, the mean (SD) number of packed RBC units transfused per month was 0.200 (0.1980) for 2 subjects in the ABP 959/Soliris treatment group and 0.238 (0.2078) for 6 subjects in the Soliris/ABP 959 treatment group.

Results for analysis of the primary efficacy endpoint for the crossover comparison of haemolysis support similarity in clinical efficacy between ABP 959 and Soliris. The point estimate of the GMR of time-adjusted AUEC (ABP 959 vs Soliris) was 0.9812, with a 2-sided 90% CI of (0.9403, 1.0239). The 90% CI was contained within a similarity margin of (0.77, 1.30).

The subgroups by RBC transfusion history, age and gender are small. Results of the subgroup analyses are overall consistent with the primary analysis.

Safety

Safety in healthy males

In the PK/PD Similarity Study 54 (76.1%) subjects experienced 128 adverse events in the ABP 959 group. In the Soliris-US group, 46 (63.9%) subjects experienced 108 events. In the Soliris-EU group, 51 (68.9%)

subjects experienced 143 events. The most common TEAEs by PT (reported in more than 5% of subjects) were headache, upper respiratory tract infection, back pain and rhinitis.

Infections were mostly mild and occurred in 20 (28.2%), 19 (26.4%) and 29 (39.2%) in the ABP 959, Soliris-US and Soliris-EU groups, respectively. There were no life-threatening TEAEs, no deaths, and no TEAEs leading to discontinuation from the study or study drug. There were no serious TEAEs in the ABP 959 treatment arm which were related to the study drug.

No meaningful difference between the groups could be seen in terms of nature, grade or frequency of TEAEs. The safety of all three investigational products was consistent with the known safety profile of Soliris.

In the PK/PD Similarity Study, treatment-emergent ADA (positive post-baseline with a negative of no result at baseline) were seen in 3/71, 3/70 and 6/73 subjects in the ABP 959, Soliris-US and Soliris-EU groups, respectively. No neutralising ADA were detected in the study. No clinically relevant immunogenicity nor differences in immunogenicity between treatment groups were observed in the study.

Safety in PNH patients

In Period 1 of the comparative efficacy and safety study, 15 (75%) subjects in the ABP 959 treatment group and 21 (96%) subjects in the Soliris treatment group reported at least 1 adverse event. In period 2, after switching, AEs were reported by 18 (85.7%) subjects in the ABP 959 treatment group and 18 (90.0%) subjects in the Soliris treatment group.

The overall subject incidences for infusion reactions were 15 (36.6%) and 15 (35.7%), and for serious infections were 3 (7.3%) and 0 (0.0%) for subjects receiving ABP 959 and Soliris respectively. The small number of serious infections precludes any conclusions on a potential imbalance. No meningococcal infection or sepsis were reported. No subjects were ADA positive at baseline an no subjects developed ADA during the 52 weeks in Period 1. Two subjects became transiently ADA positive in Period 2 after switching from Soliris to ABP 959. Both subjects were ADA negative at End of study.

Overall, no meaningful differences between the treatment groups were seen in the nature, seriousness or incidence of adverse events or immunogenicity in patients with PNH. The safety of ABP 959 was consistent with the known safety profile of Soliris.

3.3. Uncertainties and limitations about biosimilarity

Quality

None.

Non-clinical

None.

Clinical data

Pharmacokinetics

In the comparative efficacy and safety study 20150168, the AUC from week 13 to week 15 was slightly greater with Soliris than with ABP 959 both for total and free eculizumab. The number of subjects was small (n = 20 in ABP 959/Soliris group and n = 22 in Soliris/ABP 959 group) in the treatment groups. PK was only

an exploratory parameter with no equivalence margin pre-specified and 90% CIs include 1.00, so the differences in the AUCs can be considered to be not any concern.

Pharmacodynamics

During Period 1 of study 20150158, the PD results of the phase 3 study 20150168 appeared dissimilar between ABP 959 and Soliris groups, since the mean CH50 levels were somewhat higher in the ABP 959/Soliris group than in the Soliris/ABP 959 group. However, the difference was driven by 4 subjects, who had high CH50 levels already at baseline and also after switching to Soliris at one year. Data from the cross-over phase confirmed that the differences were likely due to differences in the studied individuals and not the administered treatments.

