Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

BEKEMV 300 MG CONCENTRATE FOR SOLUTION FOR INFUSION

(eculizumab)

PLGB 13832/0077

Amgen Limited

LAY SUMMARY

BEKEMV 300 mg concentrate for solution for infusion (eculizumab)

This is a summary of the Public Assessment Report (PAR) for BEKEMV 300 mg concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as BEKEMV in this lay summary for ease of reading.
For practical information about using BEKEMV, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is BEKEMV and what is it used for?

BEKEMV is a 'similar biological' medicine (biosimilar). This means that BEKEMV is similar to a biological 'reference' medicine already authorised called Soliris 300 mg concentrate for solution for infusion.

BEKEMV is used to treat adults and children with a certain type of disease affecting the blood system called Paroxysmal Nocturnal Haemoglobinuria (PNH). In patients with PNH, their red blood cells can be destroyed which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

How does BEKEMV work?

BEKEMV contains the active substance eculizumab, which belongs to a class of medicines called monoclonal antibodies. Eculizumab can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable PNH blood cells. Eculizumab binds to and inhibits a specific protein in the body that causes inflammation and so prevents the body's systems from attacking and destroying vulnerable blood cells.

How is BEKEMV used?

The pharmaceutical form of this medicine is concentrate for solution for infusion.

At least two weeks before the patient starts treatment with BEKEMV, their doctor will administer a vaccine against meningococcal infection if it was not previously administered or if their vaccination is outdated.

If the patient is a child below the age of vaccination or if the patient is not vaccinated at least two weeks before they start treatment with BEKEMV, their doctor will prescribe antibiotics to reduce the risk of infection until two weeks after the child or patient has been vaccinated.

The child's doctor will administer a vaccine to a child aged less than 18 years against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use

The treatment will be given by the patient's doctor or other health care provider by infusing a dilution of the BEKEMV vial from a drip bag through a tube directly into one of the patient's veins. It is recommended that the beginning of the patient's treatments, called the initial phase, will extend over four weeks, followed by a maintenance phase.

Use of this medicine
For adults:
• Initial phase:
Every week for the first four weeks, the patient's doctor will administer an intravenous infusion of diluted BEKEMV. Each infusion will consist of a dose of 600 mg (two vials of 30 mL) and will take 25 - 45 minutes (35 minutes ± 10 minutes).

• Maintenance phase:
- In the fifth week, the patient's doctor will administer an intravenous infusion of diluted BEKEMV at a dose of 900 mg (3 vials of 30 mL) over a 25 – 45 minute (35 minutes ± 10 minutes) period.
- After the fifth week, the patient's doctor will administer 900 mg of diluted BEKEMV every two weeks as a long-term treatment.

Children and adolescents with PNH and who are 40 kg weight and over are treated with the adult dosing.

Children and adolescents with PNH and who are under 40 kg weight require a lower dose based on how much they weigh. The patient's doctor will calculate this.

For children and adolescents with PNH aged less than 18 years:

Patient body weight	Initial phase	Maintenance phase
30 to < 40 kg	600 mg weekly × 2	900 mg at week 3; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly × 2	600 mg at week 3; then 600 mg every 2 weeks
10 to < 20 kg	600 mg weekly × 1	300 mg at week 2; then 300 mg every 2 weeks
5 to < 10 kg	300 mg weekly × 1	300 mg at week 2; then 300 mg every 3 weeks

Following each infusion, the patient will be monitored for about one hour. The patient's doctor's instructions should be carefully observed.

For further information on how BEKEMV is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of BEKEMV have been shown in studies?
As BEKEMV is a similar biological medicine to Soliris 300 mg concentrate for solution for infusion, studies have been limited to determine whether BEKEMV is similar to the reference medicine Soliris 300 mg concentrate for solution for infusion.

What are the possible side effects of BEKEMV?
As BEKEMV is a biosimilar medicine, the possible side effects are considered to be the same as those of the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was BEKEMV approved?
It was concluded that BEKEMV has been shown to be similar to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits of using BEKEMV are greater than the risks, and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of BEKEMV?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for BEKEMV. The RMP details the important risks of BEKEMV, how these risks can be minimised, any uncertainties about BEKEMV (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for BEKEMV:

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 • Sorbitol exposure in patients less than 2 years of age
Missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of BEKEMV are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the BEKEMV product information, the Marketing Authorisation Holder (MAH) has committed to additional risk minimisation activities through the (i) provision of educational materials including a physician's guide, parent's/patient's information brochure and patient safety card, (ii) controlled distribution and (iii) vaccination reminder (against *Neisseria Meningitidis*) sent to prescribers.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about BEKEMV

A marketing authorisation application for BEKEMV was received on 08 March 2022, and a marketing authorisation was granted in Great Britain (GB; consisting of England, Scotland and Wales) on 28 October 2022.
The full PAR for BEKEMV follows this summary.

This summary was last updated in February 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for BEKEMV 300 mg concentrate for solution for infusion (PLGB 13832/0077) could be approved. This product will be referred to as BEKEMV or ABP 959 in this scientific discussion for ease of reading. Note that ABP 959 is a code name used during the biosimilar product development.

The product is approved 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 of the Summary of Product Characteristics (SmPC).

Eculizumab, the active substance in BEKEMV, is a humanised monoclonal (IgG2/4κ) antibody produced in Chinese hamster ovary (CHO) cell line by recombinant DNA technology. 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 BEKEMV 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 BEKEMV resulted in a rapid and sustained reduction in complement-mediated haemolytic activity.

This application was approved under Regulation 53A of The Human Medicines Regulation 2012, as amended (previously Article 10(4) of Directive 2001/83/EC, as amended), as a biosimilar application. The reference biological product is Soliris 300 mg concentrate for solution for infusion that has been licensed for a suitable time, in line with the legal requirements.

The applicant submitted three non-clinical (pharmacology) studies and two clinical (a comparative pharmacokinetic/pharmacodynamic (PK/PD) and a comparative efficacy/safety) studies to demonstrate biosimilarity with the originator product. The clinical studies were conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 09 June 2022. The Committee provisionally concluded that further information on quality, clinical and risk

management plan aspects should be requested before the product could be approved. In response to the CHM advice, the applicant provided additional data, to address the points that had been raised. Following consideration of the responses and further data that were submitted, the approval of the marketing authorisation was recommended.

A marketing authorisation application for BEKEMV was received on 08 March 2022, and a marketing authorisation was granted in Great Britain (GB; consisting of England, Scotland and Wales) on 28 October 2022.

II QUALITY ASPECTS

II.1 Introduction

This product contains 300 mg of eculizumab (10 mg/mL) in each vial. In addition to eculizumab, this product also contains the excipients of acetic acid, sodium hydroxide, disodium edetate (EDTA), sorbitol (E420), polysorbate 80 and water for injections.

The finished product is packaged in 30 mL vials (type I glass), each with an elastomeric stopper with fluoropolymer laminated plug, and an aluminium seal with attached dust cover (elastomeric).

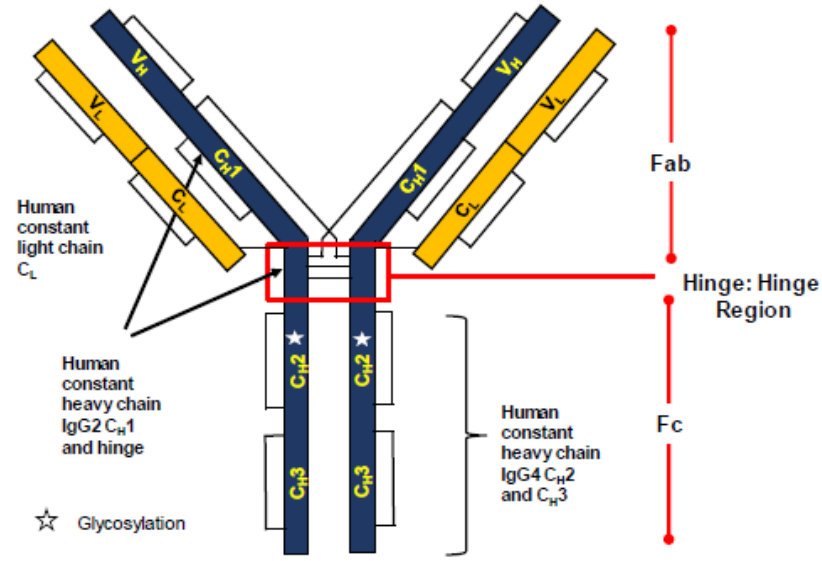
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with medicines.

II.2 ACTIVE SUBSTANCE

rINN: Eculizumab

Chemical Name:	Anti-complement human C5 monoclonal antibody
Molecular Formula:	$C_{2199}H_{3374}N_{574}O_{682}S_{19}$ - heavy chain (w/o C-terminal lysine), not including N-linked glycans $C_{1016}H_{1582}N_{271}O_{334}S_{6}$ - light chain $C_{56}H_{92}N_{4O39}$ predominant glycan moiety, A2G0F
Chemical Structure:	Eculizumab (ABP 959, BEKEMV) is a recombinant humanized monoclonal immunoglobulin isotype class G subclass 2/4 (IgG2/4) kappa antibody consisting of 2 heavy chains and 2 light chains of the kappa subclass, 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. As is typical with mammalian cell culture processes, C-terminal lysine 448 on the heavy chain is mostly removed due to the presence of carboxypeptidases during upstream production. ABP 959 is an IgG2/4 hybrid structure with CH1 and hinge regions being from IgG2 and CH2 and CH3 regions being from IgG4. The hybrid structure aims to reduce or eliminate the effector function via Fc gamma receptors and complement binding.

