CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216834Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	September 14, 2023
Reviewer:	Silvia Perez-Vilar, PhD, PharmD Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD, MA Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	ZILBRYSQ™ (zilucoplan)
Application Type/Number:	NDA 216834
Applicant:	UCB Pharma
TTT #:	2023-4635

Expedited ARIA Sufficiency for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Zilucoplan (ZILBRYSQ™, UCB Pharma) is a 15-amino acid macrocyclic peptide that is a complement component 5 (C5) inhibitor designed to prevent the generation of anaphylatoxin C5a and the membrane attack complex (MAC).[1] The proposed indication is the treatment of myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.[2] Currently FDA-approved treatments for myasthenia gravis include pyridostigmine bromide, eculizumab, efgartigimod, and rozanolixizumab. Off-label treatments include prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, plasmapheresis, intravenous immunoglobulin, and thymectomy. Zilucoplan is not currently approved in the United States or elsewhere for any indication.[3] The proposed dosing regimen is subcutaneous once-daily at a nominal dose level of 0.3 mg/kg, which is supplied as prefilled syringes of various colors according to the dose they provide: 16.6 mg (43 kg to <56 kg), 23.0 mg (56 to <77 kg; orange), and 32.4 mg (77 to <150 kg; dark blue).[4] The mean plasma terminal half-life of zilucoplan is approximately 172 hours (7 to 8 days).[5]

The New Drug Application (NDA) submission for zilucoplan included safety data from 174 adults with ACh(+) generalized myasthenia gravis enrolled in the phase III, randomized (1:1), double-blind, placebo-controlled study and from 44 adults with ACh(+) generalized myasthenia gravis enrolled in the phase II evenly randomized (1:1:1) dose-ranging study. Both studies fed into an open-label extension.[6] The proposed label (as of September 14, 2023) includes a Boxed Warning for serious meningococcal infections. Due to this risk, ZILBRYSQ™ will be available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). The proposed label also includes Warnings and Precautions for other infections and for pancreatitis and pancreatic cysts and pseudocysts.[7]

1.2. Describe the Safety Concern

The Division of Neurology 1 (DN1) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of ZILBRYSQ™ during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease Control and Prevention 2008, Food and Drug Administration 2014). Myasthenia gravis is a

[1] ZILBRYSQ (zilucoplan). Draft integrated review dated July 26, 2023. Division of Neurology 1. U.S. Food and Drug Administration
[2] See footnote 1
[3] Ibid
[4] Ibid
[5] ZILBRYSQ (zilucoplan). Proposed U.S. labeling dated September 14, 2023
[6] See footnote 1
[7] See footnote 4

serious, life-threatening, chronic autoimmune disease in which antibodies bind to acetylcholine receptors, muscle-specific kinase, or lipoprotein-related peptide 4 in the postsynaptic membrane at the neuromuscular junction (Gilhus 2016, Koneczny and Herbst 2019). Different antibodies can result in different subgroups of myasthenia gravis with variable phenotypes and severity. In most patients, the antibodies bind to acetylcholine receptors (Gilhus 2020). Coexisting conditions are common; approximately 15% of patients have a second autoimmune disease, 10% have a thymoma, and although rare, myocarditis occurs with an increased frequency in patients with myasthenia gravis (Gilhus 2016). Myasthenia gravis is a rare disorder, with an estimated prevalence in the general population of 150–250 individuals per million, and with an annual incidence of 8–10 individuals per million. Myasthenia gravis with onset below 50 years, thymic hyperplasia, and acetylcholine receptor antibodies is more common in females than in males. As both prevalence and incidence increase with increasing age, the prevalence and incidence are somewhat lower among females of reproductive age. The muscle weakness, the circulating autoantibodies, the hyperplastic thymus, and any autoimmune comorbidity may influence both mother and child health during pregnancy and also during breastfeeding (Gilhus 2020). Despite this, most pregnancy complications occur with a similar frequency in women with and without myasthenia gravis. However, preterm rupture of amniotic membranes shows an increased frequency, and especially in those with myasthenia gravis deterioration during the pregnancy (Gilhus 2020). Around 10% of the newborn develop neonatal myasthenia during the first few days after birth, which is transient and usually mild. In rare cases, transplacental transfer of acetylcholine receptor antibodies leads to permanent muscle weakness in the child, and arthrogryposis with joint contractures (Gilhus 2020).

The safety of zilucoplan in women who are pregnant or breastfeeding, and in infants who are breastfeeding, has not been characterized in clinical trials.[8] As of the clinical cutoff date, one pregnancy case with maternal exposure to zilucoplan was reported. The subject was in the placebo group during the main portion of the study and in the zilucoplan 0.1mg/kg/day dose group in the extension portion of the study. She became pregnant after discontinuation of zilucoplan 0.1mg/kg, with the date of last menstrual period 1 day before the last zilucoplan administration and after being exposed to zilucoplan for more than a year. During pregnancy, she experienced gestational diabetes and went on to have an uncomplicated full-term, live birth of a healthy baby via an elective cesarean section. No congenital malformations, failure to thrive, or developmental delay were observed in a follow-up about 16 months after delivery.[9] In an enhanced pre- and postnatal development study with an embryofetal component in cynomolgus monkeys, subcutaneous administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) to pregnant dams from gestational day 20 through 100 produced no adverse effects on pregnancy outcome or embryofetal development in groups evaluated on postnatal day 100, but in the groups dosed from gestational day 20 through birth, there was an increase in prenatal loss in all treatment groups. Complement activity was decreased by similar amounts at all doses throughout the dosing period, which could account for the lack of a dose-response.[10]

The currently proposed labeling for ZILBRYSQ™, as of September 14, 2023,[11] states in Section 8.1 (Pregnancy):

[8] See footnote 1
[9] See footnote 1
[10] ZILBRYSQ (zilucoplan). Draft Pharmacology/Toxicology IND Review And Evaluation dated August 5, 2023. Division of Neurology 1. U.S. Food and Drug Administration
[11] See footnote 5

"Risk Summary
There are no available data on ZILBRYSQ use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Administration of zilucoplan to pregnant monkeys resulted in increases in embryofetal death at maternal exposures similar to those in humans at therapeutic doses (see Animal Data).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background rate of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data
Subcutaneous administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) to pregnant monkeys throughout gestation resulted in an increase in embryofetal death at all doses, in the absence of maternal toxicity. A no effect dose for adverse developmental effects in monkeys was not identified. The lowest dose tested was associated with maternal exposures (AUC) similar to that in humans at the maximum recommended human dose of 32.4 mg/day.

Data from an ex vivo human placental transfer model demonstrated transfer of zilucoplan into the fetal compartment at a rate of 0.5% at a steady state plasma concentration of 10 µg/mL zilucoplan, which corresponds to a therapeutic dose of 0.3 mg/kg. The clinical significance of these data in human pregnancies is unknown.

The language in Section 8.2 (Lactation) is as follows:

"Risk Summary
There are no data on the presence of zilucoplan in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZILBRYSQ and any potential adverse effects on the breastfed infant from ZILBRYSQ or from the underlying maternal condition."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☐ Electronic database study without chart review

☒ Other, please specify: Descriptive pregnancy safety study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population

☐ Exposures

☒ Outcomes

☒ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on

potential covariates, such as IgG anti-acetylcholine receptor antibodies, baseline motor strength, cardiac and respiratory status, and pulmonary function tests, and lifestyle factors, such as prenatal supplement use and iodine intake.

Analytical tools: ARIA analytical tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DN1, as of July 7, 2023, for the PMR related to pregnancy outcomes:

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to ZILBRYSQ™ (zilucoplan) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

3. REFERENCES

Centers for Disease Control and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved November 24, 2021, from https://www.fda.gov/media/90160/download.

Gilhus, N. E. (2016). "Myasthenia Gravis." N Engl J Med **375**(26): 2570-2581.

Gilhus, N. E. (2020). "Myasthenia Gravis Can Have Consequences for Pregnancy and the Developing Child." Front Neurol **11**: 554.

Koneczny, I. and R. Herbst (2019). "Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture." Cells **8**(7).

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/s/

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 22, 2023

To: Michael Matthews, Regulatory Project Manager
Division of Neurology 1 (DN1)

From: Andrew Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Tracy Peters, PharmD, Associate Director for Labeling, DN1

Emily Dvorsky, PharmD, Team Leader, OPDP

Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Zilbrysq (zilucoplan) injection, for subcutaneous use

NDA: 216834

Background:
In response to DN1's consult request dated August 16, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original application for Zilbrysq® (zilucoplan) injection, for subcutaneous use.

PI/MG/IFU:
OPDP's review of the proposed PI is based on the draft labeling sent by electronic mail to OPDP on August 8, 2023, and our comments are included below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed MG and IFU, and comments were sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling sent by electronic mail to OPDP on August 8, 2023, and we have no additional comments at this time.

Thank you for your consult. If you have any questions, please contact Andrew Nguyen at 240-402-0512 or andrew.nguyen@fda.hhs.gov.

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANDREW D NGUYEN
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CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTI-INFECTIVES (DAI) CLINICAL CONSULT REVIEW MEMO

Requesting Offices/Divisions: Office of Neuroscience/Division of Neurology I (DN I); Office of Neuroscience/Division of Neurology II (DN II); Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)/Division of Non-malignant Hematology (DNH)
NDA/BLA: NDA 216834, NON-RESPONSIVE
Sponsor/Applicant: UCB, Inc; NON-RESPONSIVE
Product names: Zilbrysq (zilucoplan), NON-RESPONSIVE
NON-RESPONSIVE
DAI Reviewer: Angela Kopack, MD
DAI Team Leader: Ramya Gopinath, MBBS
DAI Deputy Director: Dmitri Iarikov, MD, PhD

Summary of the Request

The Division of Neurology I (DN I), Division of Neurology II (DN II), and the Division of Non-malignant Hematology (DNH) are considering class labeling changes for complement inhibitors to clarify recommendations for meningococcal vaccinations and antibiotic prophylaxis in individuals who have not received recommended meningococcal vaccinations. Additionally, NON-RESPONSIVE

Table 1 outlines the drugs included in this consult.

Table 1. Complement Inhibitors Included in this Consult

Mechanism of Action	NDA/BLA	Trade/Generic Names	Sponsor/Applicant	Indication(s)
C5 Inhibitor	NON-RESPONSIVE			
	NDA 216834	Zilbrysq (zilucoplan)	UCB, Inc.	gMG (proposed)
	NON-RESPONSIVE			
NON-RESPONSIVE				

NON-RESPONSIVE

All three divisions requested DAI input on the following:

1) **Prophylactic antibacterial use with C5 complement inhibitor administration**: "Please make a recommendation regarding prophylactic antibiotic use in patients taking complement C5 inhibitors 1) who have not been vaccinated with meningococcal vaccination (at least 2 weeks prior to receiving the first dose of the C5 inhibitor) or 2) who have not completed the meningococcal vaccination series, or 3) who refuse vaccination or are unable to receive vaccination. Please recommend the duration of antibiotic prophylaxis in each case, specifically indicating whether the duration is in relation to the first dose of a recommended series for patients receiving complement inhibitors based on ACIP guidelines or completion of the entire primary series.

   For patients who refuse vaccination or who are unable to receive vaccination, is antibiotic prophylaxis alone an option, or should complement C5 inhibitors be contraindicated in those patients?"

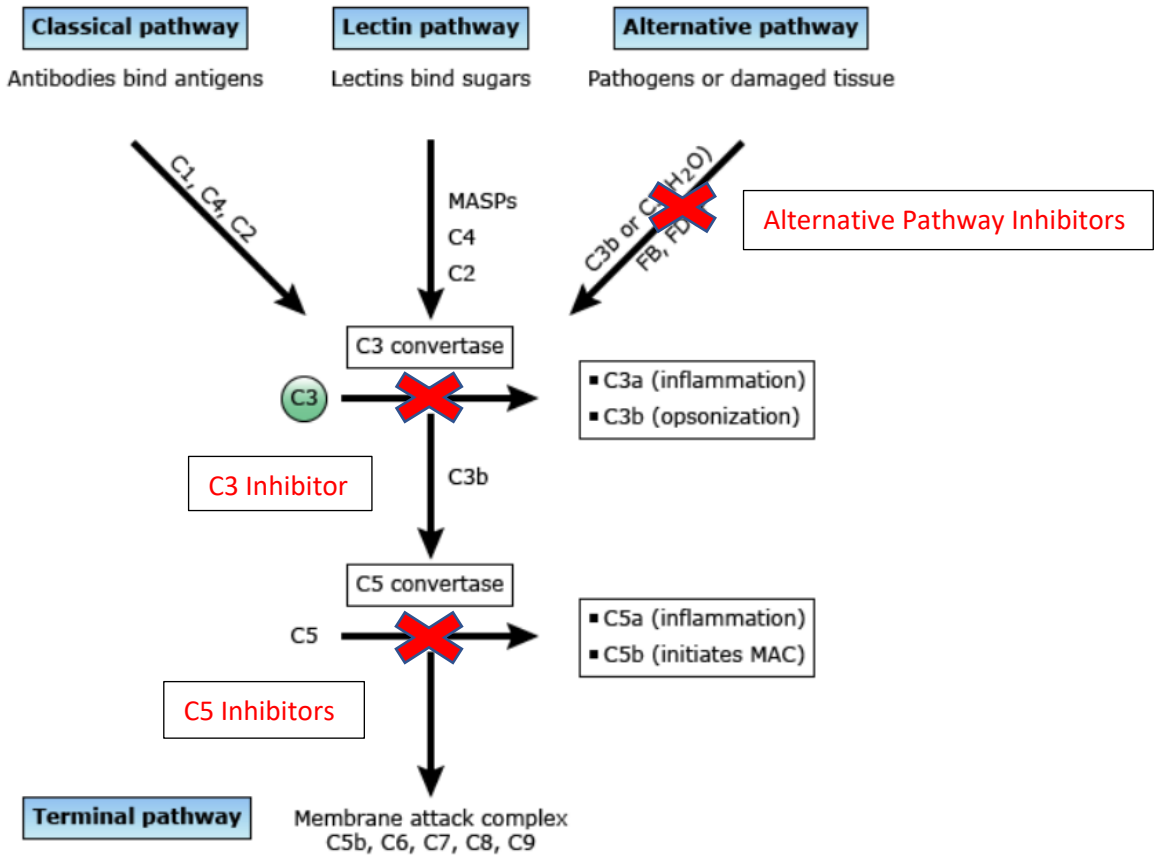
2) **Proposed labeling changes**: including recommendations for the following highlighted language: "If urgent (b) (4) therapy is indicated in a patient who (b) (4) (b) (4) for both MenACWY and MenB, administer meningococcal vaccine(s) according to ACIP recommendations as soon as possible and provide patients with antibacterial drug prophylaxis (b) (4)

3) NON-RESPONSIVE

Introduction and Background

Complement inhibitors are used in the treatment of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), generalized myasthenia gravis (gMG) with positive anti-acetylcholine receptor (AChR) antibody, and neuromyelitis optica spectrum disorder (NMOSD) with positive anti-aquaporin-4 (AQP4) antibody.[1,2,3] C5 inhibitors like Ultomiris and Soliris, are terminal complement inhibitors. C3 inhibitors and alternative pathway inhibitors are proximal compliment inhibitors. Figure 1 shows a simplified version of the complement cascade and where complement inhibitors interact. There are three initiation pathways that converge on the final common pathway. The formation of the membrane attack complex (MAC) plays an important role in defense against *Neisseria* infections.

Figure 1. Points of Interaction of Complement Inhibitors with the Complement Cascade



Source: Adapted from Figure 1 in "Overview and clinical assessment of the complement system", by Liszekwki M, Atkinson J, UpToDate, accessed August 10, 2023.

Patients treated with complement inhibitors are at increased risk of infection with *Neisseria* spp., particularly *Neisseria meningitidis*. Patients treated with Soliris have an approximately

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761108s021lbl.pdf
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125166s434lbl.pdf
[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215014s002lbl.pdf

2,000-fold increased risk of meningococcal disease compared to the general U.S. population.[2] *Neisseria meningitidis* causes invasive meningococcal disease, including meningitis and meningococcemia. The onset of invasive meningococcal disease is rapid with high morbidity and mortality. The prescribing information for FDA-approved complement inhibitors includes a boxed warning for increased risk of meningococcal disease and instructions to comply with current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations. Additionally, labeling includes recommendations to give antibacterial prophylaxis for two weeks after vaccination to individuals who were not vaccinated at least two weeks prior to starting complement inhibitor therapy. The labeling, however, does not specify whether the duration of antibacterial prophylaxis is in relation to the first dose of vaccination series or completion of the entire primary series.

NON-RESPONSIVE

Due to increased risk of meningococcal disease in persons receiving complement inhibitors, ACIP recommends vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY, against serogroups A, C, W, and Y) and serogroup B meningococcal (MenB) vaccine as well as booster doses of these vaccines at prescribed intervals.[4] Table 1 outlines the current recommended vaccination schedule for patients with complement deficiencies, including those treated with complement inhibitors.

[4] Mbaeyi SA, Bozio CH, Duffy J, Rubin LG, Hariri S, Stephens DS, MacNeil JR. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep. 2020 Sep 25;69(9):1-41. doi: 10.15585/mmwr.rr6909a1. PMID: 33417592; PMCID: PMC7527029.

Table 1: Recommended vaccination schedule and intervals for persons with persistent complement deficiencies[*] (including patients using a complement inhibitor[†]—ACIP, United States, 2020

Age group	Serogroups A, C, W, and Y meningococcal conjugate vaccines MenACWY-D (Menactra, Sanofi Pasteur)[§] *or* MenACWY-CRM (Menveo, GlaxoSmithKline)[¶] *or* MenACWY-TT (MenQuadfi, Sanofi Pasteur)**	Serogroup B meningococcal vaccines MenB-FHbp (Trumenba, Pfizer) *or* MenB-4C (Bexsero, GlaxoSmithKline)
2–23 mos	**Primary vaccination:** MenACWY-D (aged ≥9 mos): 2 doses ≥12 wks apart *or* MenACWY-CRM if first dose at age • 2 mos: 4 doses at 2, 4, 6, and 12 mos • 3–6 mos: See catch-up schedule[§§] • 7–23 mos: 2 doses (second dose ≥12 wks after the first dose and after the 1st birthday)	No recommendations for use of MenB vaccines in this population[††]
2–9 yrs	**Primary vaccination[¶¶]:** MenACWY-D*** *or* MenACWY-CRM *or* MenACWY-TT: 2 doses ≥8 wks apart **Boosters (if person remains at increased risk)[†††]:** • Aged <7 yrs: Single dose at 3 yrs after primary vaccination and every 5 yrs thereafter • Aged ≥7 yrs: Single dose at 5 yrs after primary vaccination and every 5 yrs thereafter	No recommendations for use of MenB vaccines in this population[††]
≥10 yrs	**Primary vaccination[††]:** MenACWY-D *or* MenACWY-CRM *or* MenACWY-TT: 2 doses ≥8 wks apart **Boosters (if person remains at increased risk)[†††]:** Single dose at 5 yrs after primary vaccination and every 5 yrs thereafter	**Primary vaccination[††]:** MenB-FHbp: 3 doses at 0, 1–2, and 6 mos *or* MenB-4C: 2 doses ≥1 mo apart **Boosters (if person remains at increased risk)[§§§]:** Single dose at 1 yr after completion of primary vaccination and every 2–3 yrs thereafter **Note:** MenB-FHbp and MenB-4C are not interchangeable

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; MenACWY-CRM = meningococcal groups A, C, W, and Y oligosaccharide diphtheria CRM_{197} conjugate vaccine; MenACWY-D = meningococcal groups A, C, W, and Y polysaccharide diphtheria toxoid conjugate vaccine; MenACWY-TT = meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid conjugate vaccine; MenB-4C = four-component meningococcal group B vaccine; MenB-FHbp = meningococcal group B factor H binding protein vaccine.

* Persistent complement deficiencies include C3, C5–C9, properdin, factor H, or factor D.