The applicant fitted a PKPD model to the observed phase 1 PK/PD data and used the model to simulate time-concentration profiles of eculizumab and CH50 response, and to calculate the proportion of simulated clinical trials which would establish biosimilarity between Soliris and ABP959 in terms of PK and PD endpoints. The PKPD model describes adequately the observed PD data, but the PKPD model may not generalise to other dose levels because the PKPD model assumes that the same free eculizumab concentration will always cause the same response. This assumption is incorrect because eculizumab dosing leads to build-up of the pharmacological target (C5) as a function of dose, and the same free eculizumab concentration will not necessarily lead to the same response if the target concentration is different. Therefore, the specific numbers from the modelling and simulation exercise are not agreed with; however, the applicant's overall conclusion that lower dose levels would have a decreased power to establish biosimilarity (if the products are biosimilar) is agreed with.

Efficacy

Inclusion of only subjects who are stable on eculizumab treatment already at baseline is considered insensitive and as such suboptimal in terms of comparison of efficacy, safety and immunogenicity of ABP 959 and Soliris. There are inevitable carryover effects at the time of randomisation and also between study periods. Furthermore, inclusion of only patients stable on eculizumab treatment excludes any subjects who discontinued previous eculizumab treatment due to not responding to eculizumab or tolerating it.

The primary efficacy endpoint LDH is not specific to haemolysis but is also an inflammatory biomarker, which increases due to acute infections and other illnesses, trauma and surgery. LDH values deemed by the independent LDH Review Committee to have been impacted by confounding events unrelated to efficacy of investigational product were excluded from the analysis. Further clarifications by the applicant confirmed that the decision by the reviewers and adjudicator were based on totality of data on clinical events and LDH levels. Hence, the exclusion of LDH measurements was impacted by the measured values themselves, which is not acceptable in principle. Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules. These rules should be independent from treatment or outcome. In consequence, the decision to exclude a subject from the statistical analysis must be made before bioanalysis (CHMP Guideline on the Investigation of Bioequivalence). The reviewers also considered the laboratory notes indicating tube haemolysis; however, no information was provided as to whether tube haemolysis in the specimen was detected by the lab prior to bioanalysis or otherwise independently of the result. Furthermore, there are instances where a reviewer flagged an LDH measurement for exclusion due to tube haemolysis while the other reviewer did not. This suggests that the comments from the laboratory did not clearly indicate that the specimen was found invalid due to tube haemolysis. For these

reasons the LDH review procedure leading to exclusion of LDH values from the analysis aiming to demonstrate equivalence is unacceptable in principle.

Safety

In the comparative efficacy and safety study, there were some differences in frequencies of certain TEAEs, although the total amount of AEs was comparable. Adverse events where the difference in frequency in the ABP 959 treatment group was ≥ 10% when compared with the Soliris treatment group included nasopharyngitis (9 [22.0%] subjects receiving ABP 959 and 3 [7.1%] subjects receiving eculizumab) and pyrexia (9 [22.0%] and 2 [4.8%], respectively). The frequency of these events was expected per the Soliris labelling.

Although the immunogenic potential of the reference product seems low, comparative evaluation of immunogenicity is an important part of the overall biosimilar comparability exercise. In the current programme, immunogenicity data derive from two different studies and populations: the PK/PD Similarity Study in healthy volunteers and the supportive Comparative Clinical Study in PNH. It remains uncertain whether the PK/PD study, in which 300 mg was given as single dose with last ADA assessment at day 57, was sensitive enough to detect potential differences in ADA. In particular, the evaluation may not be optimal for a comparative ADA-assessment of a biosimilar intended for long-term use. In the comparative clinical study in PNH-patients the risk of developing clinically meaningful immunogenicity was inherently low as only patients already on stable Soliris treatment were included. Moreover, as the expected incidence of ADA formation would have been around 1–2 subjects in a sample of 42 subjects even without this selection bias, it can be concluded that this study was not adequate to demonstrate similarity in terms of immunogenicity. Therefore, no final conclusion on similarity regarding immunogenicity can be made based on the clinical data, however no difference in ADA formation was seen.

Since Bekemv contains sorbitol, unlike the originator Soliris, use of Bekemv would pose a risk for subjects with hereditary fructose intolerance (HFI). As children below the age of 2 years may not yet have been diagnosed with HFI, a contraindication for use in this age group was added and the applicant has proposed risk minimisation measures for controlling this risk. Upon request, the applicant included in the Product Information also a contraindication for patients with hereditary fructose intolerance. Additionally, the outer packaging was changed to include a warning that patients with HFI and babies and children below 2 years of age must not be given this medicine due to the risk of sorbitol exposure.