Figure 1. Schematic of ABP 959 Structure (IgG2-B Isoform)



Heavy chains are shown in blue and light chains are shown in orange
V_H is the variable domain of the heavy chain
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain
V_L is the variable domain of the light chain
C_L is the constant domain of the light chain
A single consensus site for N-glycosylation exists at Asn^{298} on each heavy chain (starred region).

Molecular Mass:	144,981	kDa theoretical mass of fully assembled, disulfide-bonded ABP 959 antibody without heavy chain C-terminal lysine with fully cyclized N-terminal glutamine to form pyroglutamic acid and without the addition of the N-linked glycans
	1,445	kDa predominant glycan moiety, A2G0F (when attached to protein)
	147,869	kDa theoretical mass of glycosylated ABP 959 containing 2 predominant glycans (1 A2G0F per heavy chain)
	147,878	kDa experimentally determined predominant ABP 959 mass

Eculizumab is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable shelf-life when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

The formulation used in the clinical studies was shown to be comparable to the final commercial formulation.

All excipients comply with their respective European monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months, 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.’ is acceptable.

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, is acceptable.

After dilution, chemical, physical, and microbiological in-use stability has been demonstrated for:

- 96 hours at 2°C to 8°C
- 48 hours at room temperature

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Comparability assessment (biosimilarity)
Comparability data have been provided. An extensive (side-by-side) comparability exercise has been undertaken on a sufficient number of batches to demonstrate that the biosimilar eculizumab candidate has a "highly similar" quality profile compared to the reference product. The biosimilarity comparisons have involved analysis and comparison of a broad range of physicochemical/structural/biological properties. The types of studies performed and parameters investigated are considered appropriate for the assessment of the biosimilarity of eculizumab. They are in line with current guidelines and the data from these extensive studies was considered to acceptably support the applicant's claim of biosimilarity between BEKEMV and Soliris drug products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
Eculizumab is not pharmacodynamically active except in humans in which species it acts to inhibit C5 in the complement system, as the means by which it treats patients with paroxysmal nocturnal haemoglobinuria.

To support the application, three *ex vivo* pharmacology characterisation studies have been submitted These assessments have been conducted to evaluate similarity between eculizumab reference product and BEKEMV with respect to functional activity.

The available non-clinical data do not raise any safety concerns, nor do they impact safety.

There were no non-clinical *in vivo* studies; this is in alignment with regulatory guidance for biosimilar development.

III.2 Pharmacology
To support the application, the applicant submitted the three *ex vivo* comparative pharmacology studies that were conducted to evaluate the ability of ABP 959 and eculizumab reference product to inhibit complement pathways in models of various physiological and pathophysiological conditions in clinically relevant assays.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is a biological product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

Two clinical studies were submitted in support of this biosimilar application: a comparative PK/PD study in healthy volunteers and a comparative clinical study in adult subjects with PNH stable on eculizumab treatment.

Overview 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/m² for non-Japanese subjects; BMI 18.0 to 25.0 kg/m² for Japanese subjects	57 days	Complete; CSR/Module 5.3.3.1 (20150164)

Overview 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 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	Ongoing; Primary analysis CSR[d]/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 hemoglobinuria; 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 randomized 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-authorized reference medicinal product was used in the study. The utilization 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.

[d] The study is currently ongoing. 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. The data cutoff date for the primary analysis for the parallel comparison was 10 January 2022. The primary analysis for the crossover comparison (ie, the final analysis) will be conducted after all subjects have completed the EOS visit. The initial marketing application for ABP 959 will contain data from the primary analysis for the parallel comparison only. The final analysis CSR (including data from the primary analysis for the crossover comparison) will be submitted post-approval.

There have been several changes in the formulation of the drug product during the clinical development. The drug product used for the PK/PD study in healthy subjects had the same formulation as Soliris. Subsequently, the drug substance formulation was changed to a sorbitol formulation which was used in the comparative clinical study and EDTA has also been added to the commercial drug product. Satisfactory analytical comparability assessments have been conducted to support the ABP 959 drug product formulation changes.

IV.2 Bioanalytical assays

The validation reports for each bioanalytical assay have been provided. Overall, the methods were considered acceptable and fit for purpose.

IV. 3 and IV. 4 Pharmacokinetics and pharmacodynamics

In support of the application, the applicant submitted the following studies:

Study 1

PK/PD Study 20150164

This study was a randomised, double-blind, three-arm, parallel group, single-dose study in healthy adult male subjects.

The primary objectives of the study were to demonstrate the PK and PD similarity of BEKEMV (ABP 959) following a single intravenous (IV) infusion of 300 mg, relative to that

of a single IV infusion of 300 mg each of eculizumab sourced from the European Union (eculizumab (EU)) and eculizumab sourced from the United States of America (eculizumab (US)), and to demonstrate PK similarity of a single IV infusion of 300 mg eculizumab (US) relative to a single IV infusion of 300 mg of eculizumab (EU).

Eculizumab (US) was included in order to satisfy global regulatory requirements.

Secondary objectives were to assess the safety, tolerability, and immunogenicity of ABP 959 compared with eculizumab (US) and eculizumab (EU).

Methods

Population studied

A healthy subject population was chosen to provide a homogenous population for a sensitive assessment of PK/PD similarity of ABP 959 and eculizumab without the potential effects of confounding medical conditions or concomitant medications, which can alter an individual PK/PD or safety profile. As it is not known whether Soliris (eculizumab) or ABP 959 can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity, subject participation in the study was limited to male subjects.

Dose Justification

The use of subtherapeutic dose of 300 mg chosen for safety reasons (to reduce possible adverse event risks) in healthy volunteers is acceptable based on PK linearity.

Study Duration

The 57-day duration of the study is selected based on the coverage of more than five times the reported mean half-life ($t_{1/2}$) of the product which is agreed. Subjects received a single 300-mg IV dose of either ABP 959, eculizumab (EU), or eculizumab (US) on day 1 and returned to the study centre as dictated by the schedule of assessments for safety evaluations, antidrug antibodies (ADA) assessment, and PK/PD sample collections until day 57.

Randomisation

Eligible subjects were randomised in a ratio of 1:1:1, stratified by site (clinical pharmacology unit) and ethnicity (Japanese versus non-Japanese).

Pharmacokinetic and pharmacodynamic variables

The primary PK endpoint supporting the primary objective of Study 20150164 was area under the serum drug concentration-time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) for ABP 959 and eculizumab (US and EU) following a single 300-mg infusion. The primary PD endpoint supporting the primary objectives was area between the effect curve (ABEC) of CH50-time data.

Secondary PK endpoints included AUC from time 0 to the last quantifiable concentration (AUC_{last}), maximum observed serum drug concentration (C_{max}), terminal elimination $t_{1/2,}$ and time of C_{max} (t_{max}).

CH50 (50% total haemolytic complement activity) was chosen as a primary endpoint to provide a sensitive measure to detect potential clinical differences in C5 blockade by ABP 959 or eculizumab (US or EU) *in vivo*. The primary PD endpoint of ABEC of CH50 was calculated from CH50 serum data using noncompartmental methods.

In this study, serum samples for PK and CH50 (i.e. PD) analyses were collected on day 1 at pre-dose and up to 24 hours (day 2) post-dose; at each return visit to the clinical pharmacology unit (CPU) on days 3, 5, 8, 11, 15, 22, 29, 36, 43, and 50; and at day 57/end of study (EOS).

Antidrug Antibody Testing (ADA)

ADA sample collection was scheduled to provide a comprehensive assessment of the onset and time course of the ADA response throughout the study duration. Importantly, ADA timepoints were aligned with PK and CH50 collections to allow for assessment of ADA impact on exposure and PD. Blood samples for ADA analysis were collected prior to dosing on day 1, day 11, day 29, and day 57/(EOS). All samples were screened for binding ADA activity, and samples confirmed positive for binding ADAs were also tested for neutralizing activity. The number and percentage of subjects developing binding and neutralising ADAs were tabulated by treatment.