† Includes eculizumab (Soliris) and ravulizumab (Ultomiris). Meningococcal vaccines should be administered at least 2 weeks before the first dose of complement inhibitor, unless the risk for delaying complement therapy outweighs the risk for developing meningococcal disease.

§ Licensed in the United States only for persons aged 9 months–55 years. Vaccination of persons aged ≥56 years is considered off-label.

¶ Licensed in the United States only for persons aged 2 months–55 years. Vaccination of persons aged ≥56 years is considered off-label.

** Licensed in the United States only for persons aged ≥2 years.

†† Licensed in the United States only for persons aged 10–25 years. Vaccination of persons aged ≥26 years is considered off-label.

§§ If MenACWY-CRM is initiated at ages 3–6 months, catch-up vaccination includes doses at intervals of 8 weeks until the infant is aged ≥7 months, at which time an additional dose is administered at age ≥7 months, followed by a dose at least 12 weeks later and after the 1st birthday.

¶¶ Primary vaccination licensed as a single dose in persons aged 2–55 years for MenACWY-D and MenACWY-CRM or ≥2 years for MenACWY-TT. Two-dose primary series is considered off-label.

*** MenACWY-D should be given either before or at the same time as DTaP to avoid interference with the immune response to meningococcal vaccine in children.

††† Licensed in the United States only for a single booster dose for persons aged 15–55 years for MenACWY-D and MenACWY-CRM or aged ≥15 years for MenACWY-TT. Booster doses administered outside of these ages or administration of >1 booster dose are considered off-label.

§§§ Licensed in the United States only for a primary series. Administration of booster doses is considered off-label.

Source: Table 4 in Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020

Current ACIP recommendations note that persons using complement inhibitors should be vaccinated at least two weeks before complement inhibitor initiation unless the risks for delaying treatment outweigh the risks for developing meningococcal disease. When complement inhibitor therapy is initiated prior to vaccination, ACIP recommends antimicrobial prophylaxis (e.g., penicillin) administered alongside meningococcal vaccination and continued for two weeks after vaccination. Vaccinated patients receiving complement inhibitors remain at risk for meningococcal disease. ACIP notes that per the Centers for Disease Control and Prevention (CDC) guidance, healthcare providers may consider antimicrobial prophylaxis for the duration of complement inhibitor therapy.[4,5]

[5] McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine. MMWR Morb Mortal Wkly Rep. 2017 Jul 14;66(27):734-737. doi: 10.15585/mmwr.mm6627e1. PMID: 28704351; PMCID: PMC5687588.

*Reviewer's Comment: ACIP recommendations are ambiguous regarding whether vaccination at least two weeks prior to complement inhibitor therapy initiation refers to the first vaccine dose or completion of the vaccine series. DAI proposes that the vaccination language in various sections of the labeling be updated to remove ambiguity and clarify that meningococcal vaccines should be completed (if a series) or updated (boosters) prior to starting therapy with a complement inhibitor unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection. Please see the section below entitled "**DAI Recommendations for Meningococcal Vaccination and Antibacterial Drug Prophylaxis in Patients Receiving C5 Complement Inhibitors**."*

In addition to meningococcal vaccinations, ACIP recommends that adults ages 19 years and older with complement deficiencies receive pneumococcal vaccination (1 dose PCV followed by PPSV23 or 1 dose PCV20) and *Haemophilus influenzae* type b (Hib) vaccination (1 dose).[6] Meningococcal, pneumococcal, and Hib vaccination are also recommended in children and adolescents with complement deficiencies.[7]

Meningococcal Infection in Complement Inhibitor Recipients

As outlined above, ACIP recommends vaccination with MenACWY and MenB vaccines as well as booster doses in patients receiving complement inhibitors. However, despite robust antibody development following vaccination, patients on complement inhibitors remain at risk for meningococcal infection due to defects in opsonization and formation of the MAC (see Figure 1). There were 16 identified cases of meningococcal disease in eculizumab recipients in the United States from 2008-2016; eleven of these were caused by nongroupable *Neisseria meningitidis*, and most patients (14) had received at least one dose of meningococcal vaccine before onset of meningococcal disease. All patients had meningococcemia and six patients also had meningitis. There was one fatality.[5]

A review of Alexion's pharmacovigilance database for eculizumab from March 16, 2007, to October 1, 2016, identified 76 cases of meningococcal infection, including eight fatal cases. Almost all cases (95%) occurred in patients with a history of prior meningococcal vaccination (vaccination status was not reported in 5%). All eight patients who died had received meningococcal vaccination. In cases where the serogroup was identified, infection with serogroup B was most common (42.2%).[8]

[6] https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
[7] https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html
[8] Socié G, Caby-Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, Mujeebuddin A, Hillmen P, Vande Walle J, Haller H. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol. 2019 Apr;185(2):297-310. doi: 10.1111/bjh.15790. Epub 2019 Feb 15. PMID: 30768680; PMCID: PMC6594003.

A search of the FDA Adverse Event Reporting System (FAERS) and the literature from March 2007 to May 2017 identified 47 cases of meningococcal disease in eculizumab recipients. All 47 patients had received at least one dose of a meningococcal vaccine. There were four fatalities.[9]

In vaccinated patients receiving complement inhibitors, meningococcal disease occurs with strains targeted by vaccines as well as by nongroupable strains. In spite of antibodies induced by vaccination, complement inhibitors interfere with complement-dependent bactericidal activity and complement-mediated opsonophagocytic activity.[10]

Antibacterial Drug Prophylaxis for Meningococcal Infection in Complement Inhibitor Recipients

U.S. labeling for complement inhibitors recommends two weeks of antibacterial drug prophylaxis in patients who receive meningococcal vaccinations less than 2 weeks before initiating complement inhibitor therapy. As noted above, vaccinated complement inhibitor recipients remain at risk for meningococcal disease; thus, some clinicians as well as public health agencies in other countries recommend antibacterial drug prophylaxis for the duration of complement inhibitor therapy.[10] CDC and ACIP also note that healthcare providers may consider prophylaxis for the duration of treatment with complement inhibitors.[4,5]

There is a lack of data to support the safety and efficacy of antibacterial drug prophylaxis in complement inhibitor recipients. The optimal drug regimens for, and durations of prophylaxis have not been established. In the previously referenced study of 47 patients on eculizumab with meningococcal disease from a search of FAERS and the literature, 15 of the 47 patients were taking antimicrobial prophylaxis at the time of onset of meningococcal disease. The median time to onset of the first episode of meningococcal disease was 835 days in patients on prophylaxis, while the median time to onset of the first episode of meningococcal disease was 333 days in patients not on prophylaxis. For patients with available penicillin susceptibility results, penicillin non-susceptibility was reported more frequently in patients on prophylaxis (83%, 5 of 6 isolates) than in patients not on prophylaxis (22%, 2 of 9 isolates). The authors note that given limited data, it is not possible to determine the efficacy of antibacterial drug prophylaxis in prevention of meningococcal disease in eculizumab recipients. The development of reduced susceptibility to penicillin is a potential concern with use of antimicrobial prophylaxis.[9]

CDC has established recommendations for postexposure chemoprophylaxis for high-risk contacts of persons with invasive meningococcal disease. Recommended antimicrobials include

[9] Crew PE, McNamara L, Waldron PE, McCulley L, Christopher Jones S, Bersoff-Matcha SJ. Antibiotic prophylaxis in vaccinated eculizumab recipients who developed meningococcal disease. J Infect. 2020 Mar;80(3):350-371. doi: 10.1016/j.jinf.2019.11.015. Epub 2019 Nov 26. PMID: 31783062; PMCID: PMC7197327.

[10] Girmenia C, Barcellini W, Bianchi P, Di Bona E, Iori AP, Notaro R, Sica S, Zanella A, De Vivo A, Barosi G, Risitano A; scientific committee of the Associazione Italiana Emoglobinuria Parossistica Notturna (AIEPN). Management infection in PNH patients treated with eculizumab or other complement inhibitors: Unmet clinical needs. Blood Rev. 2023 Mar;58:101013. doi: 10.1016/j.blre.2022.101013. Epub 2022 Sep 6. PMID: 36117056.

rifampin, ceftriaxone, and ciprofloxacin.[11] Rifampin is FDA-approved for the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx.[12] However, there are no established U.S. guidelines or FDA-approved therapies for preexposure chemoprophylaxis for meningococcal infection.

NON-RESPONSIVE

[11] McNamara L, Blain A. "Chapter 8: Meningococcal Disease, Manual for the Surveillance of Vaccine-Preventable Diseases." CDC, 25 July 2023, https://www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html.
[12] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050420s073,050627s012lbl.pdf

NON-RESPONSIVE

drug regimens for antibacterial drug prophylaxis for pneumococcal or Hib infections in patients on complement inhibitors.

DAI Recommendations for Meningococcal Vaccination and Antibacterial Drug Prophylaxis in Patients Receiving C5 Complement Inhibitors

DAI concludes that despite vaccination and development of antibodies, patients receiving complement inhibitors remain at risk for infection with *Neisseria meningitidis*, including nongroupable strains. While current labeling specifies a two-week course of antibacterial prophylaxis for patients who initiate complement inhibitor therapy prior to receiving meningococcal vaccinations, there are no firm data to support this recommendation. Additionally, the optimal durations and drug regimens for antibacterial drug prophylaxis have not been studied in patients receiving complement inhibitors. DAI's current review is consistent with a prior DAI consult NON-RESPONSIVE . Given the lack of data, DAI cannot recommend a duration for antibacterial prophylaxis, and recommends deletion of the two-week duration currently in labeling because this recommendation may imply that two weeks of prophylaxis may be sufficient to protect against meningococcal infection.

Further, DAI recommends that the vaccination language in various sections of the labeling be updated to remove ambiguity and clarify that meningococcal vaccines should be completed (if a series) or updated (boosters) prior to starting therapy with a complement inhibitor.

Using (b) (4) labeling as representative of the class, labeling changes were proposed as follows to the Boxed Warning, Section 2.2 (Recommended Vaccination and Prophylaxis), Section 4 (Contraindications), Section 5.1 (Warnings and Precautions: Serious Meningococcal Infections), and Section 5.3 (Other Infections).

<u>Boxed Warning</u>

The Boxed Warning should be updated to clarify that meningococcal vaccines should be completed or updated prior to starting therapy with a complement inhibitor. The Boxed Warning currently states (b) (4) Center for Biologics Evaluation and Research (CBER) and DAI recommend deletion of language (b) (4) Proposed changes are presented in red font and proposed deletions are indicated by strikethrough:

(b) (4)

- (b) (4) at least 2 weeks prior to administering the first dose of (b) (4) unless the risks of delaying (b) (4) therapy outweigh the risks of developing a meningococcal infection. Comply

with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. [redacted]

- [redacted] - Persons receiving [redacted] are at increased risk for invasive disease caused by *N. meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Section 2.2 – [redacted] Vaccination and Prophylaxis

DAI proposes the following changes to this section with proposed changes presented in red font and proposed deletions indicated by strikethroughs:

Vaccinate patients for meningococcal [redacted] according to current ACIP guidelines [redacted] see Warnings and Precautions (5.1, [redacted])].

If urgent [redacted] therapy is indicated in a patient who is not up to date with vaccines for both MenACWY and MenB according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and p~~P~~rovide the patient with [redacted] antibacterial drug prophylaxis [redacted]

Healthcare [redacted] who prescribe [redacted] must enroll in the [redacted] REMS [see Warnings and Precautions (5.1)].

Section 4 – Contraindications

DAI recommends deletion of the following contraindication (indicated by strikethrough) as the situation outlined in the contraindication is addressed elsewhere in the labeling:

- Patients with unresolved Neisseria meningitidis infection [see Warnings and Precautions (5.1)].

[redacted]

Section 5.1 – Warnings and Precautions: Serious Meningococcal Infections

Current labeling states a recommendation for two weeks of antibacterial prophylaxis in recipients who require initiation of treatment with complement inhibitors less than two weeks after meningococcal vaccination and is unclear whether this applies to patients who have received a single dose of recommended vaccines or the series. DAI recommends:

- Highlighting that vaccinated patients on complement inhibitors remain at risk for meningococcal infections and providing additional information in this section to help providers understand why vaccination does not eliminate the risk of meningococcal infection.
- Clarifying the required immunizations and communicating the uncertainty regarding the efficacy and duration of antibacterial prophylaxis.
- (b) (4)

The language in this section should be harmonized with the language in the Boxed Warning. Proposed changes are presented in red font and proposed deletions are indicated by strikethroughs:

Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors, (b) (4) The use of (b) (4) increases a patient's susceptibility to serious and life-threatening meningococcal infections (~~septicemia~~ (b) (4) and/or meningitis)~~.~~ caused by any serogroup, including nongroupable strains. (b) (4)

Complete or update meningococcal vaccination (for serogroups A, C, W and Y [MenACWY] and serogroup B [MenB] according to ACIP recommendations at least 2 weeks prior to the first dose of (b) (4) Revaccinate patients in accordance with ACIP recommendations considering the duration of (b) (4) therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information.

(b) (4) -If urgent (b) (4) therapy is indicated in a patient who is not up to date with (b) (4) both MenACWY and MenB according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis. Various durations and regimens of antibacterial drug prophylaxis, (b) (4) have been considered (b) (4) but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients on complement

inhibitors, including [redacted] The benefits and risks of treatment with [redacted], and the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for meningococcal infection.

[redacted]

Because of inhibition of complement activity by [redacted] and risk of infection caused by nongroupable strains of *N. meningitidis*, ~~V~~vaccination [redacted] does not eliminate~~,~~ the risk of meningococcal infections~~.~~, despite the development of antibodies following vaccination. [redacted]

Closely monitor patients for early signs and symptoms of meningococcal infection [redacted] and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and [redacted] to seek immediate medical care. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. [redacted] in patients who are undergoing treatment for [redacted] meningococcal infection.

[redacted] is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions (5.2)].

Section 5.3 – Other Infections

DAI suggests the following deletion indicated by strikethrough as this statement does not add any additional information, and patients with active systemic infections would be closely monitored regardless of [redacted] therapy. Proposed additions are indicated in red font.

[redacted] blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. [redacted] Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP guidelines. [redacted]

(b) (4) Persons receiving (b) (4) are at increased risk for infections due to these (b) (4)

NON-RESPONSIVE

NON-RESPONSIVE

DAI Response to Consult Questions

1. Please make a recommendation regarding prophylactic antibiotic use in patients taking complement C5 inhibitors. Please recommend the duration of antibiotic prophylaxis in each case, specifically indicating whether the duration is in relation to the first dose of a recommended series for patients receiving complement inhibitors based on ACIP guidelines or completion of the entire primary series.

   1) who have not been vaccinated with meningococcal vaccination (at least 2 weeks prior to receiving the first dose of the C5 inhibitor)

   DAI Response*: While current labeling outlines a two-week course of antibacterial prophylaxis for patients who initiate complement inhibitor therapy prior to receiving meningococcal vaccinations, data to support this recommendation are lacking. The optimal duration and drug regimen for antibacterial drug prophylaxis have not been studied in patients receiving complement inhibitors. Given the lack of data, DAI cannot recommend a duration or drug regimen for antibacterial prophylaxis and recommends deletion of the two-week duration currently in labeling because this recommendation may imply that two weeks of prophylaxis may be sufficient to protect against meningococcal infection.*

   In these patients, DAI recommends administration of antibacterial drug prophylaxis with

administration of meningococcal vaccination as soon as possible. Using their clinical judgement, providers will need to determine the duration of prophylaxis after their patients are up to date (completed series or received boosters) with meningococcal vaccinations per ACIP recommendations. Various durations and regimens of antibacterial drug prophylaxis, including for the duration of treatment with complement inhibitors, have been considered in the literature, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients on complement inhibitors. The benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients must be considered against the known risks for meningococcal infection.

2) who have not completed the meningococcal vaccination series

***DAI Response**: See response to case 1. If meningococcal vaccination is not completed (if a series) or updated (boosters) prior to starting therapy with a complement inhibitor, patients should receive antibacterial drug prophylaxis. Various durations and regimens of antibacterial drug prophylaxis, including for the duration of treatment with complement inhibitors, have been considered in the literature, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients on complement inhibitors. The benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients must be considered against the known risks for meningococcal infection.*

3) who refuse vaccination or are unable to receive vaccination. For patients who refuse vaccination or who are unable to receive vaccination, is antibiotic prophylaxis alone an option, or should complement C5 inhibitors be contraindicated in those patients?

***DAI Response**: We do not have data on the level (if any) of risk reduction provided by meningococcal vaccinations in patients receiving complement inhibitors. Additionally, we do not have data on the optimal drug regimen and duration OR the efficacy of antibacterial drug prophylaxis in the prevention of meningococcal disease in vaccinated or unvaccinated patients receiving complement inhibitors. Thus, for patients who refuse vaccination or are unable to receive vaccination, providers would need to discuss benefits of complement inhibitor therapy and antibacterial therapy vs. risks of infection with N. meningitidis and other encapsulated bacteria and risks of long-term antibacterial treatment.*

2. Proposed labeling changes, including recommendations for the following highlighted language: “If urgent (b) (4) therapy is indicated in a patient who (b) (4) for both MenACWY and MenB, administer meningococcal vaccine(s) according to ACIP recommendations as soon as possible and provide patients with antibacterial drug prophylaxis (b) (4)

***DAI Response**: Refer to the section entitled "**DAI Recommendations for Meningococcal Vaccination and Antibacterial Drug Prophylaxis in Patients Receiving C5 Complement Inhibitors**."*

3. NON-RESPONSIVE

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Date: 2023.08.18 14:01:30 -04'00'

Angela Kopack, MD, Clinical Reviewer, DAI

Ramya Gopinath -S
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Ramya Gopinath, MBBS, Clinical Team Leader, DAI

Dmitri E. Iarikov -S
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Dmitri Iarikov, MD, PhD, Deputy Division Director, DAI

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ANGELA M KOPACK
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 17, 2023
To:	Michael Matthews Regulatory Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Andrew Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	ZILBRYSQ (zilucoplan)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 216834
Applicant:	UCB, Inc.

1 INTRODUCTION

On August 31, 2022, UCB, Inc. submitted for the Agency's review an original New Drug Application **(**NDA) 216834 for ZILBRYSQ (zilucoplan) injection, for subcutaneous use. This NDA proposes an indication for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on September 16, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ZILBRYSQ (zilucoplan) injection, for subcutaneous use.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DN1 under separate cover.

2 MATERIAL REVIEWED

- Draft ZILBRYSQ (zilucoplan) IFU received on February 28, 2023, and received by DMPP and OPDP on August 8, 2023.
- Draft ZILBRYSQ (zilucoplan) MG received on September 21, 2022, and received by DMPP and OPDP on August 8, 2023.
- Draft ZILBRYSQ (zilucoplan) Prescribing Information (PI) received on September 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 8, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 15, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216834
Product Name, Dosage Form, and Strength:	Zilbrysq (zilucoplan) injection, 16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.81 mL
Applicant Name:	UCB, Inc.
TTT ID #:	2022-1160-2
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 11, 2023 for Zilbrysq. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Zilbrysq (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous memorandum review of revised label and labeling.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Shah, M. Memorandum Review of Revised Labels and Labeling for Zilbrysq (NDA 216834). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 02. TTT ID No.: 2022-1160-1.

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Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and Related Product Applications

Intercenter Request for Consultative Review

Requested by:	CDER/OND/ORO/DRON
Submitted:	July 14, 2023
Sponsor:	Multiple
Subject:	Labeling language for complement C5 inhibitors
To:	Michael Matthews, Consumer Safety Officer
From:	Brittany Goldberg, MD, Team Lead**,** CBER/OVRR/DVRPA/CRB3
Through:	Anuja Rastogi, MD, MHS, Branch Chief, CBER/OVRR/DVRPA/CRB3
	Margaret Bash, MD, Medical Officer, CBER/OVRR/DBPAP/LBP
Date:	August 9, 2023

On July 14, 2023, CDER/OND/ORO/DRON requested an InterCenter Consult from CBER/OVRR/DVPRA to provide input on meningococcal vaccine recommendations for complement inhibitors labeling. Specifically, CDER requested that CBER provide "*meningococcal vaccination-related labeling language across complement C5 inhibitors. Serious meningococcal infections are a known risk of complement C5 inhibitors, all of which have a REMS for this risk. CDER is seeking to align meningitis vaccination-related labeling across the products, which currently refer to ACIP guidelines and have recommendations for antibiotic prophylaxis."*

Drs. Margaret Bash (CBER/OVRR/DBPAP/LBP) and Douglas Pratt (CBER/OVRR/DVRPA) provided input on the following questions.