3.4. Discussion on biosimilarity

Quality

The applicant has provided a very comprehensive analytical comparability exercise using appropriate state-of-the-art analytical methods to ensure a full understanding of the Soliris-EU and Soliris-US product profiles and the ABP 959 product developed. The presented biological and physiochemical data are extensive and convincingly support the claim of biosimilarity for ABP 959.

Nonclinical

The *in vitro* and *ex vivo* functional activity data support the biosimilarity of ABP-959 versus the Soliris-EU (and Soliris-US).

Clinical

Pharmacokinetics

The PK biosimilarity in the pivotal PK/PD study 20150164 using healthy male subjects has been formally demonstrated between ABP 959 and Soliris-EU and Soliris-US as for the primary PK parameters C_{max}, AUC_{last} and AUC_{inf}, the 90% CI for the ratio of test-to-reference/comparator fell within the acceptance range of 80.00-125.00%.

Pharmacodynamics

PD similarity was formally shown in healthy male subjects in the pivotal PK/PD study 20150164. In the phase 3 study 20150168, a small difference is seen in PD as measured by CH50 in favour of the reference product Soliris. The difference is seemingly driven by lower exposure of eculizumab in four individuals, resulting in less effective suppression of the complement pathway. Further analyses conducted on these four subjects showed no clear pattern of differences in eculizumab trough concentrations and CH50 during treatment with ABP 959 vs. Soliris, even though the values varied at different sampling points. Therefore, the lower eculizumab trough concentration and higher CH50 in these subjects is deemed to be related to patient and not to the treatment.

In scientific advice given to the applicant, the CHMP recommended that the applicant should study more than one dose level because evidence of comparability in terms of dose-response would strengthen the overall robustness of the comparability exercise. The applicant has not followed this advice, and the phase 1 study only includes one dose level (300 mg). The applicant has used modelling and simulation to justify that lower doses would have a decreased statistical power to demonstrate biosimilarity in terms of PK and PD, if the reference and test product are assumed biosimilar. Even though the CHMP does not agree with all the details pertaining to this modelling and simulation exercise, the CHMP agrees with the primary conclusion that lower doses would have a decreased statistical power to demonstrate biosimilarity due to decreasing signal-to-noise ratio. Moreover, it is acknowledged that the currently conducted phase 1 trial did explore both the maximal CH50 response measurable with the bioanalytical method, and the CH50 response at very low eculizumab concentrations. As such, not much additional information would be expected from clinical studies with additional dose levels.

Efficacy

The target population in the single phase 3 study are adult PNH subjects stable on eculizumab, who were randomised to switch to ABP 959 or to continue with Soliris, with a parallel comparative period of one year (period 1 of the study), after which the patients crossed over to the alternative treatment. This assessment is based on the parallel comparison (Period 1 of the study). This maintenance setting is considered relatively insensitive for demonstration of potential differences in efficacy and safety. Furthermore, the study is small, with only 42 participants. However, the degree of analytical and functional similarity between ABP 959 and the reference medicinal product seems to be very high. Furthermore, the efficacy results obtained reasonably support a conclusion of biosimilarity of ABP 959 and Soliris. Hence, the currently available clinical data can be considered supportive of similar efficacy.

Safety

The clinical data is limited and can only provide supportive information on comparability of safety and immunogenicity. Safety findings were presented for a total of 259 subjects. Of these 71 healthy subjects and 41 PNH patients received ABP 959. In the comparative efficacy and safety (phase 3) study, the risk of experiencing adverse events was inherently low as only patients already on stable Soliris treatment (i.e.,

subjects with established good tolerance for treatment) were included. Nevertheless, relevant safety issues would have been detectable.

In the phase 3 study, there were some differences in frequencies of certain TEAEs, although the total amount of AEs was comparable. The seemingly large percentual difference between groups regarding some of the preferred terms does not preclude biosimilarity as the number of subjects is too small for meaningful analysis and the frequency of reported AEs in both treatment arms are in line with those reported for Soliris in the SmPC. All SAEs were single events and review of the individual events did not identify any new safety concerns or new pattern of serious adverse events.

The larger single-dose study in healthy subjects showed similar frequencies of AEs and SAEs between treatment arms.

In conclusion, no meaningful difference between ABP 959 and Soliris could be seen in terms of nature, grade or frequency of adverse events. The safety of both investigational products was consistent with the known safety profile of Soliris.