Results

Disposition of Subjects and Baseline Characteristics

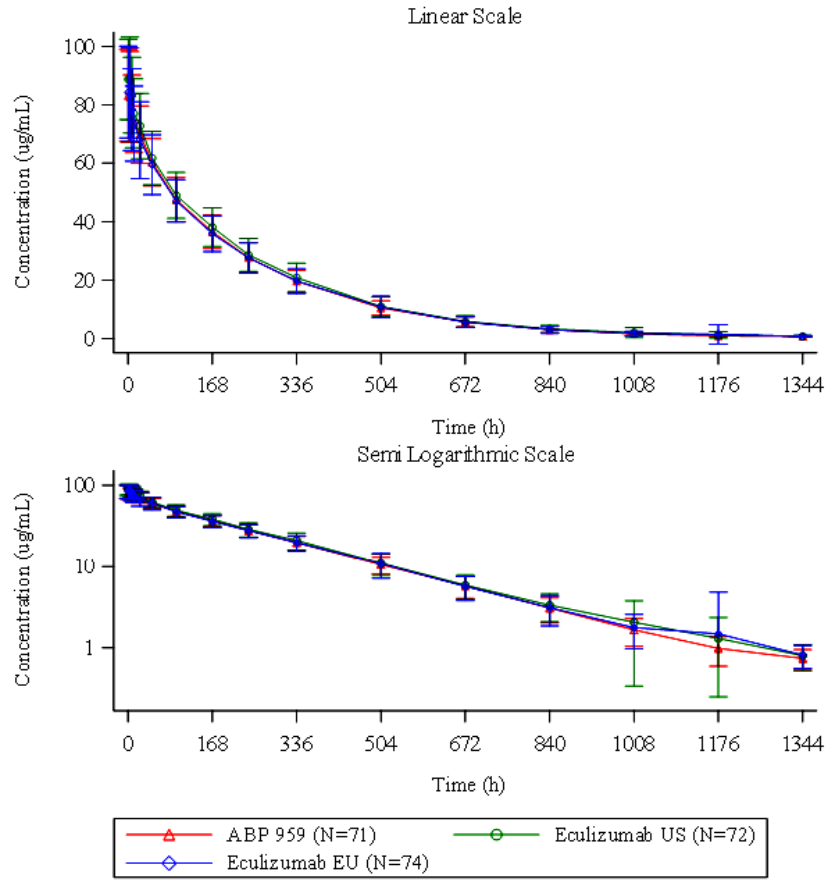
In total, there were 219 subjects in the study; 210 subjects were randomised to treatment (70 subjects each in the ABP 959, eculizumab [US], and eculizumab [EU] treatment groups) and nine additional subjects were enrolled as replacements in the ABP 959 (one subject), eculizumab (US) (four subjects) and eculizumab (EU) (four subjects) treatment groups. Of the 219 subjects, 217 (99.1%) subjects were treated with investigational product and completed the infusion. Overall, 207 (94.5%) subjects (68 [95.8%] in the ABP 959 treatment group, 67 [90.5%] in the eculizumab [US] treatment group, 72 [97.3%] in the eculizumab [EU] treatment group) completed the study and 12 (5.5%) subjects discontinued the study prematurely: seven discontinued due to subject withdrawal, and five subjects discontinued due to lost to follow-up. Subjects ranged in age from 18 to 45 years and the majority were white (65.9% of subjects overall). Demographic and baseline characteristics were well-balanced between the three treatment groups.

A total of 217 subjects were included in the PK, PD and ADA analyses. Four subjects (ABP 959 [one], eculizumab US [two], eculizumab EU [one]) terminated the study too soon for their CH50 data to have returned to baseline (although the maximal reduction was captured).

Pharmacokinetic Results

The mean (±standard deviation (SD)) ABP 959, eculizumab (US), and eculizumab (EU) serum concentration-time profiles following a single 300 mg IV infusion were similar and overlapped for all three treatments over the entire course of sampling (Figure 1).

Figure 1. Mean (±SD) ABP 959, Eculizumab (US), and Eculizumab (EU) Serum Total Concentration-time Profiles (Study 20150164 PK Concentration Population)



The results of the study demonstrated PK similarity between ABP 959 and eculizumab (US and EU) (see Table 1 below).

The 90% confidence intervals of the least squares (LS) geometric mean ratios (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 eculizumab (US) and ABP 959 to eculizumab (EU), based on total drug concentrations, were fully contained within the pre-specified equivalence criteria of 0.80 to 1.25. Additionally, PK similarity was demonstrated between eculizumab (US) and eculizumab (EU), thus establishing the PK component of the scientific bridge between eculizumab (US) and eculizumab (EU).

Table 1. Summary of Statistical Assessment of ABP 959, Eculizumab (US), and Eculizumab (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	19981.2 [70]	89.592 [71]	19902.5 [70]
Eculizumab (US)	20840.2 [68]	94.414 [72]	20711.7 [70]
Eculizumab (EU)	19937.8 [71]	89.370 [74]	19913.1 [72]
	Ratio of LS geometric means (90% CI)		
ABP 959 vs eculizumab (US)	0.9588 (0.9129, 1.0070)	0.9489 (0.9096, 0.9899)	0.9609 (0.9154, 1.0087)
ABP 959 vs eculizumab (EU)	1.0022 (0.9547, 1.0520)	1.0025 (0.9613, 1.0455)	0.9995 (0.9525, 1.0488)
eculizumab (US) vs eculizumab (EU)	1.0453 (0.9954, 1.0976)	1.0564 (1.0131, 1.1016)	1.0401 (0.9912, 1.0914)

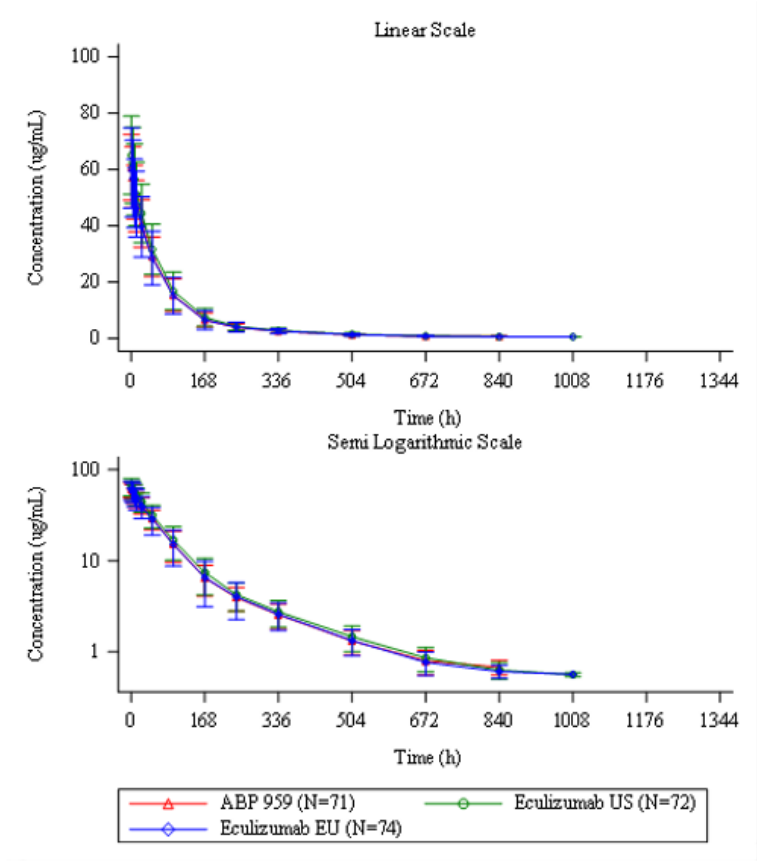
AUC_{inf} = area under the serum drug concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the serum drug concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed serum drug concentration; CSR = clinical study report; EU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

Source: Modified from Table 14-9.5.1 in CSR 20150164

The 90% confidence intervals of the least squares (LS) geometric mean ratios (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 eculizumab (US) and ABP 959 to eculizumab (EU) were fully contained within the pre-specified equivalence criteria of 0.80 to 1.25. Additionally, PK similarity was demonstrated between eculizumab (US) and eculizumab (EU), thus establishing the PK component of the scientific bridge between eculizumab (US) and eculizumab (EU).

A bioanalytical method was developed and validated to determine unbound serum concentrations of ABP 959 and eculizumab (EU and US). The mean serum unbound concentration-time profiles following a single IV infusion of all three treatments were similar and overlapped over the entire course of sampling (Figure 2).

Figure 2. Mean (±SD) ABP 959, Eculizumab (US), and Eculizumab (EU) Serum Unbound Concentration-time Profiles (Study 20150164 PK Free Concentration Population)



For each of the treatment comparisons, the 90% confidence intervals of the LS GMR were fully contained within the bioequivalence 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 eculizumab (US), ABP 959 and eculizumab (EU), and eculizumab (US) and eculizumab (EU), based on unbound drug concentrations (see Table 2).

