Office of Therapeutic Biologics and Biosimilars
Clinical, Cross-Discipline Team Leader, and Division Memo

Date	See Electronic Stamp Date
From	Frances Andrada, MSN, MPH, CRNP (Clinical Reviewer, OTBB) Thomas Herndon, MD (CTL/CDTL, OTBB) Tanya Wroblewski, MD (Division Signatory, OCHEN/DNH)
Subject	Cross-Discipline Review for 351(k) BLA Labeling Prior Approval Supplement-Category B to add the generalized myasthenia gravis (gMG) indication
Application Type	Category B supplement
BLA/Supplement Number	BLA 761340/S-003
Received Date	08/2/2024
BsUFA Goal Date	12/2/2024
Division/Office	Division of Nonmalignant Hematology (DNH)/Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)/Office of New Drugs (OND)
Proprietary Name	Epysqli
Proper Name	Eculizumab-aagh
Product Code	SB12
Reference Product	U.S.-licensed Soliris (eculizumab)
Pharmacologic Class	Complement inhibitor
Applicant	Samsung Bioepis Co., Ltd
Approved Indication(s)	-The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. -The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.
New Indication(s) and/or Population(s)	Adding indication for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.
New Dosing Regimen(s)	Same dosing regimen as reference product
Recommendation on Regulatory Action	Approval

1. Introduction

Samsung Bioepis Co., Ltd (hereafter referred to as “the Applicant”) submitted a supplemental Biologic License Application (BLA) 761340 Supplement 003 under section 351(k) of the Public Health Service (PHS) Act to expand the indications for Epysqli (proper name: eculizumab-aagh, product code: SB12) to include the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive. The Applicant’s scientific justification for extrapolation to include the gMG indication was found acceptable at the time of review of the original

BLA. The gMG indication was not included in the initial approval because, at the time of that approval, US-Soliris (eculizumab) was eligible for orphan-drug exclusivity for "the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive." US-Soliris' orphan-drug exclusivity for this indication expired on October 23, 2024.

No new clinical information is included nor required for the Applicant's submission. Epysqli is an approved biosimilar to US-licensed Soliris (US-Soliris). The Pediatric Study Plan addressing the new indication was previously submitted and reviewed by the Agency. The Applicant has provided a scientific justification for extrapolation to the gMG indication and updated labeling to include the additional indication sought for licensure. Updated labeling included the gMG indication and related information. A Risk Evaluation and Mitigation Strategy (REMS) Assessment for the gMG indication was also included.

2. Background

Epysqli (proper name: eculizumab-aagh, product code: SB12) is a monoclonal antibody 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. Epysqli was approved as biosimilar to US-Soliris under BLA 761340 on July 19, 2024 under section 351(k) of the PHS Act. Epysqli is currently approved for:

- the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that Epysqli is highly similar to US-Soliris, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Epysqli and US-Soliris in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of Epysqli (b) (4) for approval.

Epysqli is approved for the following strength and presentation:

- Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (vial) for intravenous use

The key regulatory interactions to support the addition of the generalized myasthenia gravis indication are summarized below.

Table 1. Key regulatory interactions

Meeting Type (Date[a])	Topics of Discussion and Major Agreements
BPD Type 4 (June 10, 2022)	(b) (4)
BPD Type 3 (December 8, 2022)	Discussion of the proposed justification for extrapolation to support licensure for gMG (b) (4). Requested Applicant to fully address whether inhibition of C5 in the plasma reflects the inhibition of C5 at the target site(s) (b) (4). In the future BLA, a comprehensive scientific justification addressing these concerns should be submitted. If concerns addressed the standards for biosimilarity are met, additional studies would not be expected to support extrapolation for the gMG (b) (4).
BLA Approval (July 19, 2024)	• Original BLA Approval of Epysqli as biosimilar to US-Soliris for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. • As part of the original application, scientific justification was submitted and reviewed in support of licensure of SB12 for gMG in adult patients who are anti-AChR antibody positive. The Division of Neurology 1 concluded that the Applicant provided justification in the form of publicly available data for US-Soliris from approved labeling and the literature to support the claim that the mechanism of action, pharmacokinetics, immunogenicity, and toxicity of US-Soliris are similar across approved indications. The gMG indication was not included in the initial approval because the gMG indication was protected under orphan drug exclusivity which expired October 23, 2024.

[a]Date of entry into Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)

3. Summary of Conclusions of Other Review Disciplines

3.1. Product Quality

No new product quality information was submitted nor required for this BLA supplement. On August 2, 2024, the Applicant provided a claim for categorical exclusion from the preparation of an environmental assessment per 21 CFR 25.31(b) for the additional indication being sought in this supplement (S-003). The justifications provided support a categorical exclusion from the preparation of an environment assessment for Epysqli. Overall, there are no product quality issues that would preclude approval of the indications sought for licensure.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

Not applicable.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The submission was acceptable from a medication error perspective.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this supplemental BLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indication sought for licensure.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this supplemental BLA. There are no clinical pharmacology issues that would preclude approval of the indication sought for licensure.

6. Clinical Evaluation and Recommendations

6.1. Efficacy

Epysqli (proper name: eculizumab-aagh, product code: SB12) was previously evaluated in two clinical studies, a PK similarity study (Study SB12-1001) and a comparative clinical study (Study SB12-3003). Study SB12-3003 was a randomized, double-blind, active-controlled, 2-period, cross-over study designed to demonstrate equivalence in efficacy to the comparator (both US-Soliris and EU-Soliris) and to compare the safety and immunogenicity of SB12 to the comparator in 50 adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Adequate analytical and PK bridging were performed to justify the relevance of comparative data generated using EU-Soliris to the assessment of biosimilarity. The data support a demonstration that there are no clinically meaningful differences. The data were previously reviewed and summarized in the clinical and statistical reviews of the original BLA, dated July 18, 2024. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

6.2. Safety

Epysqli was previously evaluated in two clinical studies, a PK similarity study (Study SB12-1001) and a comparative clinical study (Study SB12-3003) in patients with PNH.