CDER provided the following consult questions for CBER input:

1. Please review the attached proposed vaccination-related language for the Warnings and Precautions Section of labeling for the referenced products, and make recommendations/revisions as needed, particularly regarding vaccination recommendations and reference to ACIP guidelines.

   Clinical Reviewer Response: CBER/OVRR/DVPRA/CRB3 has reviewed the labeling and made recommendations, as discussed in the internal meetings on July 31, 2023 and August 1, 2023, and as described below in appendix A.

2. The following consult question has been presented to the Division of Antiinfectives as well, but we request that CBER also provide input as warranted. Please make a recommendation regarding prophylactic antibiotic use in patients taking complement C5 inhibitors 1) who have not been vaccinated with meningococcal vaccination (at least 2 weeks prior to receiving the first dose of the C5 inhibitor, or 2) who have not completed the meningococcal vaccination series, or 3) who refuse vaccination or are unable to receive vaccination. Please recommend the duration of antibiotic prophylaxis in each case, specifically indicating whether the duration is in relation to the first dose of a recommended series for patients receiving complement inhibitors based on ACIP guidelines or completion of the entire primary series. For patients who refuse vaccination

or who are unable to receive vaccination, is antibiotic prophylaxis alone an option, or should complement C5 inhibitors be contraindicated in those patients?

Clinical Reviewer Response: In internal meetings held July 21, 2023, July 31, 2023 and August 1, 2023, clinical reviewers from CDER and CBER discussed the role of meningococcal vaccination and antimicrobial prophylaxis as risk mitigation strategies for individuals receiving complement inhibitor therapy. As discussed at the internal meetings, the role of antimicrobial prophylaxis is poorly defined in this patient population without clear recommendations regarding the choice of antimicrobials, timing of prophylaxis relative to vaccination or duration of therapy. The benefit-risk profile of antimicrobial prophylaxis in individuals at high risk for meningococcal infection is also poorly defined, as antimicrobial prophylaxis may not prevent all cases of meningococcal disease and may be associated with an increased risk of antimicrobial resistance. In the absence of appropriately designed clinical studies, the role and best practices for antimicrobial prophylaxis in individuals receiving complement therapy with or without meningococcal vaccination is unknown. CBER/OVRR/DVPRA/CRB-3 defers labeling recommendations with regards to antimicrobial prophylaxis to CDER/OND/ORO/DRON and CDER/OND/OID/DAI.

Appendix A

Labeling for C5 Complement Inhibitors Using [redacted] as Representative for the Class

Boxed Warning

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with [redacted]. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- [redacted] at least 2 weeks prior to administering the first dose of [redacted] unless the risks of delaying [redacted] therapy outweigh the risks of developing a meningococcal infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. [redacted]
- Persons receiving [redacted] are at increased risk for invasive disease caused by *N. meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

[redacted] is available only through a restricted program called the [redacted] REMS (5.2).

CBER Labeling Comments*: The above labeling language was developed by CDER (received 1 August 2023) following proposed revisions from CBER (sent 26 July 2023). As part of the 26 July 2023 feedback, CBER provided the following comments on the proposed boxed warning for CDER's consideration:*

- *CBER noted that the boxed warning is inconsistent in the language construction, with some instructions written in command language. We recommended harmonizing the language to be consistent throughout.*
- *CBER recommended deletion of the following language from the boxed warning:* [redacted]
- *CBER noted that the proposed labeling is instructing individuals to comply with ACIP recommendation rather than to vaccinate per the FDA approved dosage and administration. While reference to ACIP recommendations is appropriate for this special population for which the vaccine PIs are silent, instructions to "comply" with outside recommendations appears problematic.*
- *CBER does not recommend stating* [redacted] *as this may provide a false sense of safety, plus it is not possible to assess* [redacted]

CBER does not have any additional comments or edits to the revised labeling (1 August 2023).

Section 2.2 – [redacted] Vaccination and Prophylaxis

Vaccinate patients for meningococcal [redacted] (serogroups A, C, W, and Y [MenACWY] and serogroup B [MenB]) according to current ACIP guidelines at least 2 weeks prior to administering the first dose of [redacted] *[see Warnings and Precautions (5.1)]*.

If urgent [redacted] therapy is indicated in a patient who [redacted] vaccines for both MenACWY and MenB according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible. Provide the patient with antibacterial drug prophylaxis. [redacted]

[redacted]

Healthcare [redacted] who prescribe [redacted] must enroll in the [redacted] REMS [see Warnings and Precautions (5.1)].

CBER Labeling Comments*: The above labeling language was developed by CDER (received 1 August 2023) following proposed revisions from CBER (sent 26 July 2023). As part of the 26 July 2023 feedback, CBER provided the following comments on the Section 2.2 for CDER's consideration:*

- *CBER does not concur with labeling revisions* [redacted]
- *As discussed in the internal meeting, the duration, timing and type of antimicrobial therapy is not well understood for individuals receiving complement inhibitors.*
    - *CBER is concerned that recommending a short duration of antimicrobial prophylaxis implies a greater degree of protection from the vaccine than may be observed in clinical use.*
    - *CBER otherwise defers to CDER/DAI with regards to antimicrobial prophylaxis.*

In subsequent discussions, CDER/OND/OCHEN/DNH raised concerns regarding the proposed changes to the labeling language regarding antimicrobial prophylaxis. In internal meetings, CBER reiterated that there was limited evidence to guide labeling recommendations regarding the role of antimicrobial prophylaxis to mitigate the risk of meningococcal infection associated with use of complement inhibitors. CBER continues to defer labeling recommendations regarding antimicrobial prophylaxis to CDER.

Section 4 – Contraindications

[redacted] is contraindicated in:

- Patients with unresolved *Neisseria meningitidis* infection [see Warnings and Precautions (5.1)].

CBER Labeling Comments*: The above labeling language was developed by CDER (received 1 August 2023) following proposed revisions from CBER (sent 26 July 2023). As part of the 26 July 2023 feedback, CBER provided the following comments on the Section 4 for CDER's consideration:*

- *We suggested deleting the following contraindication:*
    - [redacted]

(b) (4)

Section 5.1 – Warnings and Precautions: Serious Meningococcal Infections

Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors, (b) (4). The use of (b) (4) increases a patient's susceptibility to serious and life-threatening meningococcal infections (septicemia and/or meningitis) caused by any serogroup, including nongroupable strains.

Complete or update meningococcal vaccination (for serogroups A, C, W, and Y [MenACWY] and serogroup B [MenB]) according to ACIP recommendations at least 2 weeks prior to the first dose of (b) (4) Revaccinate patients in accordance with ACIP recommendations considering the duration of (b) (4) therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information.

If urgent (b) (4) therapy is indicated in a patient who (b) (4) both MenACWY and MenB according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis; (b) (4)

Because of inhibition of complement activity by (b) (4) and risk of infection caused by nongroupable strains of *N. meningitidis*, vaccination does not eliminate the risk of meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection, (b) (4) and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if these signs and symptoms occur. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

(b) (4) in patients who are undergoing treatment for (b) (4) meningococcal infection. (b) (4) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions (5.2)].

CBER Labeling Comments*: The above labeling language was developed by CDER (received 1 August 2023) following proposed revisions from CBER (sent 26 July 2023). As part of the 26 July 2023 feedback, CBER provided the following comments on the Section 5.1 for CDER's consideration:*

- *CBER recommended referring to FDA approved labeling rather than ACIP recommendations, when possible.*
- *CBER noted that the meningococcal vaccine USPIs do not have specific dosage recommendations for this population, but ACIP does.*
- *CBER recommends deleting the following sentence,* (b) (4) *The prevalence of meningococcal infection observed in the clinical study may be a function of the sample size and duration of*

follow-up. We recommend gathering additional data to assess the risk associated with novel complement inhibitors prior to incorporating any additional language in the labeling.

(b) (4)

Section 5.3 – Other Infections

(b) (4) blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae, Haemophilus influenzae,* and to a lesser extent, *Neisseria gonorrhoeae*. (b) (4) Administer vaccinations for the prevention of *Streptococcus pneumoniae and Haemophilus influenzae type b* (Hib) infections according to current ACIP guidelines. Persons receiving (b) (4) are at increased risk for infections due to these (b) (4)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 2, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216834
Product Name, Dosage Form, and Strength:	Zilbrysq (zilucoplan) injection, 16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.81 mL
Applicant Name:	UCB, Inc.
TTT ID #:	2022-1160-1
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 25, 2023 for Zilbrysq. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Zilbrysq (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study report and label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The linear barcode is missing from the container labels. Additionally, important information (e.g., strength statement, proprietary name, etc.) lacks prominence on the carton labeling. Thus, we provide recommendations for the Applicant in Section 3.

3 RECOMMENDATIONS FOR UCB, INC.

We recommend the following be implemented prior to approval of this NDA:

[a] Shah, M. Human Factors Study Report and Labels and Labeling Review for Zilbrysq (NDA 216834). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUL 14. TTT ID No.: 2022-1160; 2022-1219.

A. Container labels

1. We acknowledge your comment that "including a linear barcode would prevent having sufficient area of the syringe uncovered to allow for visual inspection of the syringe content"; however, per 21 CFR 201.25(c)(2), a linear barcode must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act. The barcode is used for additional verification before drug administration in the inpatient setting; therefore, we maintain our recommendation to include the product's linear barcode on each container as required by 21 CFR.25(c)(2). If you wish to submit a waiver from the linear barcode requirements under 21 CFR 201.25(d), please contact the Office of Compliance at CDERBarcodeQuestions@fda.hhs.gov.

B. Carton labeling (Inner Carton labeling and Outer Carton labeling)

1. The strength statement lacks prominence. Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., graphic image of the prefilled syringe).

C. Carton labeling (Outer Carton labeling)

1. As currently presented, the graphic image of the prefilled syringe is overly prominent and therefore more important information (i.e., the proprietary name, established name, route of administration, and warnings or cautionary statements, etc.) lacks prominence on the principal display panel (PDP), side, and back panels. We recommend decreasing the size of the graphic image of the prefilled syringe on the PDP, side, and back panels. Additionally, consider increasing the prominence of the proprietary name and established name on the PDP, side, and back panels by increasing the font size given the additional space after decreasing the size of the graphic image of the prefilled syringe. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

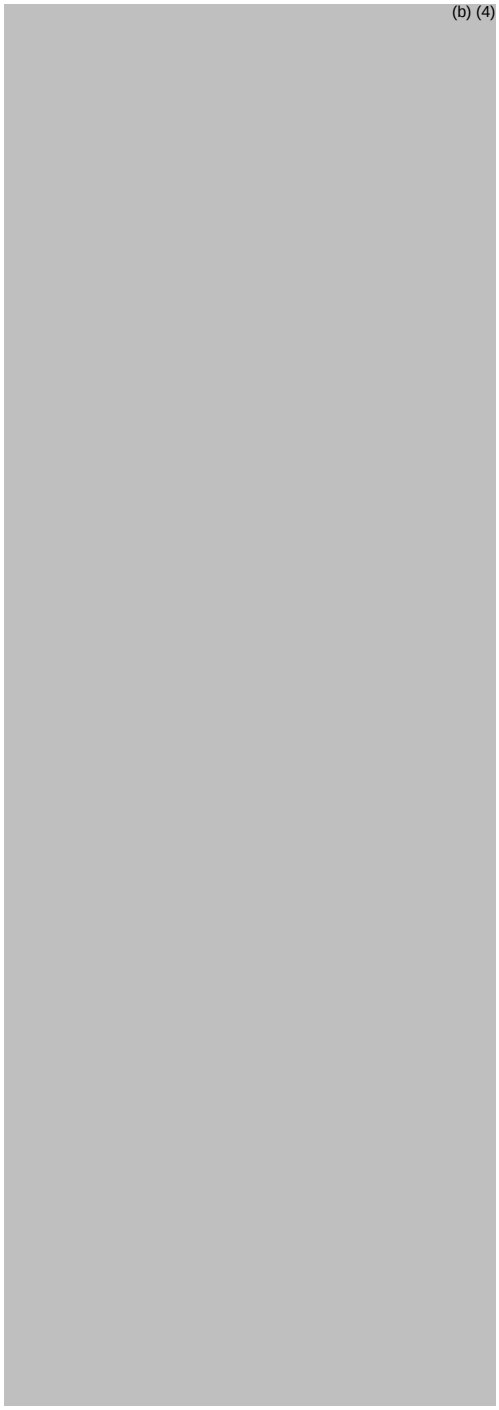
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 25, 2023

Applicant's response can be accessed in EDR via:
\\CDSESUB1\EVSPROD\nda216834\0047\m1\us\111-information-amendment\response-to-18-jul-2023-ir.pdf

Container labels

16.6 mg/0.416 mL

(b) (4)



7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

MILLIE B SHAH
08/02/2023 09:54:32 AM

COLLEEN L LITTLE
08/02/2023 10:11:48 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 14, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216834
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	Zilbrysq (zilucoplan) injection, 16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.81 mL
Device Constituent:	Pre-filled syringe (PFS)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	UCB, Inc.
FDA Received Date:	August 31, 2022, January 18, 2023, February 28, 2023, June 6, 2023
OSE RCM #:	2022-1160; 2022-1219
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Division Director	Danielle Harris, PharmD

1 EXECTUTIVE SUMMARY

Our review of the human factors (HF) validation study results for Zilbrysq (zilucoplan) injection identified use-related issues with some critical tasks; however, we find the residual risk is acceptable. Although some participants experienced use-related issues when answering knowledge task questions targeted at checking information on the prefilled syringe (PFS) prior to injection (e.g., reading the medication name, strength, and expiration

date), all participants were successful in administering a dose. We acknowledge that based on the results of these knowledge task questions from the HF validation study, the Applicant updated the PFS label to improve readability and conducted a supplemental HF validation study. The results of the supplemental HF validation study demonstrate fewer use-related issues with reading information on the PFS. Our review of the PFS label finds that additional changes are unlikely to further mitigate the risk of errors. Additionally, while there is residual risk that remains related to reading the PFS label, the PFS is housed in an outer carton that contains all the same critical information in larger, more prominent font. Thus, in the event a user has difficulty reading the PFS label, they can refer to the outer carton to confirm the information. Thus, we find the design of the product-user interface supports the safe and effective use of this product by the intended users, for its intended uses, and intended use environments.

2 REASON FOR REVIEW

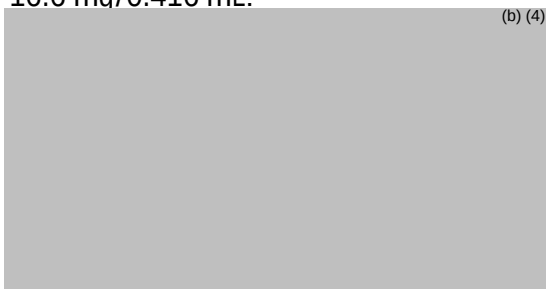
This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 216834 for Zilbrysq (zilucoplan) injection.

2.1 PRODUCT INFORMATION

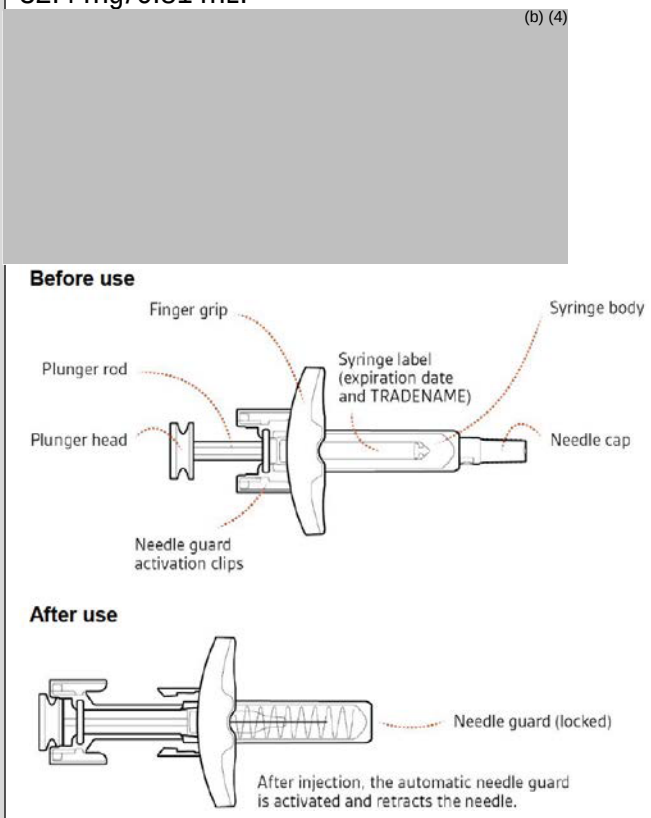
Table 1 presents relevant product information for Zilbrysq that UCB, Inc. on submitted on August 31, 2022.

<table>
<tr><th colspan="2">Table 1. Relevant Product Information for Zilbrysq</th></tr>
<tr><td>Initial Approval Date</td><td>Not Applicable</td></tr>
<tr><td>Active Ingredient</td><td>zilucoplan</td></tr>
<tr><td>Indication</td><td>treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Injection</td></tr>
<tr><td>Strength</td><td>16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.81 mL</td></tr>
<tr><td>Dose and Frequency</td><td>0.3 mg/kg once daily
<table>
<tr><th>Body weight of patient</th><th>Dose</th></tr>
<tr><td>≥43 to <56 kg</td><td>16.6 mg</td></tr>
<tr><td>≥56 to <77 kg</td><td>23 mg</td></tr>
<tr><td>≥77 to <150 kg</td><td>32.4 mg</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Carton of 7 or carton of 28 prefilled single-dose safety syringes in the following strengths:
16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.81 mL</td></tr>
</table>

<table>
<tr><td>Storage</td><td>Store ZILBRYSQ prefilled syringes refrigerated at 36° to 46°F (2° to 8°C) in the original carton until dispensing. Do not freeze.
Storage conditions after dispensing by pharmacist:<table><tr><th>Temperature</th><th>Refrigeration 36° to 46°F (2° to 8°C)</th><th>Room Temperature Up to 86°F (30°C)</th></tr><tr><td>Time Period</td><td>Until expiration date on the carton</td><td>Up to 3 months after removing from refrigerator or until expiration date on the carton, whichever occurs first</td></tr></table>Store ZILBRYSQ prefilled syringes in the original carton to protect them from light until time of use.
Do not return ZILBRYSQ to the refrigerator after it has been stored at room temperature.
Discard ZILBRYSQ if not used within 3 months at room temperature storage.
ZILBRYSQ does not contain a preservative; discard any unused portion.</td></tr>
<tr><td>Device Constituent</td><td>Prefilled syringe: (b) (4) Needle Safety Device

16.6 mg/0.416 mL:
 
(b) (4)

23 mg/0.574 mL:
 
(b) (4)</td></tr>
</table>

	32.4 mg/0.81 mL: (b) (4)  Figure 1. Zilbrysq (zilucoplan) injection PFS (top), before use (middle), after use (bottom)
Intended Users	• Healthcare professionals (HCPs) who support the treatment of gMG patients including but not limited to Registered Nurses (RNs), Licensed Practical Nurses (LPSs) and/or Nurse Practitioners (NPs) • Caregivers who are responsible for the care and support of gMG patients, often a partner, friend or relative, but whom have no medical training or background • Patients who have been diagnosed with gMG
Intended Use Environment	Home or clinical settings

2.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We searched for previous HF-related advice relevant to this current review using the term zilucoplan. Our search identified the relevant HF-related advice below.