Table 2. Summary of Statistical Assessment of Unbound ABP 959, Eculizumab (US), and Eculizumab (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]
Eculizumab (US)	6233.8 [70]	70.319 [72]	6054.0 [70]
Eculizumab (EU)	5718.2 [70]	64.593 [74]	5534.5 [72]
Ratio of LS geometric means (90% CI)			
ABP 959 vs eculizumab (US)	0.9173 (0.8477, 0.9926)	0.9345 (0.8751, 0.9979)	0.9143 (0.8434, 0.9911)
ABP 959 vs eculizumab (EU)	1.0000 (0.9241, 1.0821)	1.0173 (0.9531, 1.0858)	1.0001 (0.9231, 1.0835)
eculizumab (US) vs eculizumab (EU)	1.0902 (1.0077, 1.1794)	1.0887 (1.0202, 1.1617)	1.0939 (1.0097, 1.1851)

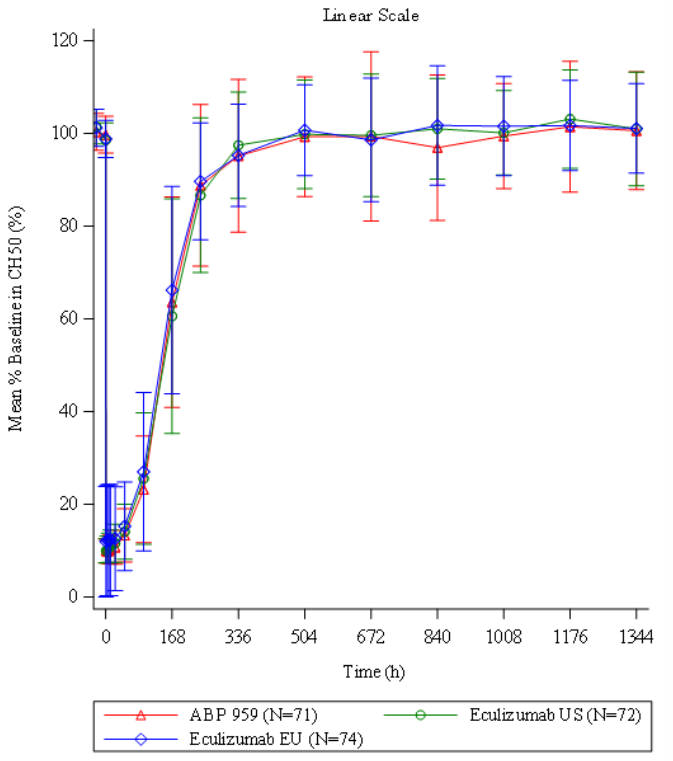
AUC_{inf} = area under the serum drug concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the serum drug concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed serum drug concentration; EU = European Union; LS = least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

Source: Modified from Table 14-9.5.1.1 in CSR 20150164

Pharmacodynamics Results

The mean percent baseline in CH50 time profiles following a single 300-mg IV infusion of ABP 959, eculizumab (US), and eculizumab (EU) were similar and overlapped over the entire course of sampling (Figure 3).

Figure 3. Mean (±SD) Percent Baseline in CH50 Time Profiles of ABP 959, Eculizumab (EU), and Eculizumab (US) (Study 20150164 PD Population)



3).

The results of the study demonstrated PD similarity between ABP 959 and eculizumab (US and EU) (Table 3).

Table 3. Summary of Statistical Assessment of ABEC of CH50 for ABP 959, Eculizumab (US), and Eculizumab (EU) (Study 20150164 PD Parameter Population)

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)

CH50 = 50% total hemolytic complement activity; CSR = clinical study report; EU = European Union; LS = least squares; PD= pharmacodynamic; US = United States
Source: Modified from Table 14-9.10.1; Table 14-9.11.1; Table 14-9.11.3 in CSR 20150164

The 90% and 95% confidence intervals of the LS GMR of ABEC of CH50 for the comparisons of ABP 959 to eculizumab (US) and ABP 959 to eculizumab (EU) were contained within the prespecified margin of 0.80 to 1.25, indicating similar inhibition of C5 activity. .

Immunogenicity Results

A summary of anti-drug antibodies (ADA) results is presented in Table 4.

Table 4. Summary of Binding and Neutralizing Antidrug Antibody Results (Study 20150164 ADA Population)

Visit	ABP 959 (N = 71)	Eculizumab (US) (N = 72)	Eculizumab (EU) (N = 74)	Overall (N = 217)
	Number and Percentage of Subjects with Binding Antibody Assay Positive Results			
Day 1, predose	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/ET)	1/70 (1.4%)	2/68 (2.9%)	1/73 (1.4%)	4/211 (1.9%)
Positive at any time during the study	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	3/71 (4.2%)	3/70 (4.3%)	6/73 (8.2%)	12/214 (5.6%)
	Number and Percentage of Subjects with Neutralizing Antibody Assay Positive Results			
Day 1, predose Day 11 Day 29 Day 57 (EOS/ET) Positive at any time during the study	All neutralizing ADA tests were negative.			

ADA = antidrug antibody; CSR = clinical study report; EOS/ET = end of study/early termination; EU = European Union; US = United States
Note: Denominator values of positive at any time during the study were the number of subjects with at least 1 ADA assessment during the study.
Source: Table 14-10.1.1 and Table 14-10.2.1 in CSR 20150164

The incidence of binding ADA was low (<10%) for the test ABP 959 and the EU eculizumab reference. The percentage of subjects that were 'positive for binding ADAs at any time during the study' and that were 'positive post-baseline with a negative or no result at baseline' is comparable between the treatment groups. All neutralising ADA tests were negative.

Comparative clinical study 20150168
Methods

See section 'IV.5 Clinical efficacy below'.

The assessment of PK similarity in PNH patients is a secondary objective of the comparative clinical study 20150168 and is intended to confirm PK similarity in PNH patients, in addition to the demonstration of PK similarity findings in the PK/PD similarity study in healthy subjects.

The total and unbound PK AUC from week 13 to week 15 of ABP 959 and eculizumab and trough PK were identified as secondary PK endpoints in this study.

In this study, serum samples for PK analysis were collected at baseline on day 1/visit 1/week 1, predose (trough) at weeks 3, 7, 13, 15, 19, 25, 27, 33, 39, 45, 51, 53, 55, 59, 65, 71, 77 and week 79/EOS, and immediately after the end-of-infusion at week 13 and at week 14. Blood sampling timepoints for PK were considered to be sufficient to adequately characterize ABP 959 and eculizumab concentration-time profiles. Serum ABP 959 and eculizumab

concentrations are summarized descriptively by actual treatment for each planned PK sampling visit.

Given the half-life of eculizumab is 271 hours, a washout period for 12 weeks from steady state eculizumab in PNH patients is expected to be sufficient; therefore, the comparison of PK AUC during a dosing interval (AUC_{tau}) is chosen between the dosing period of week 13 and 15.

Pharmacodynamic assessments for the clinical studies supporting this application included serum concentrations of CH50.

Results

Pharmacokinetic Results

A summary of the statistical assessment of total PK AUC from week 13 to week 15 is provided in Table 5 by initial treatment received. The GMR (90% CI) was provided descriptively for ease of comparison; no prespecified PK criteria were set due to the small sample size of the study.

Table 5: Summary of Statistical Assessment of Total PK Concentration AUC (µg*day/mL) from Week 13 to Week 15 (Study 20150168 PK Parameter Analysis Set)

Statistic	ABP 959 (N = 18)	Eculizumab (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/eculizumab)[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
Source: Modified from Table 14-9.1 in the Study 20150168 primary analysis CSR

A summary of the statistical assessment of unbound PK AUC from week 13 to week 15, by initial treatment received is provided in Table 6. The GMR (90% confidence intervals) was provided descriptively for ease of comparison; no prespecified PK criteria were set due to the small sample size of the study.

Table 6: Summary of Statistical Assessment of Unbound PK Concentration AUC (µg*day/mL) from Week 13 to Week 15 (Study 20150168 PK Parameter Analysis Set)

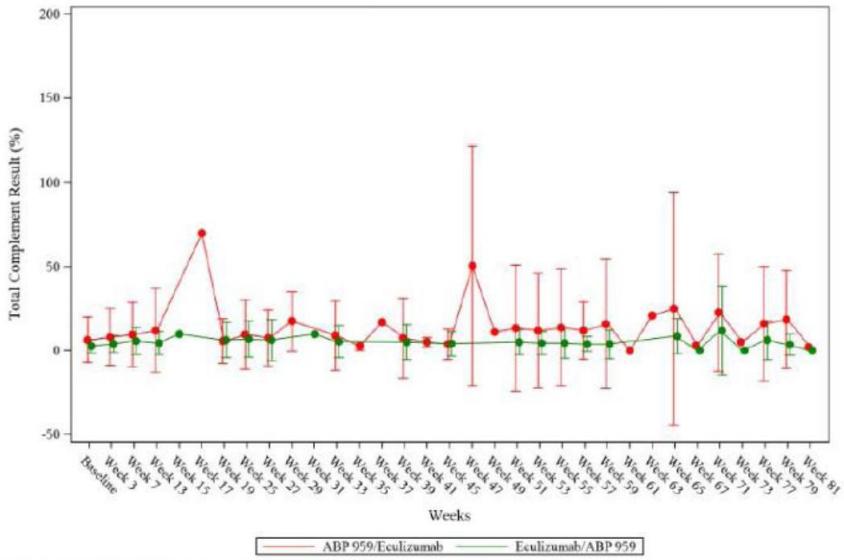
Statistic	ABP 959 (N = 18)	Eculizumab (N = 19)
n	18	19
Mean (SD)	3054.38 (1315.023)	3138.15 (1372.653)
Median	3136.12	2622.54
%CV	43.1	43.7
Minimum, maximum	1036.5, 5419.9	1774.0, 6541.5
Geometric mean	2761.19	2903.93
Geometric CV	51.3	40.6
Geometric LS mean[a]	2761.19	2903.93
GMR (ABP 959/eculizumab)[a]	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
Source: Modified from Table 14-9.2 in the Study 20150168 primary analysis CSR

Pharmacodynamic Results

Total complement (CH50) at week 27, week 39, week 53, week 65, and week 79 was a secondary efficacy endpoint of the study. Values for mean total complement (CH50) at week 27, week 39, week 53, week 65, and week 79 are provided graphically below in Figure 4.

Figure 4. Mean (SD) of Total Complement Through End of Study (Study 20150168 Full Analysis Set)



CH50 = 50% total hemolytic complement activity; CSR = clinical study report
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.
Source: Figure 14-7.1 in the Study 20150168 primary analysis CSR

Immunogenicity Results

No subjects in either treatment group tested positive for pre-existing binding ADAs or neutralising ADAs at baseline.