Overall discussion on biosimilarity

Eculizumab has a well-known and well-understood mode of action, which can be thoroughly investigated in binding and functional *in vitro* tests. In PNH-patients there is uncontrolled terminal complement activation resulting in complement-mediated intravascular haemolysis. Eculizumab is a monoclonal antibody which binds to human C5 complement protein and inhibits the activation of terminal complement, thereby inhibiting haemolysis. Therefore, efficacy of eculizumab can be seen directly related to the biological events triggered by the binding of eculizumab to its known target; the structure–function relationship is well known. Hence, a good correlation between clinical efficacy and pharmacological effect could be derived from comparable binding properties and functional characteristics. Further, there are relevant, validated PD markers (lactate dehydrogenase, a sensitive albeit not specific biochemical marker of intravascular haemolysis; and CH50, sensitive biomarker for reduced C5 functional activity), which reflect the mechanism of action of eculizumab and are suitable and sensitive to detect potential differences between the proposed biosimilar and the RMP. Additionally, other PD parameters are available to assess the comparability of the PD properties of the RMP and proposed biosimilar (like haemoglobin, haptoglobin, bilirubin, etc).

ABP 959 has been very comprehensively characterised with suitable, sensitive and orthogonal assays for structural, analytical and functional characterisation. The degree of analytical and functional similarity between ABP 959 and reference medicinal product is high. In addition, a comparative PK study demonstrated bioequivalence between Bekemv and RMP; in the same PK-study similar inhibition of C5 activity was demonstrated (via the PD-marker CH50), providing adequate clinical evidence to support biosimilarity. These data (quality and PK/PD) are considered pivotal for the biosimilarity assessment and are in this specific case considered sufficient for a conclusion of biosimilarity.

The clinical comparative efficacy and safety study 20150168 (with only 20 and 22 patients in the ABP 959 and RMP groups) is considered to be only a supportive study here in the context of biosimilarity, as sufficient evidence of biosimilarity can be inferred from other parts of the comparability exercise. Thus, even if there are uncertainties related to assessment of efficacy and safety in this comparative study, these are not considered to be of such importance, that they would question biosimilarity.

Also, considering the highly similar physicochemical characteristics and PK/PD profiles of ABP 959 and RMP,

and the overall safety data from the two clinical studies, there is sufficient reassurance that clinically relevant differences also in safety side can be excluded.

Related to immunogenicity, there is clinical experience with the RMP, which has been marketed since 2007, originally for the treatment of PNH. Research data and clinical experience have demonstrated that the immunogenic potential of eculizumab is low, and the ADAs have been of no clinical concern with eculizumab. This allows for a risk-based assessment of immunogenicity also for ABP 959.

Immunogenicity is expected for ABP 959 as for all products manufactured from a CHO cell line. Further selection of the desired cell line is achieved by growing the cells in the presence of methotrexate.
In order to mitigate the potential immunogenicity risk; all the quality attributes potentially related to immunogenicity (like protein aggregates, impurities, host cell proteins) have been established and have been shown to be highly similar between the RMP and ABP 959.
Therefore, the immunogenicity risk has been minimised in the manufacture of ABP 959 and the immunogenicity profile is expected to be similar between Bekemv and Soliris on the quality level.
This is supported by the clinical studies which showed that in the single-dose PK/PD-study only a few subjects (3/71 and 6/73 with ABP 959 and Soliris-EU, respectively) developed treatment-emergent ADAs. In the 20150168-study, only transient ADA positivity was detected in two subjects, both in the ABP 959 group. Therefore, it can be assumed with sufficient certainty that immunogenicity of ABP 959 is comparable to that of the RMP.

3.5. Extrapolation of safety and efficacy

Extrapolation to treatment-naïve and paediatric subjects has been justified by the applicant. PK/PD similarity between ABP 959 and Soliris-US and Soliris-EU was demonstrated in healthy males in study 20150164.

Since only adult PNH patients already stable on eculizumab were included in study 20150168, the expected effect size is small and sensitivity of the study for detecting differences in efficacy and safety is low. However, the obtained results on the primary efficacy endpoint LDH and secondary efficacy endpoints, including time course of LDH, other laboratory measures of haemolysis, and other indicators of disease activity (type III erythrocytes, RBC infusions) are not contradictory of similar clinical efficacy of ABP 959 with Soliris.

The PD measure CH50 was in most subjects under LLOQ in this study, questioning the sensitivity of the method for detecting difference. Furthermore, the study with only 42 subjects is small for confirmation of clinical similarity. Consequently, assessment of clinical biosimilarity of ABP 959 and Soliris is based mostly on the PK/PD study 20150164, and clinical efficacy and safety results from study 20150168 can be considered in principle supportive data. Hence, the extrapolation exercise also relies primarily on study 20150164.