- On March 29, 2019, in the Type B End of Phase 2 Preliminary Meeting Comments under IND 134340, we provided HF guidance in response to Question 6 for the Applicant to conduct a use-related risk analysis and submit the HF validation study protocol for Agency review.[a]
- On December 20, 2019, the Applicant submitted the HF validation study protocol under IND 134340. On February 14, 2020, we sent comments to the Applicant in the Human Factors Validation Study Protocol-Advice Letter.[b]

2.3 MATERIALS REVIEWED

We considered the materials listed in Error! Reference source not found. for this review.

Table 2. Materials Considered for this Review

Material Reviewed	Appendix or Section
Product Information	Section 1.1
Regulatory History Related to the Proposed Product's Human Factors Development Program	Section 1.2
Human Factors Validation Study Results Report and Related Human Factors Supporting Documents	A
Information Requests Issued During the Review	B
Labels, Labeling, and Packaging	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

The sections below provide a summary of the study design and our evaluation of the study methodology to determine if the study has been appropriately designed to evaluate the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the study design for the HF validation study and supplemental HF validation study. See Appendix A for more details on the study design.

[a] Bullock, H. Type B End of Phase 2 Preliminary Comments for RA101495 (zilucoplan). Silver Spring (MD): FDA, CDER, OND, DN1 (US); 2019 MAR 29. IND 134340.

[b] Lyons, D. Human Factors Validation Study Protocol Advice Letter for zilucoplan injection. Silver Spring (MD): FDA, CDER, OSE (US); 2020 FEB 14. IND 134340.

After completing the HF validation study, the Applicant determined there were "usability-related advantages to making changes to the zilucoplan PFS label to improve readability". Thus, the zilucoplan PFS label design was updated and evaluated in the supplemental HF validation study. Table 1 provides a comparison of the PFS label evaluated in the HF validation study and supplemental HF validation study.

Table 1. Comparison of PFS Label Evaluated in HF Validation Study and Supplemental HF Validation Study

(b) (4)

(b) (4)

Table 2. Study Methodology for Human Factors (HF) Validation Study and Supplemental HF Validation Study		
Study Design Elements	Details for HF Validation Study	Details for Supplemental HF Validation Study
Study Objectives	• Validate that the PFS can be safely used by representative users in a representative use environment. • Demonstrate that the intended users can comprehend and effectively use the labelling, including the IFU.	• Demonstrate that the intended users can comprehend and effectively use the PFS labelling.
Participants	75 participants in the following user groups: • Injection-naïve Patients (n=15) • Injection-experienced Patients (n=15) • Injection-naïve Caregiver (n=15) • Injection-experienced Caregiver (n=15) • Healthcare professionals (HCPs) (n=15)	30 participants in the following user groups: • Patients (n=15) • Caregivers (n=15)
Training	All participants were untrained	
Test Environment	• Representative of both home and clinical settings including table and chairs • Lighting and noise were representative of home and clinical settings	• Representative of both home and clinical settings including table and chairs • Lighting and noise were representative of home and clinical settings

		• 2 visits were in-home visits conducted at the participants' kitchen tables[c]
Test Materials	• Carton containing 7 PFS represented the final product in all ways related to user interactions. PFS filled with a comparable volume of placebo liquid that emulated the viscosity associated with the intended active drug in order to offer a representative force for plunger activation • Inner tray • Outer carton • Instructions for Use (IFU) • Hand Sanitizer • Gloves • Alcohol Swabs • Cotton Balls • Injection Pad • Sharps Container • Plastic Adhesive Bandages • First Aid Kit • Mannequin (to represent the patient for caregivers or HCPs).	• 1 PFS with 23 mg/0.574 mL label containing placebo The Applicant identified that the PFS filled with the middle volume (i.e., 23 mg/0.574 mL) is the worst case for readability due to plunger positioning behind the label where there is text. Therefore, only the middle dose presentation was assessed for the supplemental HF validation study. • Hand sanitizer • First Aid Kit
Sequence of Study	• Study orientation • Task Performance Evaluation (IFU optional) • Task Performance Evaluation Debrief • Knowledge-Based Assessment (IFU optional) • Knowledge-Based Assessment Debrief	• Study orientation • Knowledge-Based Assessment • Knowledge-Based Assessment Debrief

[c] We generally recommend that all participants complete the HF validation study in the test environment to minimize variability in actual use environments that may impact study results. However, in this instance, the completion of 2 participants' supplemental HF validation study test scenarios in their actual use environments does not preclude our review of the HF validation study results given the objective of the supplemental HF validation study was to demonstrate that intended users can comprehend the updated PFS labeling.

	• Break • Task Performance Evaluation (IFU required) • Task Performance Evaluation Debrief • Knowledge-Based Assessment (IFU required) • Knowledge-Based Assessment Debrief	

3.2 DISCUSSION OF METHODOLOGY

Test Materials

The IFU evaluated in the HF validation study is different from the intend-to-market IFU submitted on August 31, 2022. Most notably, the format of the IFU evaluated in the HF validation study was a 2-column format, whereas the format of the intend-to-market IFU submitted is a 1-column format. We generally expect the HF validation study evaluate the intend-to-market user interface, including the IFU. As a general matter, differences in formatting, wording, and graphics/illustrations have the potential to impact the performance of critical tasks. Thus, we sent an information request (IR) for the Applicant's justification to support that no additional HF validation data is warranted for each proposed change. On February 28, 2023, the Applicant submitted an updated intend-to-market IFU that more closely aligns with the IFU evaluated in the HF validation study and justification to support the proposed changes. In this instance, we find the changes between the IFU evaluated in the HF validation study and the submitted intend-to-market IFU do not preclude our review of the HF validation study results (See Appendix C).

4 RESULTS AND ANALYSIS

We have carefully reviewed each observed event, the Applicant's use-related risk analysis (URRA), the participants' subjective feedback, the Applicant's root-cause analysis (RCA), and the Applicant's comments and proposed mitigations (if applicable) below in **Table 3**.

Table 3. Focused Analysis of Use Errors, Close Calls and Use Difficulties and DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **uFMEA** = [user] failure mode and effects analysis; **RCA** = root cause analysis; **PINX** = Injection-Naïve Patient; **PEXP** = Injection-Experienced Patient; **CINX** = Injection-Naïve Caregiver; **CEXP** = Injection-Experienced Caregiver; **HCP** = Healthcare Professional; **KBA** = Knowledge-Based Assessment; **HFVS** = Human Factors Validation Study

Information Supplied by Applicant	DMEPA's Findings and Recommendations
Simulated Use Task: Choose injection site Success Criteria: Inject into the abdomen (except 2 inches away from the belly button), front of the thighs, back of the upper arms (only if not self-injecting) Use-Related Events: / Participant Type: UE (n=5) / Patients (PINX5, PINX8, PINX9); Caregivers (CINX4, CEXP2) CC (n=0) UD (n=0)	
Observed use-related events: • Chose inner side of forearm • Chose back of arm (patient)	
Relevant RCA/Subjective Feedback: • Negative transfer: previous experience from infusions, "wanted to get it to the vein and into the body faster based on previous understanding of how injections worked," previous experience with other shots in the back of the arm • IFU unclear: Participant stated that he missed the instructions for when someone is giving him the injection.	

<table>
<tr><td>Based on the Applicant's uFMEA, performing the task incorrectly or not at all may result in:
• Painful injection
• Injection site reaction</td><td>The Applicant did not evaluate injection into the back of the arm by a patient. The Applicant categorizes this task as non-critical; however, we consider this task to be critical because failure to choose the correct injection site (e.g., intradermal) may impact safety and/or efficacy.</td></tr>
<tr><td>Applicant's Comment and Proposed Mitigations Post-HFVS:
• Split figure into two separate pictograms; one pictogram showing the injection site for self-injection and one pictogram showing the injection site for injection supported by a healthcare professional or a caregiver.</td><td>We find the Applicant's proposed mitigation implemented post-HFVS to split the IFU figure depicting the injection sites into 2 separate figures specific to self-injection and caregiver/HCP injection sites acceptable to address the RCA of unclear IFU. In this instance, we determined this revision can be implemented without submission of additional HF validation study data for review.</td></tr>
<tr><td>Knowledge Task: What, if anything, should you check about the syringe before you inject?

Success Criteria:
• Know to check the syringe for damage before injection
• Know to check the needle cap to see if it is intact and attached to the syringe before injection
• Know to check the medication name on the syringe label before injection
• Know to check dose on device labeling
• Know to check the expiration date on the syringe label before injection

<table><tr><td>Use-Related Events:</td><td>Participant Type:</td></tr><tr><td>UE (n=42)</td><td>• HCPs (HCP1, HCP2, HCP9, HCP11, HCP12)</td></tr></table></td><td></td></tr>
</table>

		• Patients (PINX2, PINX3, PINX4, PINX5, PINX6, PINX7, PINX9, PINX12, PINX13, PINX14, PEXP1, PEXP2, PEXP3, PEXP4, PEXP5, PEXP6, PEXP7, PEXP10, PEXP14, PEXP15) • Caregivers (CINX1, CINX4, CINX5, CINX7, CINX8, CINX10, CINX12, CINX14, CEXP1, CEXP2, CEXP3, CESP5, CEXP6, CEXP7, CEXP9, CEXP10, CEXP15)	
	CC (n=0)		
	UD (n=0)		
Observed use-related events: • Did not mention any or all of the success criteria			
Relevant RCA/Subjective Feedback: • Study limitation • System design is not intuitive • IFU organization is not intuitive: suggested sub-bullets for the list of things to check so it's harder to miss, "do not" statements should be grouped together so it is easier to read, "do not" statements blended in so the whole bullet point should be bolded rather than just the beginning • Intentional misuse • System design does not meet user's needs: Did not recognize that there was text printed on the syringe label due to print size, unable to read the name, dose, and expiration date printed on the syringe so they could not look for them, label was not good enough for gMG patients who have ocular problems • Negative transfer			

Based on the Applicant's uFMEA, performing the task incorrectly or not at all may result in: • Systemic infection • Incorrect medicine • Minor adverse event (due to overdose) • Loss of efficacy (due to underdose/no dose) • Injection of degraded product	
Applicant's Comment and Proposed Mitigations Post-HFVS: While these participants missed mentioning all five items that should be checked prior to injecting, they all successfully identified the five things that should be checked on the syringe prior to use and/or knew what to do if the syringe looked damaged, the needle cap was not intact, the medication name was not present, the dose did not match their prescription, or the expiration date had passed when asked during other KBA questions. When asked to utilize the IFU while answering the same question, only n=10 were unable to list all of the items that should be checked on the syringe prior to use (LAKBA14/16/18/21/24). Again, they all successfully identified the five things that should be checked on the syringe prior to use and/or knew what to do if there was something wrong with the syringe when asked during other KBA questions. UCB chose to update the syringe label to improve readability (see Figure 3 above). A supplemental HF validation study was performed to test the updated syringe label. A summary of the supplemental HF validation study results is presented below in Table 4 and in the following narrative:	We acknowledge that despite updates to the syringe label, the root cause analysis and subjective feedback from the supplemental HF validation study continue to identify that the user interface may have contributed to use-related events related to reading information on the PFS. We also acknowledge that the root cause and subjective feedback from the supplement study were very similar or the same as the analysis of the use events seen in the first study. Specifically, some participants mentioned the size of the font, the overlap of the syringe body or the lack of background on the label as contributing factors. Additionally, they found the small text and transparent label were challenging for reading the medication name on the label. The PFS is intended to remain in the carton to protect from light until it is time to inject. The carton allows use of larger fonts and prominence of important product information. Considering the storage requirements (e.g., in the carton), we find it reasonable that the user could confirm the drug name, strength, exp date on the carton. Lastly, failure to check the syringe for damage, and failure to check that the needle cap is intact prior to use does not necessarily result in the harms listed

Table 4. Summary of Supplemental HF Validation Study Results

Knowledge-Based Question	Number of UE, CC, UD
Can you tell me the medication name printed on the label? – "Tradename"	UE: 3 CC: 4 UD: 1
Can you tell me the medication name printed on the label? – "Zilucoplan"	UE: 12 CC: 4 UD: 0
Can you tell me the dose printed on the label?	UE: 10 CC: 3 UD: 0
When does this medication expire?	UE: 0 CC: 1 UD: 0

- Of the 30 participants:
  - n=27 were able to comprehend and effectively read at least one of the medication names
  - n=20 were able to comprehend and effectively read the dose of medication
  - n=30 were able to comprehend and effectively read the expiration date

These participants may have experienced difficulties but eventually were able to identify the correct information.

in the uFMEA. Harm only occurs if the PFS is the wrong drug, strength, or expired.

Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.

- When looking at readability of the medication name, 3 participants could not read either name printed on the syringe label.
    - These participants expressed challenges with the size of the font, the overlap of the syringe body or the lack of background on the label.
    - They found the small text and transparent label to create challenges for reading the medication name on the label.

- Ten participants could not read the medication dose printed on the syringe label.
    - Five of these participants indicated they had trouble reading the dose because the syringe body occluded the first digit written on the syringe label.
    - In addition to the syringe body, the font was also mentioned by 5 of the 10 participants.

Knowledge Task: Can you tell me the medication name printed on the label?

Success Criteria: Can locate and comprehend the medication name on device labelling

Use-Related Events:	Participant Type:
UE (n=29)	• Patients (PINX2, PINX4, PINX5, PINX6, PINX11, PINX13, PINX14, PINX15, PEXP1, PEXP2, PEXP3, PEXP4, PEXP5, PEXP6, PEXP7, PEXP8, PEXP9, PEXP10, PEXP11) • Caregivers (CINX9, CINX12, CINX13, CINX14, CINX15,

	CEXP4, CEXP7, CEXP10, CEXP13, CEXP14)	
CC (n=0)		
UD (n=4)	• Caregivers (CINX5, CINX6, CEXP3, CEXP5)	
Observed use-related events: • Unable to read the label • Difficulty reading the label • Initially thought there was not a label		
Relevant RCA/Subjective Feedback: • System design does not meet user's needs: Difficulty reading the label due to the small font size and text over the (b) (4) plunger, background was clear, font was "very small for MG patients and elderly to read," glare off the plastic made it difficult to read, could tell something was there but one eye was wandering due to gMG so could not read the text and had to use a flashlight, would help if the font was bolder, not even bigger, would need a magnifying glass to read the print		
Based on the Applicant's uFMEA, performing the task incorrectly or not at all may result in: • Incorrect medicine		The Applicant's uFMEA does not include a comprehensive description of the clinical impact of the potential use error. The harm column includes a general description "incorrect medicine." The uFMEA should describe the potential impact of the safety and/or efficacy that may result from the use error (i.e., the impact and clinical sequelae of incorrect medicine).
Applicant's Comment and Proposed Mitigations Post HFVS: Participants pointed to the font size, weight of the text, the transparent background of the label, and seeing the (b) (4) plunger through the label as reasons they could not read the text.		See our analysis in the row titled "Knowledge Task What, if anything, should you check about the syringe before you inject".

UCB chose to update the syringe label to improve readability (see Figure 3 above. A supplemental HF validation study was performed to test the updated syringe label. A summary of the supplemental HF validation study results is presented below in Table 5 and in the following narrative:

Table 5. Summary of Supplemental HF Validation Study Results

Knowledge-Based Question	Number of UE, CC, UD
Can you tell me the medication name printed on the label? – "Tradename"	UE: 3 CC: 4 UD: 1
Can you tell me the medication name printed on the label? – "Zilucoplan"	UE: 12 CC: 4 UD: 0
Can you tell me the dose printed on the label?	UE: 10 CC: 3 UD: 0
When does this medication expire?	UE: 0 CC: 1 UD: 0

Of the 30 participants:

- n=27 were able to comprehend and effectively read at least one of the medication names
- n=20 were able to comprehend and effectively read the dose of medication

- n=30 were able to comprehend and effectively read the expiration date.

These participants may have experienced difficulties but eventually were able to identify the correct information.

- When looking at readability of the medication name, 3 participants could not read either name printed on the syringe label
    - These participants expressed challenges with the size of the font, the overlap of the syringe body or the lack of background on the label.
    - They found the small text and transparent label to create challenges for reading the medication name on the label.

- Ten participants could not read the medication dose printed on the syringe label.
    - Five of these participants indicated they had trouble reading the dose because the syringe body occluded the first digit written on the syringe label.
    - In addition to the syringe body, the font was also mentioned by 5 of the 10 participants.

Knowledge Task UAKBA23: Can you tell me the dose printed on the label?

Success Criteria: Can locate and comprehend the dose on device labelling

Use-Related Events:	Participant Type:
UE (n=24)	• Patients (PINX4, PINX5, PINX7, PINX11, PINX13, PINX14,

		PINX15, PEXP5, PEXP6, PEXP7, PEXP8, PEXP10, PEXP11) • Caregivers (CINX2, CINX6, CINX9, CINX11, CINX12, CINX14, CINX15, CEXP4, CEXP10, CEXP13, CEXP14)	
	CC (n=0)	•	
	UD (n=2)	• Patient (PINX3) • Caregiver (CINX13)	
Observed use-related events: • Difficulty reading the dose but knew it should be 23 mg from the prescription • Difficulty reading the dose; could read the mL but not the mg • Knew where it should be located but could not read the dose • Unable to read the label • Said the dose was 24 mg • Said the dose was 25 mg			
Relevant RCA/Subjective Feedback/Observation: System design does not meet user's needs: Trouble determining "if it is a 3 or 5" and the "coloring makes it so hard to read," thought it would be easier to read if the print had been a different color, could not read the dose due to the size of the font and (b) (4) of the plunger, more contrast between the print and the plunger or a larger size font might help, could not read due to the liquid and the transparency, could tell something was there but one eye was wandering due to gMG so could not read the text and had to use a flashlight, would need a magnifying glass to read the print, did not see anything printed			

<table>
<tr><td>Based on the Applicant's uFMEA, performing the task incorrectly or not at all may result in:
• Minor adverse event (due to overdose)
• Loss of efficacy (due to underdose/no dose)</td><td>See our analysis in row #2 above for Knowledge Task UAKBA14, UAKBA16, UAKBA18, UAKBA21, UAKBA24.</td></tr>
<tr><td>Applicant Comment and Proposed Mitigations Post HFVS:
See Applicant's Comment and Proposed Mitigations Post HFVS in Knowledge Task UAKBA20 (row #3).</td><td>See our analysis in row #2 above for Knowledge Task What, if anything, should you check about the syringe before you inject.</td></tr>
<tr><td>Knowledge Task UAKBA26: When does this medication expire?

Success Criteria: Can locate and comprehend the Expiration date on the syringe labelling

<table><tr><td>Use-Related Events:</td><td>Participant Type:</td></tr><tr><td>UE (n=16)</td><td>• Patients (PINX4, PINX13, PINX15, PEXP6, PEXP7, PEXP8, PEXP10, PEXP11)
• Caregivers (CINX2, CINX6, CINX9, CINX13, CINX14, CINX15, CEXP13, CEXP14)</td></tr><tr><td>CC (n=0)</td><td></td></tr><tr><td>UD (n=1)</td><td>• Caregiver (CEXP4)</td></tr></table></td><td></td></tr>
<tr><td>Observed use-related events:
• Read the expiration date but second-guessed themselves and believed they might have read the date incorrectly
• Knew where it should be located but could not read the expiration date
• Unable to read the label</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback/Observation:</td><td></td></tr>
</table>

System design does not meet user's needs: Could not read the date due to the size of the font and the [redacted] on the plunger made it hard to read, [redacted] plunger was obstructing view of the year, difficulty reading due to the liquid and the transparency, did not see anything printed	
Based on the Applicant's uFMEA, performing the task incorrectly or not at all may result in: • Injection of degraded product	The Applicant's uFMEA does not include a comprehensive description of the clinical impact of the potential use error. The harm column includes a general description "injection of degraded product." The uFMEA should describe the potential impact of the safety and/or efficacy that may result from the use error (i.e., the impact and clinical sequelae of injection of degraded product).
Applicant's Comment and Proposed Mitigations Post HFVS: See Applicant's Comment and Proposed Mitigations Post HFVS in Knowledge Task UAKBA20 (row #3).	See our analysis in row #2 above for Knowledge Task What, if anything, should you check about the syringe before you inject.