Through the primary analysis data cut-off, one subject in the eculizumab/ABP 959 treatment group tested positive for binding ADAs at the week 55 time point; results were transient (i.e.

negative results at the subject's last time point tested). No subjects in either treatment group tested positive for neutralising ADAs or treatment boosted ADAs.

Overall conclusion on pharmacokinetics and pharmacodynamics
Pivotal PK/PD data is provided from study 20150164. The design of this study is acceptable. The results of the PK/PD study showed that the mean serum concentration profiles overlapped for the test ABP 959 and the EU eculizumab reference product, with 90% confidence intervals for the PK parameters, AUC_{inf}, C_{max} and AUC_{last} of the total and the free (unbound) eculizumab, all contained within the 0.8 to 1.25 limits demonstrating biosimilarity. Similarly, biosimilarity was demonstrated for the PD endpoint CH50 for the test ABP 959 versus the EU eculizumab reference where the 95% confidence intervals were within the 0.8 to 1.25 limits.

The incidence of ADA was low and comparable between the treatment groups. No subjects developed neutralising ADAs.

Supportive PK/PD data is provided from the comparative clinical study 20150168. The design of the PK/PD aspects of this study is acceptable. Although the confidence intervals were outside the lower boundary of the 0.8 to 1.25 limits for the PK results of the comparative clinical study, these results are acceptable as the study is not powered to demonstrate biosimilarity. Whilst the median PK exposure appeared to be comparable between ABP 959 and eculizumab, it was noted that the ABP 959 exposure appeared to have higher variability. Similarly, the PD endpoint CH50 appeared to have higher variability for ABP 959 as compared to eculizumab. Further detailed analysis of this finding revealed that this was driven by data from four subjects. These findings are consistent with the observations reported in the scientific literature for patients with PNH who are treated with eculizumab. A review of additional safety, efficacy and immunogenicity data from these four subjects showed that the observed high CH50 and low serum trough concentrations did not translate into clinically impactful findings.

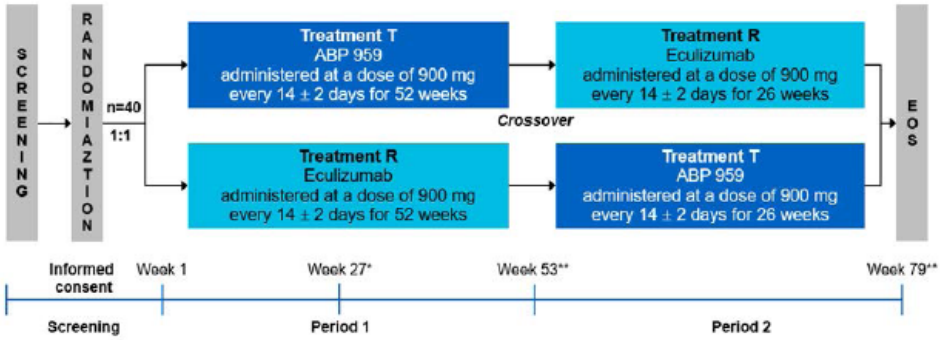
The incidence of ADA was low with only 1 subject in the eculizumab/ABP 959 treatment group testing transient positive for binding ADAs.

In conclusion, these results confirm the biosimilarity of the test ABP 959 and the EU eculizumab reference product from a PK/PD perspective.

IV.5 Clinical efficacy

In support of the application, the applicant submitted the primary analysis data (through the data cut-off date) from the following comparative clinical study.

Comparative clinical study 20150168
This study was a randomised, double-blind, active-controlled, two-period, crossover comparative clinical study in adult subjects with PNH who are stable on eculizumab treatment.



AUEC = area under the effect curve; EOS = end-of-study; LDH = lactate dehydrogenase; R = reference; T = test

Note: The study is currently ongoing. 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. The planned data cutoff date for the primary analysis for the parallel comparison was 10 January 2022. The primary analysis for the crossover comparison (ie, the final analysis) will be conducted after all subjects have completed the EOS visit. The initial marketing application for ABP 959 will contain data from the primary analysis for the parallel comparison only. The final analysis clinical study report (including data from the primary analysis for the crossover comparison) will be submitted post-approval.

*Parallel LDH endpoint at week 27 (European Medicines Agency requirement)

**Crossover AUEC of LDH endpoint at week 13 to week 27, week 39 to week 53, and week 65 to week 79 (Unites States Food and Drug Administration requirement)

The study design was developed to satisfy global regulatory requirements. The study is composed of two periods; the first period was to satisfy the European Medicines Agency (EMA) requirements for a 12-month parallel comparative efficacy and safety assessment (i.e. 52 weeks total). This period of the study (parallel comparison) is complete and will be the focus of this assessment.

Period 2 has been included to satisfy Food and Drug Administration (FDA) requirements for the primary endpoint for crossover comparison measuring area under the effect curve (AUEC) of LDH from week 13 to week 27, week 39 to week 53 (Period 1) and from week 65 to week 79 (Period 2), Furthermore in order to minimise the carry-over effects from the prior treatment, the MAH has introduced a washout period for at least 12 weeks for each study period before the primary endpoint measurement begins. By crossover at week 53, the carryover drug effects from the prior treatment would be minimal and allows the new treatment phase to be assessed at steady state.

The study was conducted at 25 centres across 14 countries.

Methods

Study participants

Main inclusion and exclusion criteria

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 for ≥ 6 months and were receiving 900 mg of eculizumab. Subjects were to have haemoglobin ≥ 9.0 g/dL for at least 6 weeks before randomisation and lactate dehydrogenase (LDH) < 1.5 x the upper limit of normal (ULN) at screening. Subjects must have been vaccinated against *Neisseria meningitidis.* Subjects were excluded from participation if they had a history of known or suspected hereditary complement deficiency, required red blood cell transfusion within 12 weeks before randomisation, and/or experienced ≥ 2 breakthrough events in the previous 12 months before screening. A complete list of subject inclusion and exclusion criteria was provided in the study protocol.

Treatments
Eculizumab sourced from both the US and the EU was utilised in this study. This is supported by satisfactory quality bridging data and clinical PK/PD bridging data from the PK/PD study (Study 20150164).

In line with the approved eculizumab posology for PHN, investigational product was administered at a dose of 900 mg via IV infusion every 14 ± 2 days. Dose adjustments of investigational product based on signs and symptoms of intravascular haemolysis, including LDH levels, were allowed during the study.

Objectives
Primary objective
- To evaluate the efficacy of ABP 959 compared with that of eculizumab based on control of intravascular haemolysis.

Secondary objectives
- To assess the safety, PK, and immunogenicity of ABP 959 compared with that of eculizumab.

Outcomes/endpoints

Primary endpoint
Parallel comparison
- Haemolysis, as measured by LDH at week 27.

Week 27 was chosen for the analysis of LDH in the parallel comparison because assessment at this time point is more than sufficient to eliminate the possibility of carryover effects of drug exposure from prior Soliris treatment in subjects with stable PNH given the 11-day half-life ($t_{1/2}$) of Soliris and also allows sufficient time for LDH response to ABP 959 for those subjects randomised to ABP 959 in Period 1. Thus, at the week 27 timepoint, patients will have reached steady state of LDH following the change of treatment from Soliris to ABP 959.

Crossover comparison
- 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.

Secondary endpoints
- 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
- crossover comparison of haemolysis as measured by LDH at week 53 and week 79
- LDH-time profile
- RBC transfusion
- PK area under the curve (AUC) of ABP 959 and eculizumab from week 13 to week 15, and trough PK (discussed in Section IV. 4 above).

Due to the non-specificity of LDH with the potential for conditions other than haemolysis to cause a rise in levels, an independent LDH review committee was established for this study.

Randomisation
Subjects were randomised to receive one of the two treatment sequences (ABP 959/eculizumab or eculizumab/ABP 959). The randomisation occurred within eight days before the first dose of investigational product and was stratified by red blood cell (RBC) transfusion received within the last 12 months before randomisation (yes vs no).

Results

Participant flow
42 subjects were randomised and treated in period 1 of this study: 20 in the ABP 959/eculizumab treatment group and 22 in the eculizumab/ABP 959 treatment group.

Table 7: Study and investigational product disposition (Full analysis set (FAS))

Variable	ABP 959/Eculizumab (N=20) n (%)	Eculizumab/ABP 959 (N=22) n (%)	Total (N=42) N (%)
Subjects randomised	20 (100.0)	22 (100.0)	42 (100.0)
Subjects treated with IP in period 1	20 (100.0)	22 (100.0)	42 (100.0)
Subjects who completed period 1 IP dosing	20 (100.0)	21 (95.5)	41 (97.6)
Subjects who discontinued IP during period 1	0 (0.0)	1 (4.5)	1 (2.4)
Subjects treated with IP in period 2	20 (100.0)	21 (95.5)	41 (97.6)
Subjects who completed period 2 IP dosing	9 (45.0)	7 (31.8)	16 (38.1)
Subjects who discontinued IP during period 2	1 (5.0)	1 (4.5)	2 (4.8)
Subjects who completed the study	8 (40.0)	6 (27.3)	14 (33.3)
Subjects who discontinued the study early	1 (5.0)	2 (9.1)	3 (7.1)

In period 1, one subject in the Eculizumab/ABP 959 group discontinued IP due to an adverse event (asthenia and fatigue). In period 2, two subjects discontinued IP: one subject in the ABP 959/Eculizumab group due to ‘consent withdrawal for treatment’ and one subject in the Eculizumab/ABP 959 group due to ‘other – patient’s personal needs’.