The data were previously reviewed and summarized in the clinical and statistical reviews of the original BLA, dated July 18, 2024. No new safety data were submitted nor required for this BLA supplement. There are no clinical safety issues that would preclude approval of the indication sought for licensure.

6.3. Extrapolation

Epysqli is an approved biosimilar for the treatment of PNH and aHUS. In this supplement, the Applicant referenced the original BLA application and the scientific justification that was provided for extrapolation of the data and information to support licensure of Epysqli for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.

Scientific considerations for the extrapolation of data and information to support licensure for the gMG indication are outlined below:

- Biosimilarity has previously been established between Epysqli and US-Soliris. The data supporting its approval included comparative analytical characterization data, and comparative PK, efficacy, safety, and immunogenicity data demonstrating that Epysqli is biosimilar to US-Soliris.
- In Supplement 003, the Applicant referenced the scientific justification provided in the original application. The Applicant has provided adequate scientific justification supporting the extrapolation of data and information from the original BLA submission that addresses the mechanism of action, PK, immunogenicity, and safety for (b) (4) indication for which the applicant is seeking licensure (b) (4).
- The Mechanism of Action, relevant to paroxysmal nocturnal hemoglobinuria (PNH; the studied population) is also relevant to gMG.
- PK similarity was demonstrated between Epysqli and US-Soliris. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between Epysqli and US-Soliris in the gMG indication. A similar PK profile would be expected between Epysqli and US-Soliris in patients being treated for gMG.
- Immunogenicity and safety profiles were shown to be similar in Epysqli and US-Soliris. Similar immunogenicity and safety profiles would be expected between Epysqli and US-Soliris in patients being treated for the gMG indication.

In conclusion, the totality of evidence and scientific justification discussed above are adequate to justify extrapolating data and information submitted to this BLA to support licensure of Epysqli for the indication to treat generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive.

7. Labeling

Labeling for Epysqli was updated to include the indication of generalized myasthenia gravis.

Labeling consultants, including Office of Therapeutic Biologics and Biosimilar (OTBB)-labeling, Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP) reviewed the proposed labeling. The final label will be included in the approval letter.

8. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. (b) (4)

The original application included the October 5, 2022, agreed initial pediatric study plan (iPSP) and a document titled, "Pediatric Administration Information," which referenced the iPSP and set forth the iPSP's submission history. In the agreed iPSP, the Applicant addressed the gMG indication by referencing the guidance for industry, "Questions and Answers on Biosimilar Development and the BPCI Act," and noted that the labeling for US-Soliris does not include adequate information for the treatment of gMG in pediatric patients 0-17 years of age.

On March 26, 2024, the PeRC agreed with the Applicant's approach for the gMG indication. On July 19, 2024, Epysqli was approved by FDA as biosimilar to US-Soliris.

On October 22, the PeRC agreed that the Applicant is exempt from additional requirements.

9. REMS and Postmarketing Requirements and Commitments

9.1. Recommendations for Risk Evaluation and Mitigation Strategies

The proposed REMS modification to add the indication: treatment of adult patients with generalized Myasthenia Gravis who are anti-acetylcholine receptor antibody positive for Epysqli (eculizumab-aagh) as submitted on August 02, 2024, and amended on October 09, 2024, is acceptable. The REMS materials were amended to be consistent with revised labeling.

The timetable for submission of assessments of the REMS remains the same as that approved on July 19, 2024.

The REMS Assessment Plan is not changing and will remain the same as that that described in the July 19, 2024, Approval letter.

9.2. Recommendations for Postmarket Requirements and Commitments

None.

10. Other Regulatory Issues

None.

11. Recommended Regulatory Action

Approval.

12. Recommended Comments to the Applicant

None.

13. Division Director or Designated Signatory Comments

I concur with the review team's assessment of the data and information submitted in this supplemental BLA and support the regulatory action.

The Applicant submitted this supplement 003 to expand the indications for Epysqli to include the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive. The gMG indication was not included in the initial Epysqli approval because, at the time of that approval, US-Soliris (eculizumab) was eligible for orphan-drug exclusivity for "the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive". US-Soliris's orphan-drug exclusivity for this indication expired on October 23, 2024.

Data and information from the Applicant's original application was referenced in this supplemental BLA. No new clinical information is included nor required for the Applicant's submission. The Pediatric Study Plan addressing the new indication was previously submitted and found acceptable by the Agency at the time of review of the original BLA. The Applicant has provided a scientific justification for extrapolation to gMG indication and updated labeling and Risk Evaluation and Mitigation Strategy (REMS) assessment to include the additional indication sought for licensure.

14. Appendices

14.1. References

Guidances for Industry
Guidance for industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015) https://www.fda.gov/media/82647/download.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENDY M STREIGHT
11/14/2024 04:28:38 PM

FRANCES C ANDRADA
11/14/2024 04:35:31 PM

THOMAS M HERNDON
11/14/2024 07:20:56 PM

RAINER PAINE
11/14/2024 09:09:27 PM

LAURA A JAWIDZIK
11/15/2024 07:25:49 AM

CARRIE E DIAMOND
11/15/2024 12:04:55 PM

TANYA M WROBLEWSKI
11/15/2024 12:41:37 PM