4.1 ANALYSIS OF OTHER USE ERRORS, CLOSE CALLS, OR USE DIFFICULTIES

The HF validation study showed use errors, use difficulties, and close calls with the tasks evaluated by simulated use or knowledge-based assessments (KBAs) listed below in this section. However, based on our review of the available assessment of these use errors, use difficulties, close calls, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), and the Applicant's root cause analysis, we find the proposed user interface has been appropriately designed and we did not identify further need for risk mitigation strategies at this time to address the use errors, use difficulties, and close calls with the tasks below.

- Remove device from packaging without using the plunger rod or needle cap, or dropping the device
- Remove needle cap by pulling it straight off
- Clean chosen injection site with alcohol swab
- Dispose of the product in a sharps container
- KBA: When, if ever, can you touch the needle guard activation clips?
- KBA: When, if ever, can you pull on the syringe plunger?
- KBA: Can you inject more than once per day?
- KBA: When, if ever, can you miss a dose of the medicine?
- KBA: When, if ever, can you rub the injection site after injections?
- KBA: What supplies, if any, do you need to gather on a flat surface prior to administering the injection?
- KBA: How should you store the syringe?
- KBA: When, if ever, can the syringe be stored in room temperature?
- KBA: When, if ever, should you store the syringe in the freezer?
- KBA: What, if anything, should you check on the carton label before you inject?
- KBA: Before you inject the medicine, what, if anything, should you do with the syringe after taking it out of the fridge?
- KBA: What, if anything, should you not do to warm up the syringe to room temperature?
- KBA: What, if anything, should you check about the liquid medication before you inject?
- KBA: What, if anything, should you do if the medication name does not appear on the label?

- KBA: What, if anything, should you do if the dose on the label does not correspond to prescription?
- KBA: What, if anything, should you do if the medication has expired?
- KBA: When, if ever, should you remove the needle cap?
- KBA: After cleaning the injection site, when if ever, can you touch it again?
- KBA: After removing the needle cap, when, if ever, can you recap the needle?
- KBA: When, if ever, can you throw away the syringe in household trash?
- KBA: When, if ever, can you throw away the used sharps disposal container in household trash?
- KBA: When, if ever, can you recycle the used sharps disposal container?

5 LABELS AND LABELING

Table 6 and Table 7 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table 6. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The dosage instructions do not specify if ideal body weight or actual body weight should be used for weight-based dosing in the Dosage and Administration section of the Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI).	To ensure that the intended dose is calculated correctly to prevent wrong dose errors.	We recommend specifying whether ideal body or actual body weight should be used to calculate the recommended dosage in the Dosage and Administration section of the HPI and FPI.
2.	As currently presented, the dosing table in the Dosage	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the symbols “≥” and “<” with their intended meaning, “greater

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	and Administration sections of the HPI and FPI contains the symbols "≥" and "<".		than or equal to" and "less than," respectively in the Dosage and Administration sections of the HPI and FPI. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
3.	The dose and strength are presented with a trailing zero (e.g., 23.0 mg) in the Dosage and Administration and Dosage Forms and Strengths sections of the HPI and FPI and How Supplied/Storage and Handling Sections of the FPI.	Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 23.0 mg is seen as 230 mg).[d]	We recommend revising the dose and strength statement to remove the trailing zeros (i.e., revise to 23 mg). See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
4.	The table in the HPI, Table 1 in Section 2.2, and the table in Section 16.1 can be improved to clarify which aspects of the of the PFS are rubine red, orange, or dark blue because based on the Applicant's information request response dated June 6, 2023, the colors refer only to the plunger rod color.	Incorrect and inconsistent descriptions of the device components may result in confusion.	We recommend revising the title of the last column in the aforementioned tables to "Plunger rod color of Prefilled Syringe" and remove (b) (4) from each row.

[d] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2022 DEC 28]. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration and Section 16 How Supplied			
5.	As currently presented, Section 2.3 Preparation Instructions and the table in Section 16.1 include the term [redacted] (b) (4) The term, [redacted] (b) (4) is the inconsistent with the correct package type term.	Consistent use of the correct package type term will promote proper use of the drug product.	We recommend revising Section 2.3 and 16.1 to be consistent with the appropriate package type term (i.e., "single-dose.")

Table 7. Identified Issues and Recommendations for UCB, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (Commercial Label, Inner Label) and Carton Labeling (Commercial Box, Inner Box, Outer Box)			
1.	The strength statements are presented with a trailing zero (i.e., "23.0" and " 0.810 mL").	Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 23.0 mg is seen as 230 mg).[e]	Revise the strength statement to remove the trailing zeros (i.e., "23 mg" and "0.81 mL"). See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
2.	The format for the expiration date is not defined.	We are unable to assess the expiration date format from a medication error perspective.	Define the expiration date format. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA

[e] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2022 DEC 28]. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.[f]
Container Labels (Commercial Label, Inner Label)			
1.	The linear barcode is missing from the container labels.	The linear barcode is used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label and is required per 21 CFR 201.25(c)(2).	Include the products' linear barcode to each container as required by 21 CFR.25(c)(2). Additionally, ensure the linear barcode is placed in a vertical position to improve scannability of the barcode. Barcodes placed in a horizontal position may not scan due to the prefilled syringe curvature.[g] Furthermore, ensure the linear barcode is surrounded by

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[g] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
Carton Labeling (Commercial Box, Inner Box, Outer Box)			
1.	The net quantity statement (i.e., 7 and 28) on the principal display panel of the 7 and 28 day pack size competes in prominence with the strength presentation.	Product selection or dosing errors can occur if the net quantity is mistaken for the product strength, leading to underdosing or overdosing.[h]	We recommend decreasing the size of the net quantity statement (i.e., 7 and 28) on the principal display panel.
2.	The strength statement is presented (b) (4) and the mg amount has more prominence than the mL amount. Additionally, the use of a dash (-) to separate the mg from the mL in the strength statement is inconsistent with the use of a slash (/) in the USPI.	The strength statement can be improved for consistency with the presentation in the USPI.	We recommend revising the strength statement (b) (4) so that the entire strength statement is presented on a single line (b) (4) and the mg amount is separated from the mL amount by a slash (e.g., "16.6 mg/0.416 mL"). Ensure the mg amount and mL amount have equal prominence. Alternatively, consider removing (b) (4) with the strength statement and revising the statement, (b) (4) to "16.6 mg/0.416 mL". Make corresponding changes for all strength presentations.
3.	The net quantity statement, (b) (4)	The strength statement is unnecessary in the net quantity statement.	We recommend revising the net quantity statement to read,

[h] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) on the 7 and 28 day pack size can be improved to minimize redundancy with the strength statement located elsewhere on the cartons.		"7 Single-Dose Prefilled Syringes".
4.	The back panel includes the Usual Dose statement, (b) (4) which is in the incorrect format.	Per 21 CFR 201.55, "…labels for prescription drugs bear a statement of the recommended or usual dosage." Additionally, the "Usual Dose" statement should be aligned with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to, "Recommended Dosage: See prescribing information."
5.	As currently presented, the inclusion of a machine-readable product identifier is not indicated.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA)*. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the machine readable (2D data matric barcode) product identifier to the carton labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.
Carton Labeling (Outer Box)			
6.	The 28 day pack includes the prominent	It is general practice for pharmacists to provide the	We recommend removing the statement, (b) (4)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	statement, (b) (4) along with space to write the date.	(b) (4) on the patient-specific pharmacy label. Therefore, we find that (b) (4) is unnecessary and it detracts from other important information (i.e., storage information).	(b) (4) along with space to write the date.
Inner Carton Labeling			
7.	The proposed inner carton labeling includes the image below; however, your response to the information request dated June 6, 2023 indicates that the image was not present and tested during the human factors (HF) validation study.	Without information and/or data, it is unclear whether the unvalidated image on the inner carton labeling introduces new or unique risks.	We recommend removing the image from the inner carton labeling. Alternatively, you may consider providing information and/or data to demonstrate that the image does not introduce new or unique risks as compared to the inner carton labeling that was tested in your HF validation study.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		

6 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation study identified use errors, close calls, and use difficulties with critical tasks; however, based on our review, we find the residual risks are acceptable or can be further mitigated via additional labels and labeling revisions for these use-related events. Thus, in this specific instance, we find the simulated use HF validation study results are acceptable provided our recommendations are implemented.

We provide recommendations that we advise are implemented during this review cycle of NDA 216834. These changes can be implemented without submitting additional HF validation testing results for Agency review. Above, we have provided recommendations in Table 6 for the Division and Table 7 for the Applicant. We ask that the Division convey Table 7 in its entirety to the Applicant so that recommendations are implemented prior to approval of NDA 216834.

6.1 RECOMMENDATIONS FOR UCB, INC.

Our review of the results of your human factors (HF) validation study for Zilbrysq (zilucoplan) injection identified areas of vulnerability in your labels and labeling that may lead to medication errors. We provide recommendations in the Identified Issues and Recommendations for UCB, Inc. and we recommend that you implement these recommendations and submit the revised labels and labeling. We have determined that in this instance, you may implement these revisions without submitting additional HF validation data for Agency review.

APPENDICES:

APPENDIX A. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT, HUMAN FACTORS SUPPORTING DOCUMENTS AND SUPPLEMENTAL HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

- The Use Failure Mode Effect Analysis (uFMEA) can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216834\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gmg\5354-other-stud-rep\md-q-103087\md-q-103087.pdf
- The HF validation study results report can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216834\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gmg\5354-other-stud-rep\md-q-103477\md-q-103477.pdf
- The Supplemental HF validation study results report can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216834\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gmg\5354-other-stud-rep\md-q-103939\md-q-103939.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On 1/12/2023, we issued an Information Request (IR) to request a comparison between the IFU tested in the HF validation study and the intend-to-market IFU and justification to support that no additional HF validation data is warranted for each proposed change.
- On 1/18/2023, the Applicant provided a side-by-side comparison of the IFUs and justification for the changes that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216834\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gmg\5354-other-stud-rep\md-q-103477\ucb-response-to-human-factors-request-for-information-202301.pdf
- On 2/13/2023, we provided comments in the Mid-Cycle Communication Agenda regarding our concerns with the number and type of post-HF validation IFU changes introduced.
- On 2/28/2023, the Applicant submitted an acceptable response with an updated IFU that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216834\0019\m1\us\114-labeling\draft\history\history-202207b.pdf
- On 06/01/2023, we issued an IR to clarify what aspect of the PFS the colors correspond to in the USPI and to clarify whether the image on the inner carton labeling was present on the carton evaluated in the HF validation study.
- On 06/06/2023, the Applicant provided a response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda216834\0041\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gmg\5354-other-stud-rep\md-q-103477\nda-20230601-resp-qua-1-2.pdf. We provide a recommendation in Section 4 regarding the image on the inner carton labeling.

APPENDIX C. LABELS, LABELING, AND PACKAGING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis [i] along with postmarket medication error experiences with similar products, we reviewed the following Zilbrysq labels and labeling submitted by UCB, Inc.

- Container labels submitted on August 31, 2022
- Carton labeling submitted on August 31, 2022
- Instructions for Use (image not shown), submitted on August 31, 2022 available from \\CDSESUB1\EVSPROD\nda216834\0001\m1\us\114-labeling\draft\labeling\ifu-202207-sub.pdf
- Instructions for Use (image not shown), submitted on February 28, 2023 available from \\CDSESUB1\EVSPROD\nda216834\0019\m1\us\114-labeling\draft\labeling\ifu-202207-sub.pdf
- Medication Guide (image not shown), submitted on August 31, 2022 available from \\CDSESUB1\EVSPROD\nda216834\0001\m1\us\114-labeling\draft\labeling\medguide-202207-sub.pdf
- Prescribing Information (image not shown), submitted on August 31, 2022 available from \\CDSESUB1\EVSPROD\nda216834\0001\m1\us\114-labeling\draft\labeling\cir-202207-sub.pdf

C.2 Label and Labeling Images

Container labels

16.6 mg/0.416 mL

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

MILLIE B SHAH
07/14/2023 01:06:22 PM

COLLEEN L LITTLE
07/14/2023 03:22:32 PM

LOLITA G STERRETT
07/14/2023 04:17:17 PM

DANIELLE M HARRIS
07/18/2023 06:57:20 AM

Clinical Inspection Summary

Date	7/7/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Michael Matthews, Regulatory Project Manager John Troiani, M.D., Ph.D., Medical Officer Laura Jawidzik, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	NDA #216834
Applicant	UCB Inc.
Drug	Zilucoplan
NME	Yes
Proposed Indication	Treatment of generalized myasthenia gravis
Consultation Request Date	10/7/2022
Clinical Inspection Summary Goal Date	6/30/2023, extended to 7/7/2023
Priority/Standard Review	Standard
Action Goal Date	8/31/2023
PDUFA Date	8/31/2023

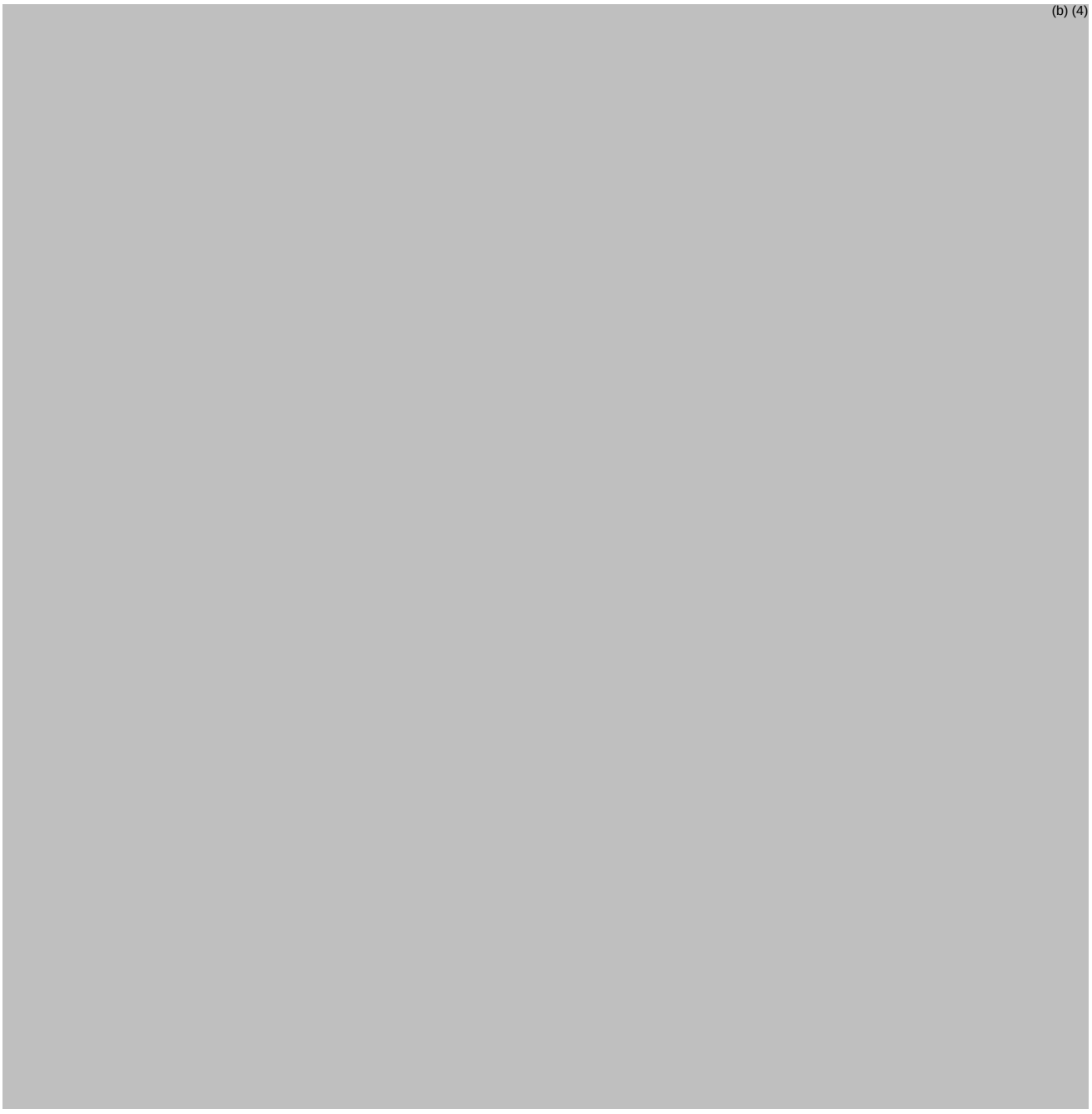
I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Hinton (Site #41), Leite (Site #119), and Smilowski (Site #195) were inspected in support of this NDA covering Protocol MG0010. Despite some protocol deviations occurring at Site #119, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Primary efficacy data, Myasthenia Gravis-Activities of Daily Living (MG-ADL) scores, and secondary efficacy data, Quantitative Myasthenia Gravis (QMG) scores, were verified. There was no evidence of under-reporting of adverse events.

Several protocol deviations occurring at Site #119 were identified and reported to FDA. Per protocol, one of the eligibility criteria stated that subjects were not to take anticholinesterase inhibitors (AChEI) within 10 hours of the screening or baseline QMG assessment. At this site, three (3) of 14 (21.4%) randomized subjects had deviated from this eligibility criterion (see inspection summary below for details). According to documents present at the site, these deviations were not identified until the date of database lock, one to two years after the

deviations had occurred. The review division may wish to conduct a sensitivity analysis with regard to this study site.



II. BACKGROUND

Zilucoplan injection for subcutaneous use is being developed under IND #134340 for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Initial development of zilucoplan was conducted by Ra Pharmaceuticals, Inc., which was acquired by UCB, the current sponsor of this NDA.

The sponsor has submitted the results of one Phase 3 study (Protocol MG0010), under NDA #216834, to support the efficacy and safety of zilucoplan for this indication.

Protocol MG0010 (RA101495-02.301)

Title: "A phase 3, multicenter, randomized, double-blind, placebo-controlled study to confirm the safety, tolerability, and efficacy of zilucoplan in subjects with generalized myasthenia gravis"

Subjects: 174

Sites: 68 sites in North America (32), Western Europe (15), Eastern Europe (11), Asia/Pacific (10)

Study Initiation and Completion Dates: 9/17/2019 to 12/30/2021

Database Lock Date: 1/18/2022

This was a randomized, double-blind, placebo-controlled study in subjects with generalized myasthenia gravis (gMG). Main eligibility criteria included males and females; ≥18 to <75 years of age; diagnosis of gMG (Myasthenia Gravis Foundation of America Class II-IV) at screening; positive serology for acetylcholine receptor (AChR) binding autoantibodies; Myasthenia Gravis-Activities of Daily Living (MG-ADL) score ≥6 at screening and baseline; Quantitative Myasthenia Gravis (QMG) score ≥12 at screening and baseline; four or more QMG test items scored ≥2 at screening and baseline; no change in corticosteroid dose or immunosuppressive therapy (including dose) for at least 30 days prior to baseline and during study; meningococcal vaccination at least 14 days prior to first dose of investigational product (IP).

The study was comprised of three periods: screening period, treatment period, and safety follow-up:

Screening Period (Day -28 to -1)
During this period, study eligibility was determined. Study procedures included, but were not limited to, medical history, physical examination, ECG, labs, anti-drug antibody, MG-ADL, QMG.

Treatment Period (Day 1 [baseline] to Day 84 [Week 12])
Subjects were randomized (1:1) to the following study arms:

- Zilucoplan 0.3 mg/kg subcutaneous (SC) injection once daily for 12 weeks
- Placebo SC injection once daily for 12 weeks

Randomization was stratified by baseline MG-ADL score, QMG Score, and geographical region. Subjects received IP administered SC at the Day 1 visit (baseline). Following education and training at the clinical site, all subjects self-administered daily SC doses of IP using single use pre-filled syringes in injection devices. Subjects were instructed to inject IP into the abdomen (preferred site), thigh, or upper arm.

During the Treatment Period, study visits occurred at Weeks 1, 2, 4, 8, and 12. Subjects who completed the 12-week treatment period had the option to receive zilucoplan in a separate extension study.