Only two subjects required dose adjustments during the study, one subject in the eculizumab/ABP 959 treatment group (outside of the window for the primary efficacy endpoint analysis) and one subject in the ABP 959/eculizumab treatment group.

Baseline data
The demographic and baseline physical characteristics were generally comparable between the two treatment groups.

Table 8: Demographic and baseline physical characteristics (FAS)

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

In order to be eligible for inclusion in the study subjects had to be stable on eculizumab treatment for ≥ 6 months. In both groups the mean and median treatment duration prior to study enrolment was significantly longer than 6 months; it was longer in the ABP 959/eculizumab group compared with the eculizumab/ABP 959 group. These differences are

not considered likely to significantly impact the study outcome. The remaining baseline disease characteristics were comparable between the two treatment groups.

Numbers analysed

Table 9: Subject analysis sets (All subjects)

Population	ABP 959/ Eculizumab	Eculizumab/ ABP 959	Total
Subjects screened			47
Subjects randomized (FAS)	20	22	42
PPP analysis set - n (%)[a]	20 (100)	22 (100)	42 (100)
Protocol deviation affecting evaluation for primary parallel comparison	0	0	0
Safety analysis set - n (%)[a]	20 (100)	22 (100)	42 (100)
Did not receive IP	0	0	0
PK concentration analysis set - n (%)[a]	20 (100)	22 (100)	42 (100)
Not in safety analysis set	0	0	0
Did not have at least 1 PK serum concentration	0	0	0
PK parameter analysis set - n (%)[a]	18 (90.0)	19 (86.4)	37 (88.1)
Not in safety analysis set	0	0	0
Did not have evaluable serum concentration profile from weeks 13 to 15[b]	2 (10.0)	3 (13.6)	5 (11.9)

FAS = full analysis set; IP = investigational product; LDH = lactate dehydrogenase; PK = pharmacokinetic; PPP analysis set = per-protocol analysis set for the primary endpoint of LDH at week 27 for the parallel comparison

a Percentage of subjects randomized within treatment group.
b Excluded due to 1 or more PK samples not valid or missing.

LDH values excluded by the independent review committee.

At the time of the primary analysis data cut-off, 12 LDH values were excluded in nine subjects in the ABP 959/eculizumab treatment group and nine LDH values were excluded in six subjects in the eculizumab/ABP 959 treatment group. The most common reason for exclusion was haemolysis in the tube. Only four values were excluded between week 13 and 27 (the time period used in the modelling for analysis of the primary efficacy endpoint for the parallel comparison) in the ABP 959/eculizumab group and two in the eculizumab/ABP 959 group. These LDH values were excluded from the efficacy analyses only and were included in the safety analyses.

Outcomes and estimation

Primary analysis for the parallel comparison

Table 10: 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
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
n = number of subjects included in the mixed model
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, 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.

The 1-sided 97.5% upper CI of 1.158 was contained well within the non-inferiority margin of 2.873, thus establishing similarity in clinical efficacy between ABP 959 and eculizumab in the parallel comparison.

Sensitivity analysis
All subjects from the FAS were included in the PPP analysis set; thus, results from the sensitivity analysis were identical with results from the primary efficacy analysis.

To assess the potential impact of the LDH exclusions, an additional sensitivity analysis was requested without excluding these values. The results were similar to those of the primary efficacy analysis, with the 1-sided 97.5% upper CI of 1.170 contained well within the non-inferiority margin of 2.873.

Secondary 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

Overall, the secondary endpoints through the crossover in treatment at week 53 support biosimilarity. As the data are not yet mature, meaningful conclusions cannot be drawn post week 53.

Total complement

Several subjects in the ABP 959/eculizumab treatment group had higher total complement (CH50) values prior to ABP 959 dosing that remained high throughout the treatment period. This resulted in slightly higher mean values for the ABP 959/eculizumab treatment group through the crossover in treatment at week 53, especially given the small sample size of the study. CH50 values for these subjects remained high following the switch to eculizumab at week 53. The occurrence of high CH50 values is not unexpected in the study population of subjects with stable PNH. Overall, the CH50 values were well suppressed across both treatment groups, and the slight differences in mean values were not considered to be clinically meaningful.

Table 11: Summary of continuous efficacy lab endpoints by visit (Full Analysis set FAS)) – total complement

	ABP 959/Eculizumab (N = 20)		Eculizumab/ABP 959 (N = 22)	
Efficacy Lab Endpoint Time Point	Value	Change from Baseline	Value	Change from Baseline
Total Complement (%)				
Baseline				
n	20		22	
Mean (std)	6.4 (13.48)		2.6 (4.11)	
Median	0.5		0.0	
Q1, Q3	0.0, 6.5		0.0, 4.0	
Min, Max	0, 56		0, 17	
Week 27				
n	19	19	21	21
Mean (std)	7.5 (16.68)	1.2 (6.93)	6.3 (12.24)	3.9 (11.46)
Median	0.0	0.0	1.0	0.0
Q1, Q3	0.0, 1.0	-2.0, 0.0	0.0, 5.0	0.0, 2.0
Min, Max	0, 50	-6, 22	0, 50	-2, 50
Week 39				
n	17	17	21	21
Mean (std)	7.4 (23.80)	4.1 (18.31)	5.1 (10.36)	2.7 (9.25)
Median	0.0	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	-1.0, 0.0	0.0, 3.0	0.0, 1.0
Min, Max	0, 98	-3, 75	0, 37	-6, 37
Week 53				
n	20	20	21	21
Mean (std)	12.0 (34.29)	5.6 (30.99)	4.6 (6.84)	2.1 (5.87)
Median	0.5	0.0	0.0	0.0
Q1, Q3	0.0, 2.0	-2.0, 0.0	0.0, 8.0	0.0, 4.0
Min, Max	0, 144	-12, 136	0, 20	-6, 18
Week 65				
n	10	10	9	9
Mean (std)	25.0 (69.52)	20.0 (62.90)	8.6 (10.50)	6.0 (9.41)
Median	1.0	0.0	6.0	1.0
Q1, Q3	0.0, 3.0	0.0, 1.0	1.0, 9.0	0.0, 9.0
Min, Max	0, 222	-1, 199	0, 29	-4, 22
Week 79				
n	8	8	6	6
Mean (std)	18.6 (29.06)	4.6 (26.61)	3.5 (6.32)	2.2 (5.91)
Median	1.0	-0.5	0.5	0.5
Q1, Q3	0.0, 39.0	-4.5, 19.5	0.0, 4.0	-1.0, 4.0
Min, Max	0, 69	-38, 46	0, 16	-4, 13

Total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, type III erythrocytes values and degree of haemoglobinuria

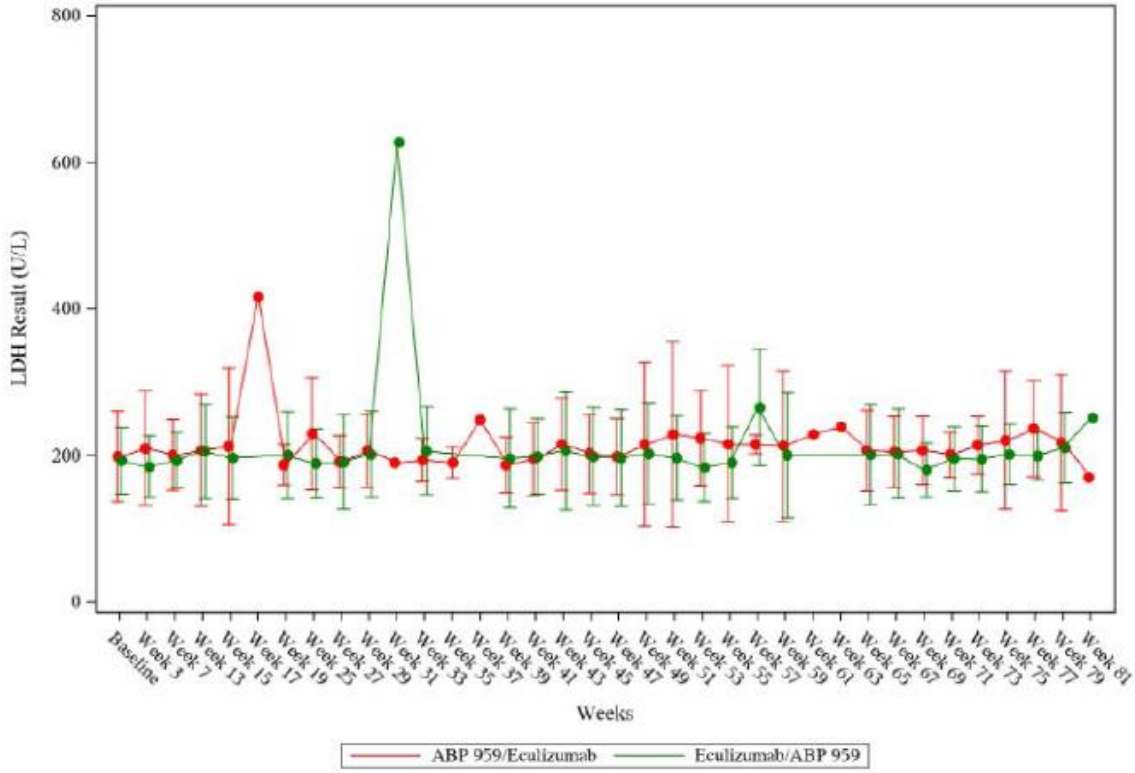
In general, total haemoglobin, serum-free haemoglobin, haptoglobin, bilirubin, type III erythrocytes values and degree of haemoglobinuria were stable over time and results were generally comparable between the two treatment groups through the crossover in treatment at week 53, when taking into consideration the baseline values and small sample size of this study.