The applicant refers to published literature on the reference product Soliris. The mode of action of eculizumab is similar across approved indications of Soliris and across different patient groups with PNH. Dedicated studies to evaluate the PK of Soliris or ABP 959 have not been conducted in special patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment. However, the PK of Soliris was evaluated in a phase I/II study in PNH paediatric patients (ranging in age from 11 to 17 years), and population PK analyses on data collected across studies demonstrated that age, gender, race, and renal function do not influence the PK of eculizumab. Consistent PK parameters were seen across PNH patient populations, including those naïve to Soliris treatment, those stable on Soliris treatment, and across both adult and paediatric PNH patients. The applicant also provides a brief summary of publicly available results from studies in PNH regarding impact of intrinsic (such as age, gender, race, body weight, or renal

impairment) and extrinsic factors (concomitant medications) on the PK, safety, or effectiveness of eculizumab. Population PK analyses on data collected across studies showed that age (geriatric), gender, or race do not influence the PK of eculizumab. Body weight was a significant factor resulting in a lower eculizumab clearance in paediatric/adolescent patients, consequently, body weight based eculizumab dosing is required for paediatric PNH patients. Renal impairment did not affect the PK of eculizumab in PNH patients.

Soliris product information and published studies support the conclusion that there is a consistent and comparable safety profile across the approved patient populations. Anti-drug-antibody responses have been detected infrequently across indications and patient populations approved for Soliris, and there has been no observed correlation of antibody development to efficacy and safety.

As a conclusion, the justifications given by the applicant regarding all PNH-related indications and the available data for ABP 959 are deemed sufficient for extrapolation to the sought indication for use: "BEKEMV is indicated in adults and children for the treatment of paroxysmal nocturnal haemoglobinuria (PNH)".

3.6. Additional considerations

ABP959 (in contrast to the reference product) is a sorbitol-containing product. Medicines containing sorbitol/fructose given intravenously may be life-threatening in patients with HFI and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available (https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-fructose-sorbitol-used-excipients-medicinal-products-human-use_en.pdf). Children below 2 years of age may not yet be diagnosed with HFI. Therefore, Bekemv was decided to be contraindicated in children below 2 years of age and in subjects with HFI.

Wording of the indication

It is considered that the exact wording of the indication of Bekemv should remain the same as with the reference medicinal product Soliris, i.e. without any age limits, even though there is a new contraindication for Bekemv (compared to the RMP) in all children less than 2 years of age and subjects with hereditary fructose intolerance (regardless of age) due to large amounts of sorbitol in the formulation. This is in line with "the Wording of therapeutic indication, A Guide for Assessors of Centralised Applications EMA/CHMP/483022/2019", where it is clearly stated that if the benefit/risk is negative in a subgroup based on safety issue, this should be reflected in a contraindication (not in the indication). Furthermore, the risk minimisation measures (educational material etc.) are considered adequate for mitigating this risk, in addition to the contraindication, and therefore no restriction of the indication is considered necessary for children below 2 years of age.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Bekemv is considered biosimilar to Soliris. Therefore, a benefit/risk balance comparable to the reference product can be concluded with one exception. Due to the metabolic risk caused by the relatively high sorbitol content of Bekemv, use of Bekemv is contraindicated for patients with hereditary fructose intolerance (HFI) and for children <2 years of age, whereas Soliris contains no sorbitol and can be used also in these subgroups.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

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

Bekemv 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 professionals 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 guide 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).
- Sorbitol content warning and the risks for patients with HFI when intravenously exposed to sorbitol.

- Bekemv contraindication in patients with HFI (regardless of their age), and in children below 2 years of age, who may not yet be diagnosed with HFI.
- 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 professional that he/she is receiving treatment with eculizumab
    - the requirement for vaccinations/antibiotic prophylaxis
    - the risks of serious metabolic harms due to treatment with Bekemv if the patient also has HFI

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 risks of serious metabolic harms (potentially life-threatening) due to treatment with Bekemv if the patient also has HFI.
- Bekemv contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI.

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.
- Sorbitol content warning and potentially life-threatening risks of patients with HFI who are intravenously exposed to sorbitol-containing medicines.

- Bekemv contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI.
- Contact details where a health care professional can receive further information.

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

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

Not applicable.