Safety Follow-up
For subjects who discontinued study drug, a safety follow-up visit was to occur 40 days after the last dose of IP.

The *primary efficacy endpoint* was the change from baseline to Week 12 in the MG-ADL total score. The MG-ADL assesses the impact on daily functions of 8 symptoms typically affected in generalized MG. Each item is assessed on a 4-point scale; total scores range from 0 to 24 with higher scores indicating more impairment. A *secondary efficacy endpoint* was the change from baseline to Week 12 in the QMG total score. The QMG total score is a 13-item categorical grading system that assesses muscle weakness. Each item is assessed on a 4-point scale; total scores range from 0 to 39 with higher scores indicating more impairment.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the BIMO CDER Clinical Investigator Site Selection Tool (CISST), numbers of enrolled subjects, and prior inspectional history. The site in Poland was chosen due to the greater effect size of sites in Poland compared to the US.

III. RESULTS

1. **John Hinton, M.D.**
   Site #41
   Mobile Infirmary Medical Center and Clinic
   1700 Springhill Avenue
   Suite 100
   Mobile, AL 36604
   Inspection Dates: 1/31/2023 – 2/2/2023

   At this site for Protocol MG0010, 7 subjects were screened, and 5 subjects were randomized and completed the study.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability,

inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary (Myasthenia Gravis-Activities of Daily Living [MG-ADL]) and secondary (Quantitative Myasthenia Gravis [QMG]) efficacy endpoint data.

MG-ADL and QMG individual item data were entered into electronic tablets provided by the vendor, ERT. MG-ADL total scores were automatically calculated from the individual item scores. For the QMG assessments, the value of the individual item was entered into the electronic tablet (e.g., % forced vital capacity via spirometer) and the severity score (i.e., 0, 1, 2, 3) for that individual item, with the total QMG score automatically calculated. The MG-ADL and QMG total scores in the ERT database were verified against the sponsor data line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. There were four serious adverse events (SAEs) occurring in two subjects during this study. Narratives for these SAEs are included in the NDA submission.

2. Maria Isabel da Silva Leite, M.D.
Site #119
John Radcliffe Hospital
Headley Way
Oxford University Hospitals NHS Trust
Oxford, United Kingdom
Inspection Dates: 1/9/2023 – 1/13/2023

At this site for Protocol MG0010, 16 subjects were screened, and 14 subjects were randomized and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary (MG-ADL) and secondary (QMG) efficacy endpoint data.

MG-ADL and QMG individual item data were entered into electronic tablets as described above. The MG-ADL and QMG individual and total scores in the ERT database were verified against the sponsor data line listings; no discrepancies were identified.

Three of 14 (21.4%) randomized subjects did not meet inclusion criterion 6 “QMG score $\geq$12 at screening and baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours).” These three subjects had taken the acetylcholinesterase inhibitor (AChEI) pyridostigmine within 10 hours of the QMG assessment. These protocol deviations were included in the sponsor’s data line listing.

Table 1. Subjects with Eligibility Protocol Deviations

Subject	Treatment Arm	Visit	Time of AChEI Dose Relative to QMG Assessment	QMG Score	Date Randomized
(b) (6)	Zilucoplan	Screening	5 hours prior	21	11/9/2020
	Placebo	Screening	3 hours prior	36	12/21/2020
		Baseline	6 hours prior	34	
	Placebo	Screening	5 hours prior	19	4/27/2021

A protocol deviation log was provided to the site by the sponsor after completion of the study. According to this log, these eligibility deviations were identified on the same date as the database lock date (1/18/2022), approximately one to two years after they had occurred and 2 weeks after study completion. Study personnel entered the day and time of the last dose of AChEI taken prior to QMG assessments into the electronic tablet provided by the vendor, ERT (now Clario) (b) (4) performed clinical monitoring until (b) (4) was acquired by (b) (4) approximately 5 months prior to completion of the study. According to one of the monitors present during the inspection, the monitors checked the electronic tablet for completeness of data entry, but did not verify the timing of the AChEI relative to the QMG assessment.

Reviewer comments: Three of 14 randomized subjects had an eligibility protocol deviation by taking an AChEI within 10 hours of the screening and/or baseline QMG assessment, a secondary efficacy endpoint. All three subjects met the QMG eligibility score cut-off of ≥12. The timepoint of interest for the efficacy analysis is baseline; therefore, the screening eligibility deviations would not impact the overall efficacy analysis. For Subject (b) (6) randomized to placebo, taking an AChEI within 10 hours of the baseline QMG assessment would be expected to improve MG symptoms at baseline.

This reviewer reviewed the sponsor's protocol deviation line listing (Listing 16.2.6.4) and identified 12 of 174 (6.9%) subjects who failed to meet inclusion criterion 6 "QMG score ≥12 at screening and baseline (off anticholinesterase inhibitor therapy for at least 10 hours)." Of these 12 subjects, 6 were randomized to zilucoplan and 6 were randomized to placebo. QMG scores were reviewed and all of these subjects met the QMG cut-off score at screening and baseline. Therefore, these eligibility deviations pertained to AChEI therapy received within 10 hours of the assessment. OSI recommends that the review division take these eligibility protocol deviations into account in the efficacy analyses.

Protocol MG0010 also required that subjects not take an AChEI within 10 hours of the MG-ADL and QMG assessments throughout the study. Subject (b) (6) took an AChEI (pyridostigmine) within 10 hours of QMG assessments at screening and baseline (see Table 1 above) but also took pyridostigmine less than 10 hours prior to QMG assessments on Day 8 (6 hours prior), Day 15 (7 hours prior), Day 29 (5 hours prior), Day 57 (3 hours prior), and Day 84 (6 hours prior). Since MG-ADL and QMG assessments are conducted on the same day, it is likely that an AChEI

was taken within 10 hours of the MG-ADL assessment as well. These deviations were also identified on the day of database lock, after study completion.

Reviewer comments: Subject (b) (6)*, randomized to placebo, took an AChEI within 10 hours of the QMG assessments throughout the study, including the timepoint of interest for the efficacy analyses, baseline (as noted in Table 1) and Day 84. Taking an AChEI within 10 hours of the QMG and MG-ADL assessments would be expected to improve MG symptoms in this subject who was randomized to placebo and, therefore, is less likely to favor zilucoplan in the efficacy analyses.*

There was no evidence of underreporting of adverse events. There was one SAE occurring at this site. Subject (b) (6), randomized to zilucoplan, experienced angioedema. The narrative for this SAE is included in the NDA submission.

3. Marek Smilowski, MD
Site #195
Wielospecjalistyczna Poradnia Lekarska Synapsis
Ul. Boleslawa Czerwinskiego 8
Katowice, Poland
Inspection Dates: 1/9/2023 – 1/12/2023

At this site for Protocol MG0010, 8 subjects were screened, 7 subjects were randomized, and 6 subjects completed the study. Subject (b) (6), randomized to placebo, discontinued the study due to the SAE cerebral hemorrhage resulting in death. The narrative for this SAE is included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary (MG-ADL) and secondary (QMG) efficacy endpoint data.

MG-ADL and QMG individual item data were entered into electronic tablets as described above. The MG-ADL and QMG individual and total scores in the ERT database were verified against the sponsor data line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. There was one SAE occurring at this site as noted above.

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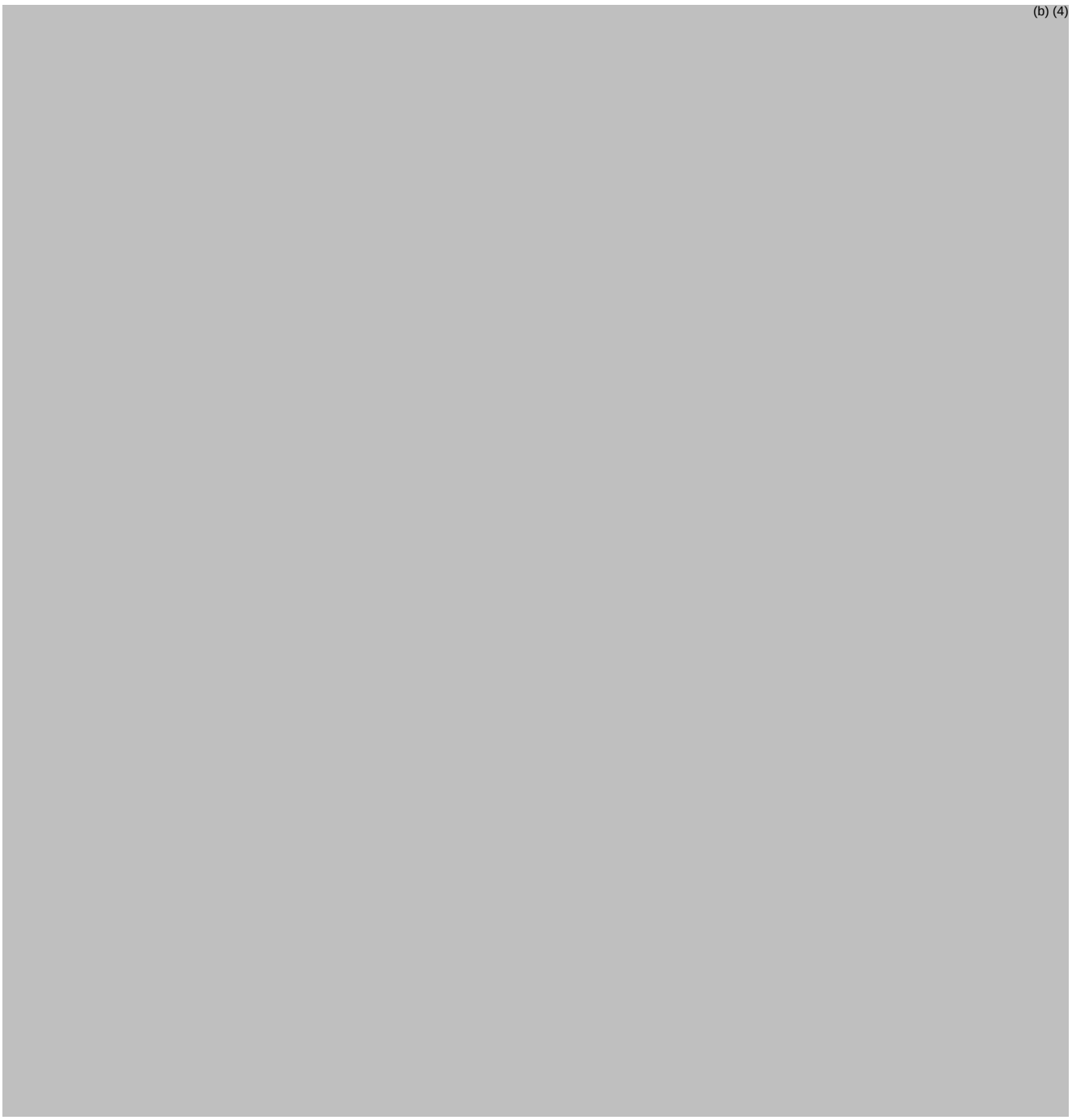

{See appended electronic signature page}

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Central Document Room/NDA 216834
Division of Neurology 1/Division Director/Teresa Buracchio
Division of Neurology 1/Deputy Division Director/Emily Freilich (Acting)
Division of Neurology 1/Medical Team Leader/Laura Jawidzik
Division of Neurology 1/Medical Officer/John Troiani
Division of Neurology 1/Project Manager/Michael Matthews
CDER/OTS/OB/DBI/Statistical Reviewer/Jinnan (Joanne) Liu
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
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OSI/DCCE/GCPAB Program Analyst/Yolanda Patague
OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

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/s/

CARA L ALFARO
07/06/2023 12:24:11 PM

PHILLIP D KRONSTEIN
07/06/2023 01:05:34 PM

JENN W SELLERS
07/06/2023 01:28:38 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	5/8/2023		
To:	Erica Keafer, Regulatory Health Project Manager		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	DRBPMI
From	Papatya Kaner OPEQ/OHT3/DHT3C/THT3C3		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C/THT3C1		
Through (Division) *Optional	CAPT. Alan M. Stevens, Assistant Director OPEQ/OHT3/DHT3C/THT3C1		
Subject	NDA 216834, Zilucoplan ICC2200748 ICCR 00868990		
Recommendation	**Filing Recommendation Date: 10/13/2022** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies		
	Mid-Cycle Recommendation Date: 4/28/2023 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 5/5/2023 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Papatya Kaner -S Digitally signed by Papatya Kaner -S Date: 2023.05.08 11:00:32 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2023.05.12 13:45:06 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 216834
Sponsor	UCB, Inc.
Drug/Biologic	Zilucoplan
Indications for Use	Treatment of generalized myasthenia gravis (gMG)
Device Constituent	Pre-Filled Syringe
Related Files	

Important Dates	
Filing	10/13/2022
74-Day Letter	N/A
Midcycle Meeting/IRs due	4/28/2023
Final Lead Device Review Memo Due	5/8/2023
PDUFA Date	8/31/2023

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

3. PURPOSE/BACKGROUND

3.1. Scope

UCB, Inc. is requesting approval of Zilucoplan. The device constituent of the combination product is a Pre-Filled Syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Technical engineering consult request for a new NME Standard Review submission for NDA 216834 received on 8/31/2022. The device component information for this NDA can be found in Module 1.2, Device Presentations Reviewer's Guide which outlines the device data organization within this submission.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

☒ Device performance
☒ Biocompatibility of the patient contacting components
☐ Sterility
☒ Stability – device performance on stability
☒ Essential Performance Requirements (EPR) Control strategy
☐ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Zilucoplan	Treatment of generalized myasthenia gravis (gMG)
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
Sequence 0001	Modules 1, 2, 3

4. DEVICE DESCRIPTION

4.1. Device Description

1 CONTAINER CLOSURE SYSTEM
1.1 Primary container closure
1.1.1 Pre-filled syringe

The primary packaging for the zilucoplan drug product consists of a 1mL long [redacted] glass prefilled syringe (PFS) fitted with a staked 29G, ½" thin wall needle. The syringe is closed using a [redacted] rubber plunger stopper. The needle is protected with a rigid needle shield (RNS) consisting of a [redacted] elastomer needle shield and a [redacted] rigid shield. Figure 1.1 provides a simplified overview of the primary packaging components.

Figure 1.1: Overview of the primary packaging components

Table 1.1: Materials of construction of the primary packaging

Component	Description	Supplier/Manufacturer
Syringe with RNS	Glass barrel: 1 mL long [redacted] glass Needle: Staked stainless steel, 29G ½" thin wall needle Needle shield: [redacted] elastomer Rigid shield: [redacted]	[redacted]
Plunger stopper	[redacted] rubber	

Material used for the glass barrel is in conformance with Ph. Eur. 3.2.1, USP <660> and JP 7.01; the needle shield with Ph. Eur. 3.2.9 and USP<381>; the plunger stopper with Ph. Eur. 3.2.9. and USP <381>. The primary packaging material components (syringe and plunger stopper) (b) (4) The tests and specifications for the syringe and the plunger stopper are provided in Section 3.2.P.7 – PFS.

1.1.2 Finished product

The PFS is assembled with functional secondary packaging to produce the finished product (zilucoplan-SS). The zilucoplan-SS device components, excluding the primary packaging components, do not have any fluid path and therefore do not have any contact with the drug product contained within the PFS. The zilucoplan-SS consists of the zilucoplan pre-filled syringe assembled with the safety syringe components. The zilucoplan-SS consists of an already marketed (b) (4) (b) (4) Needle Safety Device (NSD) which has 510(k) clearance in the USA (510(k) number (b) (4)), a plunger rod (PR) and an Add-on Finger Flange (AFF).

The function of the NSD is to protect the user from the needle following injection of the contents of the syringe. The PR allows the injection and the AFF allows ease of injection with better grasp of the SS. The safety syringe components do not have any fluid contact pathways and do not have any contact with the drug product contained within the pre-filled syringe. The zilucoplan- SS has a limited contact duration with intact skin.

1.1.2.1 Safety syringe

The zilucoplan-SS consists of the drug product in the PFS and the following device components which are shown in Figure 1.2.

- Plunger rod (PR)
- Needle safety device (NSD) (b) (4)
- Add-on finger flange (AFF)

Figure 1.2: Overview of the zilucoplan-SS

(b) (4)

The plunger rod, add-on finger flange and the needle safety device are customized components designed to improve the handling of the safety syringe by the users. Table 1.2 provides an overview of the materials of construction for each device component.

Table 1.2: Materials of construction of the device components

(b) (4)

1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

1.1 Description of the dosage form

Zilucoplan drug product is supplied as a sterile, preservative-free solution, suitable for administration by subcutaneous injection. The drug product is supplied in a 1mL long (b) (4) glass pre-filled syringe. Each single-use syringe contains zilucoplan drug substance at a nominal concentration of 40mg/mL in an iso-osmotic buffered solution of monobasic sodium phosphate/dibasic sodium phosphate, sodium chloride and water for injection (WFI). The finished product is a combination of the pre-filled syringe containing zilucoplan and the safety syringe components. It is a single-use pre-filled syringe with safety needle guard for self-administration by subcutaneous injection, available in 3 dose presentations (16.6mg, 23.0mg and 32.4mg).

All 3 dose presentations employ the same pre-filled syringe whereby dose variation is accomplished by varying the syringe fill volume. A color-coded plunger rod and carton will help differentiate each dose strength: rubine red for low, orange for medium and dark blue for high dose.

Zilucoplan drug product is manufactured to provide an extractable volume of not less than:
− 0.416mL per syringe for 16.6mg dose;
− 0.574mL per syringe for 23.0mg dose;
− 0.810mL per syringe for 32.4mg dose.

Throughout this section, when the primary container is mentioned, it is referred to as the prefilled syringe. The finished product will be the zilucoplan safety syringe device presentation (zilucoplan-SS).

1.2 Composition

The composition of zilucoplan drug product is provided in Table 1.1.

Table 1.1: Qualitative and quantitative composition

Component	Quality Standard	Function	Quantity (mg/mL)	Quantity per dose (mg)		
				16.6mg	23.0mg	32.4mg
Zilucoplan drug substance[a]	In-house specification	Active ingredient	40.00	16.6 (b) (4)	2 (b) (4)	32.40
Monobasic sodium phosphate, monohydrate	USP	(b) (4)	2.90	(b) (4)		

Table 1.1: Qualitative and quantitative composition

Component	Quality Standard	Function	Quantity (mg/mL)	Quantity per dose (mg)		
				16.6mg	23.0mg	32.4mg
Dibasic sodium phosphate, anhydrous	Ph. Eur./USP/JPE	(b) (4)	4.11	(b) (4)		
Sodium chloride	Ph. Eur./USP/JP		4.42			
Water for injection	Ph. Eur./USP-NF/JP		(b) (4)			

[a] Correspond to the free acid

(b) (4)

1.1 Description of the dosage form

The zilucoplan safety syringe device presentation (zilucoplan-SS) is a combination of the prefilled syringe containing zilucoplan and the safety syringe components. It is a single-use PFS with safety needle guard for self-administration by subcutaneous injection available in low, medium and high dose presentations (16.6mg – Figure 1.1, 23.0mg – Figure 1.2 and 32.4mg –Figure 1.3). A color-coded plunger rod and carton will help differentiate each dose strength: rubine red for low, orange for medium and dark blue for high dose.