Lactate dehydrogenase time profile

Lactate dehydrogenase values were stable over time; results were comparable between the two treatment groups. The week 17 LDH value for the ABP 959/eculizumab treatment group

and the week 31 LDH value for the eculizumab/ABP 959 treatment group contain values for one subject each at the particular visit.

Figure 5: Mean (+/- SD) LDH values (U/L) through end of study (FAS)



Red blood cell transfusion

In Period 1, for the time period of week 13 to the end of Period 1, the mean (SD) number of packed red blood cell (RBC) units transfused per month was 0.160 (0.0707) for two subjects in the ABP 959/eculizumab treatment group and 0.278 (0.1446) for five subjects in the eculizumab/ABP 959 treatment group.

In Period 2 (through the primary analysis data cut-off), for the time period of week 65 to EOS, the mean (SD) number of packed RBC units transfused per month was 0.950 (SD data not available) for one subject in the ABP 959 treatment group.

Overall conclusions on clinical efficacy

In view of the mechanism of action of eculizumab, the efficacy of Soliris is directly related to the biological events triggered by the binding of the active to its known targets. As the quality comparability exercise and the pivotal PK/PD study supports biosimilarity, it is considered that a similar efficacy profile for BEKEMV (ABP 959) and the reference product Soliris can already be concluded. This is in-keeping with the principles in the MHRA ‘Guidance on the licensing of biosimilar products’.

Despite significant limitations to the comparative efficacy study in patients with only 42 subjects randomised due to rarity of PNH, the data from the comparative clinical study 20150168 support this conclusion. Whilst the non-inferiority margin for the analysis of the primary endpoint comparison of haemolysis, as measured by LDH at week 27, is clinically quite wide, the feasibility constraints of increasing the sample size to reduce the NI margin in PNH as a rare condition are acknowledged and the results fell well within this margin. The secondary endpoints also support biosimilarity of ABP 959 to Soliris (eculizumab).

IV.6 Clinical safety

The clinical safety data to support this application are from the completed pivotal PK/PD study in 217 healthy volunteers (Study 20151064) and 42 subjects with PNH in the comparative clinical study (Study 20150168).

The data are presented separately for each study given the different subject populations.

PK/PD study 20150164

Patient exposure

Two hundred and seventeen subjects received a single 300 mg dose of study drug: ABP 959 (71 subjects), US-eculizumab (72) or EU-eculizumab (74). There were 12 subjects who did not complete the study (three in the ABP 959 group, seven in the eculizumab [US] group, two in the eculizumab [EU] group); of these 12 subjects, five subjects were lost to follow up and seven subjects withdrew from the study.

Adverse events

Overview of adverse events

Table 12: Overall summary of treatment-emergent adverse events (TEAEs) by treatment (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.

Overall, the number of subjects with any TEAE was broadly similar between the treatment groups. The majority of TEAEs were grade 1 or 2 in severity. One subject in each treatment group reported at least one grade 3 TEAE of which only one event of ‘headache’ in the eculizumab EU group was considered probably related to treatment. No grade 4 or 5 events were reported.

Common adverse events
The common adverse events were in-keeping with the known safety profile of Soliris (see Table 13 below).

Table 13: Summary of TEAEs reported in ≥5 subjects in any treatment group by preferred term in descending order of frequency and by treatment (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 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]

Serious adverse events and deaths, other significant events

Deaths
There were no deaths in this study.

Serious adverse events
The number of subjects reporting at least 1 SAE was low and comparable between the two treatment groups. Only one SAE of ‘headache’ in the eculizumab EU group was considered probably related to treatment.

Table 14: Summary of serious TEAEs by preferred term and treatment (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]

Adverse events of special interest
Adverse events of special interest in this study included infections, infusion reactions, meningococcal infection, sepsis, and haematologic abnormalities.

Adverse events of interest were reported more frequently in the eculizumab EU group, this was driven by a higher incidence of infections in this group. The number of subjects that experienced an infusion reaction was similar across the treatment groups. Four subjects experienced a grade 1 or 2 infusion reaction coinciding with study drug infusion or the day afterwards: 3 subjects in the ABP 959 group (cough, pyrexia, skin reaction) and 1 subject in the eculizumab EU group (infusion related reaction).

Table 15: Overall summary of TEAEs of interest of any grade (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]

Laboratory assessments and vital signs
Overall, no clinically relevant changes from baseline in laboratory values, vital signs or ECG parameters were observed.

Safety in special populations
Not applicable for biosimilars.

Immunological events
Of the 19 subjects with positive binding ADA results at any time during the study, nine subjects also reported adverse events of interest. The nine subjects were balanced across the treatment groups. Except for one event in the eculizumab (US) group that was retrieved within the search strategy of infusion reactions, the events were all within the search strategy of infections.

Safety related to drug-drug interactions and other interactions
Not applicable to biosimilars.

Discontinuation due to adverse events
This was a single dose study therefore no subjects discontinued investigational product due to a TEAE.

No subjects discontinued the study due to a TEAE.

Post marketing experience
Not applicable.

Comparative clinical study 20150168
Prior to enrolment in the comparative clinical study, all subjects had been stable on eculizumab treatment for ≥ 6 months and were receiving 900 mg of eculizumab.

When discussing safety data for Period 1, treatment groups are identified by initial treatment received; when discussing safety data for Period 2, treatment groups are identified by the crossover treatment received.

The small number of subjects limits the safety assessment in this study.

Patient exposure
All 42 randomised subjects were treated with investigational product and were included in the safety analysis set.

Period 1
Period 1 of the study is complete and the exposure during this period is comparable between the two treatment groups.

Table 16: Investigation product exposure period 1 (safety analysis set)

Variable	ABP 959 (N = 20)	Eculizumab (N = 22)
Subjects receiving at least one dose	20	22
Total number of doses administered		
n	20	22
Mean (std)	26.3 (1.16)	25.2 (4.07)
Median	26.0	26.0
Q1, Q3	26.0, 26.0	26.0, 26.0
Min, Max	25, 31	7, 27
Total number of doses administered - n (%)		
7	0	1 (4.5)
25	1 (5.0)	0
26	17 (85.0)	20 (90.9)
27	1 (5.0)	1 (4.5)
31	1 (5.0)	0
Total dose received (mg)		
n	20	22
Mean (std)	23642.8 (1059.56)	22663.6 (3659.89)
Median	23400.0	23400.0
Q1, Q3	23400.0, 23400.0	23400.0, 23400.0
Min, Max	22500, 27900	6300, 24300
Duration of IP exposure (weeks)		
n	20	22
Mean (std)	52.249 (0.3813)	50.368 (8.3155)
Median	52.140	52.140
Q1, Q3	52.140, 52.215	52.140, 52.140
Min, Max	51.86, 53.57	13.14, 52.43

Period 2

Period 2 of the study is ongoing. At data cut-off, the exposure was higher in the eculizumab group compared with the ABP 959 group.

Table 17: Investigation product exposure period 2 (safety analysis set)

Variable	ABP 959 (N = 21)[a]	Eculizumab (N = 20)[a]
Subjects receiving at least one dose	21	20
Total number of doses administered		
n	21	20
Mean (std)	7.7 (4.61)	9.0 (4.42)
Median	6.0	9.0
Q1, Q3	3.0, 13.0	5.5, 13.0
Min, Max	1, 13	1, 15
Total number of doses administered - n (%)		
1	1 (4.8)	1 (5.0)
2	2 (9.5)	0
3	3 (14.3)	2 (10.0)
5	3 (14.3)	2 (10.0)
6	2 (9.5)	3 (15.0)
7	1 (4.8)	2 (10.0)
10	1 (4.8)	0
11	0	1 (5.0)
12	1 (4.8)	0
13	7 (33.3)	8 (40.0)
15	0	1 (5.0)
Total dose received (mg)		
n	21	20
Mean (std)	6900.0 (4147.17)	8055.0 (3976.71)
Median	5400.0	8100.0
Q1, Q3	2700.0, 11700.0	4950.0, 11700.0
Min, Max	900, 11700	900, 13500
Duration of IP exposure (weeks)		
n	21	20
Mean (std)	14.877 (9.6101)	17.193 (9.1651)
Median	11.860	17.425
Q1, Q3	6.860, 26.000	9.430, 26.140
Min, Max	0.14, 27.14	0.14, 26.57

Adverse events

Overview of adverse events

Period 1

Overall, the percentage of subjects with any TEAE was lower in the ABP 959 group compared with the eculizumab group (75% vs 96%). The majority of TEAEs were grade 1 or 2 in severity. Two (10%) subjects in the ABP 959 group and eight (36%) subjects in the eculizumab group experienced grade 3 TEAEs. No grade 4 or 5 events were reported.

Table 18: Overall summary of adverse events in period 1 (safety analysis set)

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)

[a] Identified using the hypersensitivity SMQ (broad) and infusion reaction AMQ (broad) search strategies [b] Identified using the infections and infestations SOC (broad) search strategy

Period 2

Overall, the number of subjects with any TEAE was comparable between the treatment groups. The majority of TEAEs were grade 1 or 2 in severity.

Table 19: Overall summary of AEs in period 2 (safety analysis set)

Adverse Event Category	ABP 959 (N = 21)[a] n (%)	Eculizumab (N = 20)[a] n (%)
Any adverse event	14 (66.7)	14 (70.0)
Any grade ≥ 3 adverse event	3 (14.3)	1 (5.0)
Any fatal adverse event	0 (0.0)	0 (0.0)
Any serious adverse event	4 (19.0)	0 (0.0)
Any adverse event leading to discontinuation of IP/study	0 (0.0)	0 (0.0)
Any EOI	6 (28.6)	3 (15.0)
Infusion reaction adverse event[b]	4 (19.0)	3 (15.0)
Serious infection adverse event[c]	2 (9.5)	0 (0.0)

AMQ = Amgen MedDRA Query; CSR = clinical study report; 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 summarized. For each category, subjects were included only once, even if they experienced multiple events in that category.

[a] N is the number of subjects in the safety analysis set who were treated with investigational product in Period 2.

[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

Common adverse events

Period 1

Table 20: Adverse Events Experienced by ≥ 10% of Subjects in Any Treatment Group by preferred term in Period 1

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)

The common adverse events were in-keeping with the known safety profile of Soliris, except for events of ‘vaccine complication’. In most cases the term ‘vaccine complication’ referred to a reaction to a COVID-19 vaccination.

A higher number of subjects reported events of ‘Pyrexia’ in the ABP 959 group compared with the eculizumab group (6 vs 1). Pyrexia is a known ADR for eculizumab. No imbalance in the number of subjects reporting events of pyrexia was seen in study 20150164 in healthy volunteers or in the data currently available for period 2. In period 1, only 1 subject in each treatment group reported at least one event of pyrexia in the context of potential infusion related reactions.

Period 2

Table 21: 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	2 (9.5)	2 (10.0)
Vaccination complication	2 (9.5)	2 (10.0)
Asthenia	1 (4.8)	2 (10.0)

COVID-19 = coronavirus disease 2019; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities

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

[a] N is the number of subjects in the safety analysis set who were treated with investigational product in Period 2.

Serious adverse events and deaths

There were no deaths in either period of this study.

Serious adverse events

In period 1, three (15.0%) subjects in the ABP 959 treatment group experienced a total of 8 serious adverse events, and 1 (4.5%) subject in the eculizumab treatment group experienced a serious adverse event. One event of vertigo CNS origin was reported as related to the investigational product by the investigator, however there were confounding factors for the event's aetiology. The serious adverse event in the eculizumab group was 'anaemia', which is a listed event for eculizumab, however it is also an important characteristic of background disease of PNH; it was considered unrelated to investigational product or study by the investigator.

In period 2, up to the primary analysis data cut-off, four (19.0%) subjects in the ABP 959 treatment group experienced a total of six serious adverse events. None of the serious adverse events were considered related to investigational product. No subjects in the eculizumab treatment group experienced serious adverse events.

Adverse events of special interest

Adverse events of special interest in this study included serious infections (meningococcus, aspergillus and other serious infections/sepsis) and infusion reactions.

Period 1

The percentage of subjects reporting any adverse events of interest was broadly similar between the two treatment groups.

Table 22: Overall summary of events of interest in period 1 (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 summarized. 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

No subject reported the preferred term of 'infusion-related reaction' and review of all adverse events retrieved by the search strategy identified only one subject in the ABP 959 treatment group with probable infusion-related reaction events. The adverse events of eye pruritus and flushing resulted in the subject only receiving a partial dose of investigational product. They received treatment with IV chlorpheniramine and oral paracetamol. The events resolved on the same day and did not recur with further investigational product administrations. One subject in the ABP 959 treatment group experienced a serious infection event of interest of grade 2 serious adverse event of gastroenteritis.

Period 2

Table 23: Overall summary of events of interest in period 2 (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	6 (28.6)	3 (15.0)	13.6 (-13.5, 39.3)
Infusion reactions[c]	4 (19.0)	3 (15.0)	4.0 (-21.3, 29.8)
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 summarized. 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 strategy

No subject reported the preferred term of 'infusion-related reaction' and review of all adverse events retrieved by the search strategy did not identify any probable infusion-related reaction events. Two subjects in the ABP 959 treatment group experienced serious infections of grade 2 serious COVID-19 and grade 3 non-serious streptococcal urinary tract infection

Laboratory findings
Overall, no clinically relevant changes from baseline in laboratory values or vital signs were observed.

Safety in special populations
Not applicable for biosimilars.

Safety related to drug-drug interactions and other interactions
Not applicable to biosimilars.

Discontinuation due to adverse events
Period 1
No subjects in the ABP 959 treatment group discontinued investigational product or study due to adverse events. One subject in the eculizumab treatment group discontinued both investigational product and the study due to grade 2 adverse events of asthenia and fatigue.

Period 2
No subjects in either treatment group discontinued investigational product or study due to adverse events.

Overall conclusions on clinical safety
Safety data is available from 217 healthy volunteers that received a single 300 mg dose of study drug: ABP 959 (71 subjects), US-eculizumab (72) or EU-eculizumab (74) in the pivotal PK/PD study.

Due to the rarity of PNH there are significant limitations to the strength of the safety data in patients, with only 42 subjects randomised. However, the safety profile of the reference product is largely predicted from on-target side effects and similarity of BEKEMV is informed by the clinical experience and quality attributes of the reference product Soliris. As the quality comparability exercise and the pivotal PK/PD study supports biosimilarity (including a comparable safety and immunogenicity profile), it is considered that a similar safety and immunogenicity profile for ABP 959 and Soliris can be concluded. This is in-keeping with the principles in the MHRA ‘Guidance on the licensing of biosimilar products’.

BEKEMV contains 50 mg sorbitol (E420) in each mL, this excipient is not present in Soliris. A warning is included in section 4.4 of the SmPC regarding the sorbitol content and use in patients with hereditary fructose intolerance (HFI). BEKEMV is contraindicated in babies and young children below 2 years of age since they may not yet be diagnosed with HFI. ‘Sorbitol exposure in patients less than 2 years of age’ has been included as an important potential risk in the RMP (see section IV.7 below).

IV.7 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional risk minimisation measures have been proposed:

Table 24 Summary Table of Pharmacovigilance Activities and risk Minimisation Activities by Safety Concern

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

Table 24 Summary Table of Pharmacovigilance Activities and risk Minimisation Activities by Safety Concern

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

Table 24 Summary Table of Pharmacovigilance Activities and risk Minimisation Activities by Safety Concern

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: • Specific adverse reaction follow-up questionnaire 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

Table 24 Summary Table of Pharmacovigilance Activities and risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Sorbitol exposure in patients less than 2 years of age	Routine risk minimization measures: • SmPC Section 4.3, SmPC Section 4.4, and PL Section 2, where a warning that BEKEMV is contraindicated and must not be given to babies and young children (below 2 years of age), who may not yet be diagnosed with HFI, is included. • 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
Missing Information		
None		

IV.8 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to:

1. Soliris 300 mg concentrate for solution for infusion, with regard to content (EMEA/H/C/000791; Alexion Europe SAS)
2. Kyprolis 10 mg, 30 mg and 60 mg powder for solution for infusion (EMEA/H/C/003790/0000; Amgen Europe BV), with regards to design/layout and format.

The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

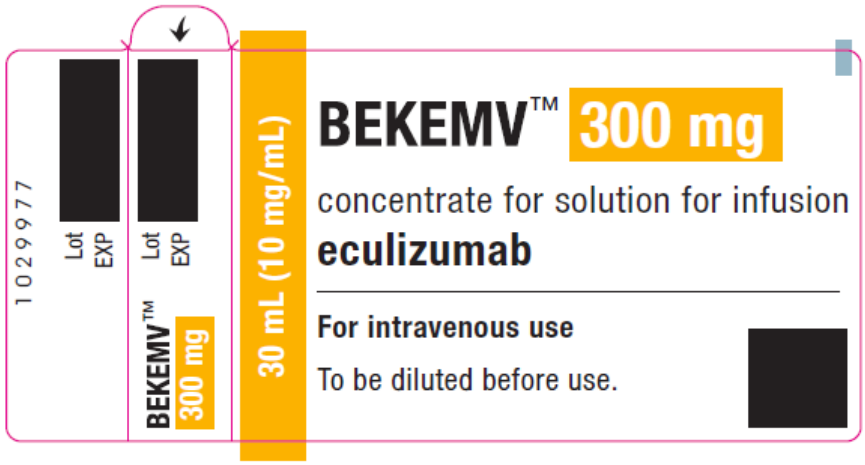
Based on the review of the submitted data, BEKEMV is considered biosimilar to Soliris. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

The SmPC, PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved GB versions of the SmPC and

PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**