Figure 1.1: Zilucoplan-SS with rubine red plunger rod – low dose (0.416mL)

(b) (4)

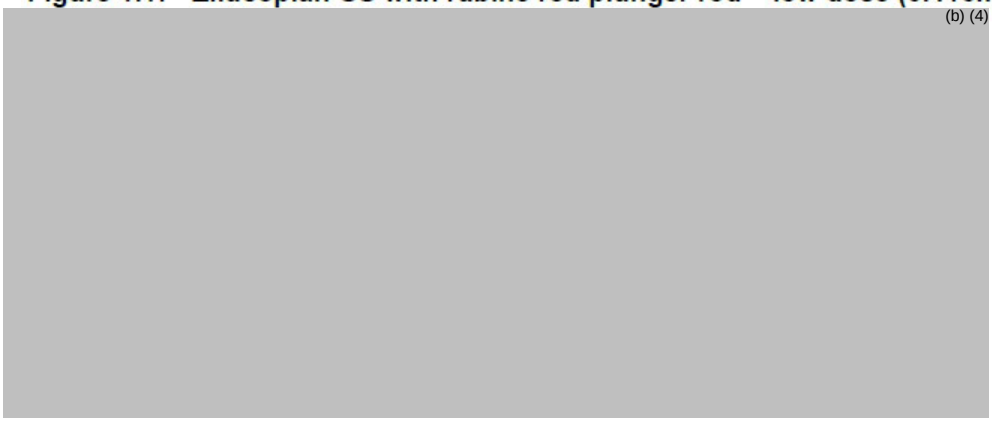
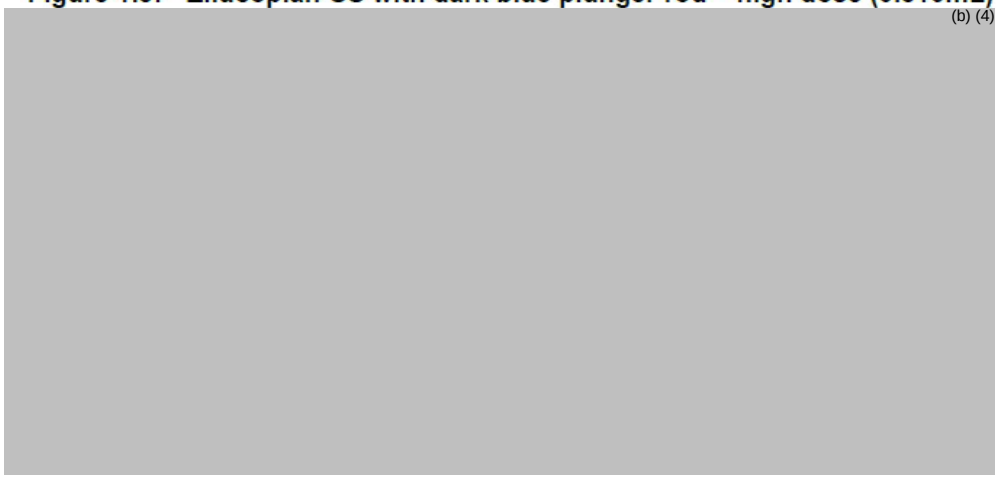


Figure 1.2: Zilucoplan-SS with orange plunger rod – medium dose (0.574mL)

(b) (4)

Figure 1.3: Zilucoplan-SS with dark blue plunger rod – high dose (0.810mL)

(b) (4)



4.2. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Device description is acceptable.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist	
Description	**Present**

		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility	X		
	Shelf Life, Aging and Transportation of EPRs	X		
Quality Systems/ Manufacturing Controls Check	Description of Quality Systems	X		
	Control Strategy provided for EPRs	X		

5.2. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☑ Yes ☐ No ☐ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☑ No Inspection Needed ☐ N/A
CDRH completed a review of the Quality Systems	☐ Yes ☑ No ☐ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in Appendix B

5.3. Filing Recommendation

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance
☑ No Inspection ☐ N/A

Site(s) needing inspection: None

Reviewer Comments
Facilities review was completed under ICCR #00869002 / ICC #2200747 on 10/19/2022. Final facilities memo is copied in Appendix B for convenience.

Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A

74-Day Letter Deficiencies: ☐ Yes ☑ No ☐ N/A

☑ **No Additional Information Requests to add**

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		**Data Adequate**		
		Yes	**No**	**N/A**
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☑	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☐	☐	☑
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☑
Needle/Sharps		**Data Adequate**		
		Yes	**No**	**N/A**
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☑	☐	☐
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☑
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☑	☐	☐
Luer Lock		**Data Adequate**		
		Yes	**No**	**N/A**
Connection	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications **(replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings	☐	☐	☑
Other		**Data Adequate**		
		Yes	**No**	**N/A**
[Other]	[Other]	☐	☐	☑

6.1.2. Device Performance Evaluation

Finished product

The release and shelf-life testing performed on the assembled safety syringes (zilucoplan-SS) are provided in Table 1.2.

Table 1.2: Release and shelf-life specifications for zilucoplan-SS

Test parameter	Release acceptance criteria	Shelf-life acceptance criteria	Method
General characteristics			
Extractable volume 16.6mg dose 23.0mg dose 32.4mg dose	NLT 0.416mL NLT 0.574mL NLT 0.810mL		Ph. Eur. 2.9.17, USP<697>, JP 6.05
Functional tests			
RNS removal force	NA[a]	NMT (b) (4) N	RNS removal force
Maximum break-loose force	NA[a]	NMT N	Break-loose/gliding force
Maximum gliding force	NA[a]	NMT N	
Activation force	NA[a]	NMT N	Activation force
Resistance to compression force	NA[a]	Pass	Resistance to compression force
Separation force	NA[a]	NLT (b) (4) N	Separation force
Visibility of drug compartment	NA[a]	(b) (4)	Spin test
Lock-out confirmation	(b) (4)		Lock-out confirmation

[a] Testing not performed at release

Table 1.10: Zilucoplan-SS finished product justification of specifications overview

Test parameter	Release acceptance criteria	Shelf-life acceptance criteria	Justification
Extractable volume 16.6mg dose 23.0mg dose 32.4mg dose	 NLT 0.416mL NLT 0.574mL NLT 0.810mL	 NLT 0.416mL NLT 0.574mL NLT 0.810mL	Ensures the required dose is delivered from the zilucoplan-SS.
RNS removal force	Not tested	NMT (b) (4) N	Ensures the user will apply adequate force to remove the RNS of the zilucoplan-SS.
Maximum break-loose force	Not tested	NMT N	Based on historical release and stability data, literature and human factor studies.
Maximum gliding force	Not tested	NMT (b) (4) N	Based on historical release and stability data, literature and human factor studies.
Activation force	Not tested	NMT (b) (4) N	To keep the force required from the user to activate the needle safety lockout mechanism to an acceptable level for the intended users.
Resistance to compression force	Not tested	Pass	Ensures the user will apply enough force to override the activated, locked guard of the safety syringe from the locked activated position to the un-activated position by pushing the body back into the guard.
Separation force	Not tested	NLT (b) (4) N	Ensures the user applies the minimum force required to separate the needle guard from the body of the SS after it has been activated.
Visibility of drug compartment	Not tested	(b) (4)	To confirm that the user can rotate the PFS inside the zilucoplan-SS to read information printed on the label and to inspect the drug content.
Lock-out confirmation	(b) (4)		To confirm the effective lock-out of the zilucoplan-SS in the locked activated position.

Table 1.10: Zilucoplan-SS finished product justification of specifications overview

Test parameter	Release acceptance criteria	Shelf-life acceptance criteria	Justification
	(b) (4)		

6.1.3. Stability Review Summary

Shelf-life:	36 months at 5°C±3°C
Storage **conditions**:	A shelf-life of 36 months is proposed for zilucoplan drug product at the long-term storage temperature of 5°C±3°C. Additionally, a period of storage for 3 months at up to 30°C within the 36-months shelf-life is proposed.
Time period and storage conditions provided for accelerated aging:	Accelerated aging performed at 25°C ± 2°C / 60% ± 5% RH and 30°C ± 2°C / 65% ± 5% RH or 30°C ± 2°C / 75% ± 5% RH and stressed aging performed at 40°C ± 2°C / 75% ± 5% RH storage conditions. Additionally, to support storage at higher temperatures during the shelf-life period (i.e., for patient convenience), additional accelerated testing (30°C+/-2°C/75+/-5%RH) was performed on aged material (after 30 or 42 months of real-time aging).
Time period and storage conditions provided for real-time aging:	Real-time aging at 5°C ± 3°C for 42 months

*Endpoint evaluation is provided in section 6.1.2.

1.1 Stability summary and conclusion

1.1.1 Drug product

A shelf-life of 36 months is proposed for zilucoplan drug product at the long-term storage temperature of 5°C±3°C. Additionally, a period of storage for 3 months at up to 30°C within the 36-months shelf-life is proposed.

1.1.1.1 Summary of drug product stability studies

Batches of zilucoplan drug product, in pre-filled syringes (PFS) manufactured by (b) (4) (b) (4) and (b) (4) have been placed on stability. The stability studies are being performed at the long-term (5°C ± 3°C), accelerated (25°C ± 2°C / 60% ± 5% RH and 30°C ± 2°C / 65% ± 5% RH or 30°C ± 2°C / 75% ± 5% RH) and stressed (40°C ± 2°C / 75% ± 5% RH) storage conditions. Additionally, to support storage at higher temperatures during the shelf-life period (i.e., for patient convenience), additional accelerated testing (30°C+/-2°C/75+/-5%RH) was performed on aged material (after 30 or 42 months of long-term storage).

Details of the zilucoplan drug product batches placed on stability are provided in Table 1.1. The stability protocols detailing the stability storage conditions and tests applied at scheduled testing time points are provided in Table 1.2 for drug product batches manufactured at (b) (4), Table 1.3, Table 1.4 and Table 1.5 for batches manufactured at (b) (4) Table 1.6 for room temperature study following storage of 42 months at 5°C ± 3°C and, Table 1.7 for room temperature study following storage of 30 months at 5°C ± 3°C. Stability data for long term study, accelerated and stressed storage conditions are presented in Section 3.2.P.8.3.

In addition, forced degradation and photostability studies have been performed. The forced degradation study conditions are summarized in Table 1.8 and the photostability stress conditions are provided in Table 1.9.

Moreover, a thermal cycling stability study was performed on one of the PPQ batches of drug product (RBUD05). The PFS were subjected to 3 consecutive cycles of:

Cycle 1: 2 days at -20°C followed by 2 days at +30°C±2°C/75%RH±5%RH
Cycle 2: 2 days at -20°C followed by 2 days at +30°C±2°C/75%RH±5%RH
Cycle 3: 2 days at -20°C followed by 2 days at +30°C±2°C/75%RH±5%RH

The commercial drug product specification is detailed in Section 3.2.P.5.1. The clinical specifications were in place at the time of these stability studies. The test parameters part of the commercial specification was reported against the commercial acceptance criteria and the test parameters not part of commercial specification were reported against the clinical acceptance criteria.

1.1.1.2 Drug product stability study conclusions

The 36-month shelf life is supported by long-term data (42 months) at 5°C±3°C, with drug product manufactured at (b) (4). Comparability between the (b) (4) and (b) (4) drug product has been demonstrated (see Section 3.2.P.2.3 – PFS). This shelf-life is further confirmed by long-term data of primary registration stability batches (30 months on 6 batches and 24 months on 3 batches) at 5°C±3°C for drug product manufactured at (b) (4) All stability data meet the proposed commercial specification acceptance criteria, and all trends support the 36-month shelf-life for drug product at 5°C±3°C.

Statistical trend analyses, performed on the primary registration stability batches for assay and purity test parameters estimated the shelf-life of higher than 36 months, supporting the proposed shelf-life of 36 months.

Stability data and shelf-life predictions from the shelf-life study at higher temperatures (25°C±2°C/60%±5%RH and 30°C±2°C/75%±5%RH) support a storage of 3 months at up to 30°C, at the final point of use within the product shelf-life (36 months).

Forced degradation studies confirmed the assay and purity method (b) (4) are stability indicating and enabled to identify the potential degradation products.

Based on the photostability and photokinetic results, zilucoplan drug product has been shown to be sensitive to light, indicating that the product should be protected from light and the secondary packaging of drug product, protects the drug product from light-induced degradation.

The zilucoplan drug product was also evaluated after 3 thermal cycles (at least 2 days at -20°C followed by 2 days at +30°C±2°C/75%RH±5%RH) and subsequent long-term storage at 5°C±3°C. No significant changes were observed in any tested parameter (except appearance clarity and degree of opalescence) monitored after the thermal cycle. The initial data support temperature excursions, including temperatures down to -20°C, which may occur during shipping.

1.1.2 Finished product

The PFS is assembled into a single-use safety syringe to become the combination product (zilucoplan-SS). The zilucoplan-SS components do not have any fluid path and do not have any contact with the zilucoplan solution contained within the PFS. Therefore, the stability of the zilucoplan drug product in the PFS is not impacted by assembly into the zilucoplan-SS.

The commercial specification for the zilucoplan-SS is detailed in section 3.2.P.5.1 – SS. The specifications are justified in section 3.2.P.5.6 – SS and the overall control strategy is defined in section 3.2.P.2.3 – SS. The specifications applicable to each stability study are presented in Module 3.

1.1.2.1 Shelf-life of the device components and pre-assemblies

(b) (4)

Table 1.10: Accelerated aging strategy

Aged components	Precondition temperature	Timepoint at preconditioning temperature (hours)	Cumulative shelf life supported
Passive needle guard pre-assemblies[a]	(b) (4)		
Device components and pre-assemblies			

[a] Representative of the device components and pre-assemblies of the zilucoplan-SS.

1.1.2.2 Long-term stability

Long-term stability testing is being performed to generate functional stability data on process performance qualification (PPQ) batches of the zilucoplan-SS, (b) (4) at the long-term storage condition of 5±3°C. The protocol is provided in Table 1.11. In addition, zilucoplan-SS will be stored at 30±2°C for 4, 5 and 7 months following the storage of zilucoplan-SS at 5°C±3°C for 32 months as per the protocol provided in Table 1.12. The details of the batches placed on stability are provided in Table 1.13, Table 1.14 and Table 1.15 respectively.

Table 1.11: Zilucoplan-SS long-term stability testing timepoints

Test parameter	Study conditions	Samples stored at 5±3°C					
		Timepoints (months)					
	Initial	3	6	12	24	30	36
Extractable volume	X	X	X	X	X	X	X
RNS removal force	X	X	X	X	X	X	X
Maximum break-loose force	X	X	X	X	X	X	X
Maximum gliding force	X	X	X	X	X	X	X
Activation force	X	X	X	X	X	X	X
Resistance to compression force	X	X	X	X	X	X	X
Separation force	X	X	X	X	X	X	X
Visibility of drug compartment	X	X	X	X	X	X	X
Lock-out confirmation	X	X	X	X	X	X	X
Container Closure Integrity (CCIT) [a]	X	X	X	X	X	X	X

[a] Container closure integrity test (CCIT) testing was performed for the PPQ batches and will not be part of the commercial specification of the zilucoplan-SS.
X = tested

Table 1.12: Additional storage condition at 30±2°C/75%±5%RH (after 32 months at 5±3°C)

Test parameter	Samples stored at 30±2°C/75%±5%RH (after 32 months at 5±3°C)		
	Timepoints (months)		
	4	5	7
Extractable volume	X	X	X
RNS removal force	X	X	X
Maximum break-loose force	X	X	X
Maximum gliding force	X	X	X
Activation force	X	X	X
Resistance to compression force	X	X	X
Separation force	X	X	X
Visibility of drug compartment	X	X	X
Lock-out confirmation	X	X	X

X = tested

Table 1.13: Zilucoplan-SS 16.6mg (0.416mL) batch details for the long-term stability study

Batch Number	Date of assembly	Batch size (units)	PFS batch number	Latest data available
326240	14 Apr 2021	(b) (4)	RBUA011	6 months
326618	20 Apr 2021		RBUA011	6 months

Table 1.14: Zilucoplan-SS 23.0mg (0.574mL) batch details for the long-term stability study

Batch Number	Date of assembly	Batch size (units)	PFS batch number	Latest data available
326617	20 Apr 2021	(b) (4)	RBUA012	6 months
326244	17 May 2021		RBUA012	6 months

Table 1.15: Zilucoplan-SS 32.4mg (0.810mL) batch details for the long-term stability study

Batch number	Date of assembly	Batch size	PFS batch number	Latest available data
323681	5 Mar 2021	(b) (4)	RBTJ02	6 months
326616	19 Apr 2021		RBTJ02	6 months

1.2 Post-approval stability protocol and stability commitment

1.2.1 Drug product

The applicant commits to continue the ongoing long-term stability studies in accordance with the protocol provided in Section 3.2.P.8.1 – PFS.

In addition, annually at least one batch of zilucoplan drug product will be placed on stability and monitored at the intended storage condition of 5±3°C, in accordance with the post-approval stability protocol provided in Table 1.16. To

ensure stability data is generated for each dose presentation, the 3 different product fill volumes will be alternated on stability (1 fill volume per year and each fill volume every 3 years). In the event that zilucoplan drug product batches are not manufactured during a given year; a stability study is not required.

The applicant will inform regulatory authorities of any confirmed out-of-specification results.

Table 1.16: Post-approval annual stability protocol for zilucoplan drug product

Storage Condition	Time points (months)			
	0	12	24	36
5°C±3°C	X	XY	XY	XY

Where:
X = Appearance - degree of coloration, appearance - clarity and degree of opalescence, pH, assay by ultra-high performance liquid chromatography (UHPLC), purity by UHPLC, visible particulates, sub-visible particulates
Y = Container closure integrity test

1.2.2 Finished product

The applicant commits to continue the ongoing long-term stability studies in accordance with the protocol provided in Section 3.2.P.8.1 – SS.

In addition, annually at least one batch of zilucoplan-SS will be placed on stability and monitored at the intended storage condition of 5±3°C, in accordance with the post-approval stability protocol provided in Table 1.17. To ensure stability data is generated for each dose presentation, the 3 different product fill volumes will be alternated on stability (1 fill volume per year and each fill volume every 3 years). In the event that zilucoplan-SS batches are not assembled during a given year; a stability study is not required.

The applicant will inform regulatory authorities of any confirmed out-of-specification results.

Table 1.17: Post-approval annual stability protocol for zilucoplan-SS

Storage condition	Time points (months)			
	0	12	24	36
5°C±3°C	X	XY	XY	XY

Where:
X = Extractable volume and lock out confirmation
Y = Rigid needle shield removal force, maximum break-loose and maximum gliding force, activation force, resistance to compression force, separation force and visibility of drug compartment

1.3 Stability data

1.3.1 Drug product

An overview of the zilucoplan drug product stability studies discussed in Module 3 is provided in Table 1.18. The full data are provided in Section 3.2.P.8.3 – PFS.

Table 1.18: Details of batches used for stability studies of zilucoplan PFS

Batch #	Dose presentation	Storage Condition	Data available	Study status
0000487952	16.6mg	5±3°C	42	Complete
		25±2°C/60±5% RH	36	Complete
		30±2°C/65±5% RH	36	Complete
		40±2°C/75±5% RH	9	Complete
0000486005	23.0mg	5±3°C	42	Complete
		25±2°C/60±5% RH	36	Complete
		30±2°C/65±5% RH	36	Complete
		40±2°C/75±5% RH	9	Complete
0000485207	32.4mg	5±3°C	42	Complete

Table 1.18: Details of batches used for stability studies of zilucoplan PFS

Batch #	Dose presentation	Storage Condition	Data available	Study status
		25±2°C/60±5% RH	36	Complete
		30±2°C/65±5% RH	36	Complete
		40±2°C/75±5% RH	9	Complete
0000485865	32.4mg	5±3°C	36	Complete
		30±2°C/65±5% RH	6	Complete
RBSA011	16.6mg	5±3°C	30	In-progress
		25±2°C/60±5% RH	24	Complete
		30±2°C/75±5% RH	24	Complete
		40±2°C/75±5% RH	9	Complete
RBSA012	23.0mg	5±3°C	30	In-progress
		25±2°C/60±5% RH	24	Complete
		30±2°C/75±5% RH	24	Complete
		40±2°C/75±5% RH	9	Complete
RBSA013	32.4mg	5±3°C	30	In-progress
		25±2°C/60±5% RH	24	Complete
		30±2°C/75±5% RH	24	Complete
		40±2°C/75±5% RH	9	Complete
RBSC021	16.6mg	5±3°C	30	In-progress
		25±2°C/60±5% RH	24	Complete
		30±2°C/75±5% RH	24	Complete
		40±2°C/75±5% RH	9	Complete
RBSC022	23.0mg	5±3°C	30	In-progress
		25±2°C/60±5% RH	24	Complete
		30±2°C/75±5% RH	24	Complete
		40±2°C/75±5% RH	9	Complete
RBSC023	32.4mg	5±3°C	30	In-progress
		25±2°C/60±5% RH	24	Complete
		30±2°C/75±5% RH	24	Complete
		40±2°C/75±5% RH	9	Complete

Table 1.18: Details of batches used for stability studies of zilucoplan PFS

Batch #	Dose presentation	Storage Condition	Data available	Study status
RBSG031	16.6mg	5±3°C	24	In-progress
		25±2°C/60±5% RH	24	In-progress
		30±2°C/75±5% RH	24	In-progress
		40±2°C/75±5% RH	9	Complete
RBSG032	23.0mg	5±3°C	24	In-progress
		25±2°C/60±5% RH	24	In-progress
		30±2°C/75±5% RH	24	In-progress
		40±2°C/75±5% RH	9	Complete
RBSG033	32.4mg	5±3°C	24	In-progress
		25±2°C/60±5% RH	24	In-progress
		30±2°C/75±5% RH	24	In-progress
		40±2°C/75±5% RH	9	Complete
RBTC011	23.0mg	5±3°C	9	In-progress
		25±2°C/60±5% RH	9	In-progress
		30±2°C/75±5% RH	9	In-progress
RBTC012	32.4mg	5±3°C	9	In-progress
		25±2°C/60±5% RH	9	In-progress
		30±2°C/75±5% RH	9	In-progress
RBUC03	32.4mg	5±3°C	12	In-progress
RBUC04	23.0mg	5±3°C	12	In-progress
RBUD05	16.6mg	5±3°C	12	In-progress
RBUD06	32.4mg	5±3°C	12	In-progress
RBUF07	16.6mg	5±3°C	9	In-progress
0000487952	16.6mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
0000486005	23.0mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
0000485207	32.4mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/65±5% RH		In-progress

Table 1.18: Details of batches used for stability studies of zilucoplan PFS

Batch #	Dose presentation	Storage Condition	Data available	Study status
RBSA011	16.6mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
RBSA012	23.0mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
RBSA013	32.4mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
RBSC021	16.6mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
RBSC022	23.0mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress
RBSC023	32.4mg	25±2°C/60±5% RH	3	In-progress
		30±2°C/75±5% RH		In-progress

1.3.2 Finished product

A summary of zilucoplan-SS stability studies discussed in Module 3 is provided in Table 1.19 and Table 1.20. The full data are provided in Section 3.2.P.8.3 – SS.

Table 1.19: Summary of zilucoplan-SS [redacted](b) (4) stability studies

Storage condition	Dose presentation (mg)	Batch number	Data available
Long term (5°C±3°C)	16.6mg	326618	6 months
	23.0mg	326617	6 months
	32.4mg	326616	6 months

Table 1.20: Summary of zilucoplan-SS [redacted](b) (4) stability studies

Storage condition	Dose presentation (mg)	Batch number	Data available
Long term (5°C±3°C)	16.6mg	326240	6 months
	23.0mg	326244	6 months
	32.4mg	323681	6 months

6.1.4. Biocompatibility Evaluation

☑ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]

☐ Biocompatibility was not evaluated **because**: Click or tap here to enter text.

Reviewer Comment

The Zilucoplan-SS consists of zilucoplan pre-filled syringe assembled with 510(k)-cleared [redacted](b) (4) Needle Safety Device [redacted](b) (4) in addition to customized components, plunger rod (PR) and add-on finger flange (AFF). The [redacted](b) (4) Needle Safety Device's biocompatibility has been evaluated under its 510(k). Sponsor addressed the biocompatibility of the plunger rod (PR) and add-on finger flange (AFF) in their response to Midcycle Deficiency #1-RESOLVED. Please see Section 6.2 below for the deficiency and Sponsor's response.

6.1.5. Sterility Evaluation

☑ Sterility of the [redacted] Needle Safety Device, plunger rod and add-on finger flange **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)

☑ Sterility of the prefilled syringe with needle is not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

Reviewer Comments

- The [redacted] Needle Safety Device is provided [redacted] which is acceptable since it is only skin contacting and mounted on the exterior of the prefilled syringe. In their response to Midcycle Deficiency #1-RESOLVED, Sponsor clarified that the plunger rod (PR) and add-on finger flange (AFF) are [redacted] Please see Section 6.2 below for the deficiency and Sponsor's response.
- We issued Midcycle Deficiency #2-RESOLVED for how the sterility of the syringe glass barrel with staked needle, rigid needle shield (RNS) and plunger stopper [redacted]

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments We issued Midcycle Deficiencies #1-2 to address our biocompatibility and sterility concerns.		
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 4/28/2023	**Date/Sequence Received: 5/3/2023**
Midcycle Deficiency #1	You stated that the Zilucoplan-SS consists of zilucoplan pre-filled syringe assembled with 510(k)-cleared [redacted] Needle Safety Device [redacted] in addition to customized components, plunger rod (PR) and add-on finger flange (AFF). However, it is unclear whether the plunger rod and add-on finger flange are sterilized components and whether they have been evaluated for their biocompatibility. Please provide sterility and biocompatibility assessment of these components for our review.	
Sponsor Response	[redacted]	

	(b) (4)
Reviewer Comments	Biocompatibility reports of the plunger rod (PR) and add-on finger flange (AFF) included cytotoxicity, sensitization and irritation testing, which acceptable for these skin-contacting components.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: **4/28/2023**	**Date/Sequence Received:** **5/3/2023**
Midcycle Deficiency #2	You indicated that the syringe glass barrel with staked needle and rigid needle shield (RNS) (b) (4)	
Sponsor Response	(b) (4)	
Reviewer Comments	Sponsor provided validation (b) (4); response is acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

7. CONTROL STRATEGY REVIEW

(b) (4)

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(b) (4)

[redacted]

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments We issued Midcycle Deficiency #3 to understand why Sponsor (b) (4) [redacted] Please see below for the deficiency and Sponsor's response.		
CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 4/28/2023	**Date/Sequence Received:** 5/3/2023
Midcycle Deficiency #3	(b) (4) [redacted]	
Sponsor Response		

	(b) (4)
Reviewer Comments	Sponsor explained (b) (4) Sponsor's rationale is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

N/A

8.2. Mid-Cycle Information Requests sent on 4/28/2023

1) You stated that the Zilucoplan-SS consists of zilucoplan pre-filled syringe assembled with 510(k)-cleared (b) (4) (b) (4) Needle Safety Device (b) (4) in addition to customized components, plunger rod (PR) and add-on finger flange (AFF). However, it is unclear whether the plunger rod and add-on finger flange are sterilized components and whether they have been evaluated for their biocompatibility. Please provide sterility and biocompatibility assessment of these components for our review.

2) You indicated that the syringe glass barrel with staked needle and rigid needle shield (RNS) (b) (4)

3) (b) (4)

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on *Click or tap to enter a date.*

N/A

9. APPENDIX B: FACILITIES & QUALITY SYSTEMS REVIEW

9.1. Facility Inspection Report Review

Table 1.2: List of Manufacturing and Testing Sites

Site Name	Site Address	FEI/DUNS	Manufacturing Step(s) or Type of Testing
[redacted] (b) (4)			
UCB Pharma S.A.	Chemin du Foriest, 1420 Braine-l'Alleud, Belgium	FEI: 3003909356 DUNS: 372274485	Drug substance: stability testing
[redacted] (b) (4)			

Site Name	Site Address	FEI/DUNS	Manufacturing Step(s) or Type of Testing
[redacted] (b) (4)			
UCB Pharma S.A.	Chemin du Foriest, 1420 Braine-l'Alleud, Belgium	FEI: 3003909356 DUNS: 372274485	Drug product: quality control testing, storage, batch release, and stability testing Finished product: Assembly, secondary packaging and labeling, quality control testing, batch release, and stability testing

Information request sent to Sponsor on 9/26/2022:

In Sequence 001, Module 1.2 Cover Letters, you provided a list of clinical and manufacturing sites. However, it is unclear to us which sites are responsible for major activities related to the manufacturing and testing of the final combination involving device constituent parts. Please clearly identify the site that is responsible for device manufacturing, development and testing.

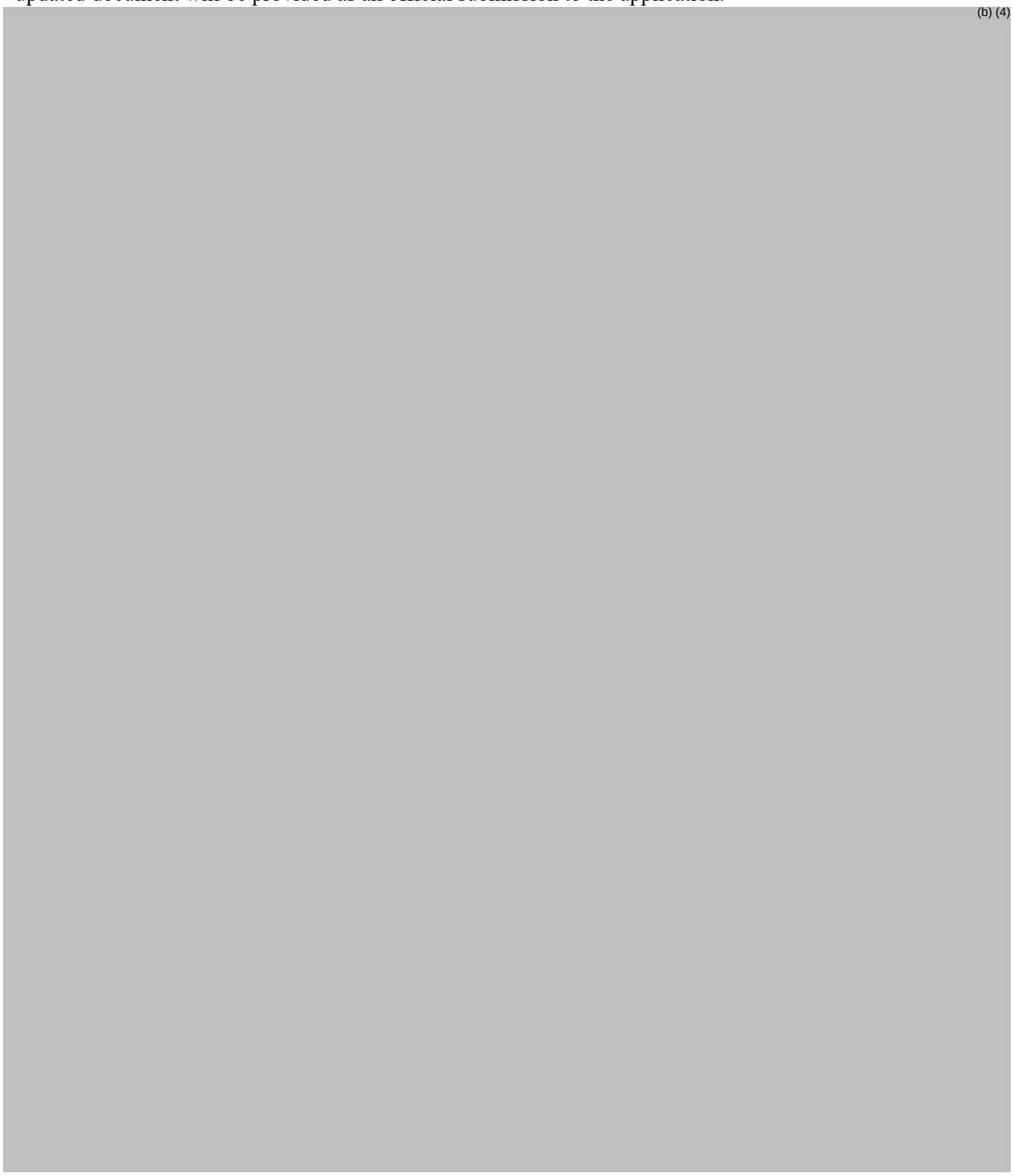
Sponsor response received on 9/27/2022:

UCB Pharma S.A. in Braine l'Alleud, Belgium is responsible for the manufacture, development and testing of the final combination product, also referred to as the "finished product" throughout the application.

The list of clinical and manufacturing sites provided in Sequence 001, Module 1.2 Cover Letters has been updated to define the terms "drug product" (zilucoplan solution in a pre-filled syringe) and "finished product" (drug product assembled in a needle safety device).

A revised version of the list of clinical and manufacturing sites is attached in this e-mail. This clarification and the updated document will be provided as an official submission to the application.

(b) (4)



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(b) (4)

Reviewer Comments

1. Facilities review was completed under ICCR #00869002 / ICC #2200747 on 10/19/2022. Final facilities memo is copied above for convenience.
2. Please note that CDRH facilities review was conducted only for the sites involved in drug product manufacturing highlighted above in Table 1.2; facilities review for drug substance manufacturing sites is deferred to CDER.
3. An analysis of the inspection history for (b) (4) showed that these facilities have not been inspected in the past two years. However, a device inspection is not required for (b) (4) facilities because they are not responsible for major activities related to the manufacturing and development of the device constituent part.
4. UCB Pharma S.A. (FEI: 3003909356) is responsible for drug product quality control testing, storage, batch release, and stability testing, in addition to final finished product assembly, secondary packaging and labeling, quality control testing, batch release, and stability testing. An inspection for UCB Pharma S.A. is not required because a recent 2022 device inspection of the firm was found acceptable.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☑ Yes	☐ No

9.2. Quality Systems Documentation Review

N/A

9.3. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments We sent one interactive deficiency to the Sponsor on 9/26/2023, please see below.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	Date/Sequence Received:

	9/26/2022	9/27/2022
Information Request #1	In Sequence 001, Module 1.2 Cover Letters, you provided a list of clinical and manufacturing sites. However, it is unclear to us which sites are responsible for major activities related to the manufacturing and testing of the final combination involving device constituent parts. Please clearly identify the site that is responsible for device manufacturing, development and testing.	
Sponsor Response	UCB Pharma S.A. in Braine l'Alleud, Belgium is responsible for the manufacture, development and testing of the final combination product, also referred to as the "finished product" throughout the application. The list of clinical and manufacturing sites provided in Sequence 001, Module 1.2 Cover Letters has been updated to define the terms "drug product" (zilucoplan solution in a pre-filled syringe) and "finished product" (drug product assembled in a needle safety device). A revised version of the list of clinical and manufacturing sites is attached in this e-mail. This clarification and the updated document will be provided as an official submission to the application.	
Reviewer Comments	Sponsor clarified that UCB Pharma S.A. in Braine l'Alleud, Belgium is responsible for the manufacture, development and testing of the final finished combination product.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

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/

ERICA F KEAFER
05/12/2023 02:46:40 PM

IMMUNOGENICITY ASSESSMENT

Application Type	NDA
Application Number	216834
Submit Date	08/31/2022
Received Date	12/06/2022
Division/Office	DN1
Review Completion Date	05/01/2023
Product Code Name	RA101495
Proposed Proper Name[1]	Zilucoplan
Proposed Proprietary Name[1]	
Pharmacologic Class	Synthetic peptide with an attached ethylene glycol moiety (C5 inhibitor)
Applicant	UBC, Inc
Applicant Proposed Indication(s)	Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive

Immunogenicity Assessors

Primary Assessor(s)	Ha Na Lee PhD
Secondary Assessor (s)	Mohanraj Manangeeswaran, PhD
Tertiary Assessor (s)	Daniela Verthelyi, MD PhD

Immunogenicity Consult request

DN1 requested OBP to review the validation reports for anti-drug antibody (ADA, Validation report # NCD3824) and anti-PEG antibody (APA, validation report # NCD3825) assays regarding NDA216834.

Assessor Recommendation:

The sponsor supplied validation exercises for two immunoassays to measure the presence of ADA to Zilucoplan and PEG. These assays have deficiencies. In addition, they were unable to develop assays to characterize the presence of neutralizing antibodies (Weisslab assay, RBC lysis assay and cell-based assay).

- The ADA assay and the corresponding validation exercise has deficiencies, including an undetermined sensitivity due to the assay format and choice of suitability controls. Specifically, the use of a rabbit polyclonal antibodies as positive control and anti-rabbit specific secondary antibodies did not allow for quantification of ADA bound by anti-human antibodies. Further, data provided in the IR suggests that the sensitivity of the 2ry Abs for human immunoglobulins, which appears to be between 100 and 1000ug/ml, does not support the stated sensitivity of the assay (19.4ng/ml). The available data, however, suggests that the incidence and titers of ADA are low, and no changes in PK/PD were observed over time (to be confirmed by the clinical pharmacology reviewer in OCP). Moreover, it is important to note

that the immunogenicity risk for this product is low as it is a small (15 amino acid), synthetic and macrocyclic peptide and anti-Zilucoplan antibodies are not expected to cross-react or cross-neutralize endogenous targets. **Therefore, we consider that there is no need to ask the sponsor to re-develop the assay and re-test the samples unless there is PK and PD or clinical data that suggests that there is clinical impact.**

- The Neutralizing antibody assay was not developed and no data was provided, however, a neutralizing antibody assays may not be needed in this case as:

1. Anti-Zilucoplan antibodies are not expected to neutralize an endogenous target.

2. No changes in PK/PD were observed over time (to be confirmed by the clinical pharmacology reviewer in OCP).

3. The incidence of subjects that develop ADA to Zilucoplan appears to be low, which is concordant with its predicted immunogenicity potential.

Therefore, the requirement for NAB assessment will be waived and a PMC will not be issued unless there are indications from the clinical data that one may be needed.

2. Review

Document Reviewed	Link to Document	Submission Date
Validation of an analytical method for the determination of anti-Zilucoplan antibodies (ADA) in human serum by LBA	\\CDSESUB1\EVSPROD\nda216834\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ncd3824\ncd3824rep.pdf	08/31/2022
Validation of an analytical method for the determination of anti-PEG_Zilucoplan antibodies (ADA) in human serum by LBA	\\CDSESUB1\EVSPROD\nda216834\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ncd3825\ncd3825rep.pdf	08/31/2022
Integrated summary of immunogenicity	\\CDSESUB1\EVSPROD\nda216834\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gmg\5353-rep-analys-data-more-one-stud\isi-mg\isi-zilucoplan-mg.pdf	08/31/2022

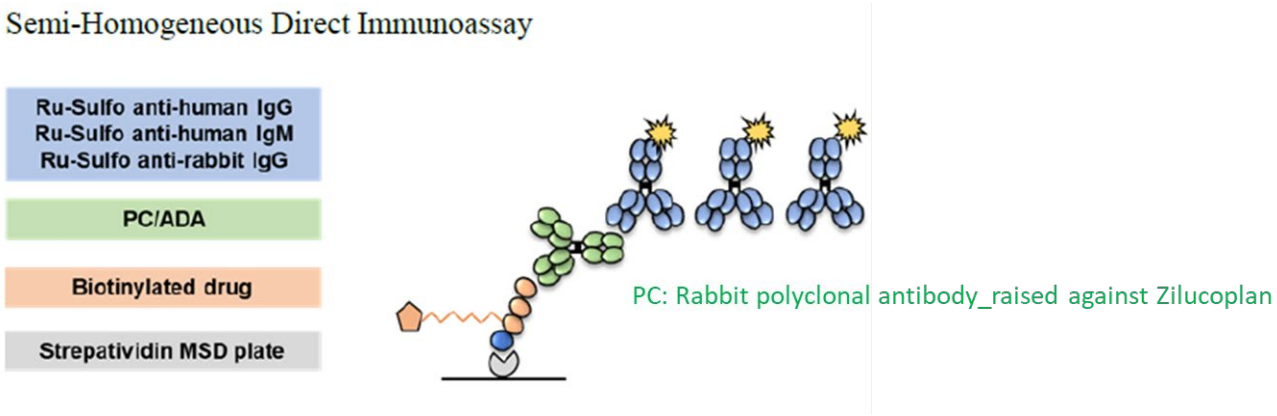
Validation of Anti-Drug Antibody Assays

The sponsor has provided validation exercises for the detection of ADA against Zilucoplan and PEG but no a Nab assays. These assays are multi-tiered with a screening, confirmatory, and titering component, however, NAb assays (the Weisslab assay, RBC lysis assay and cell-based assays) were inadequate due to drug and target tolerance issues.

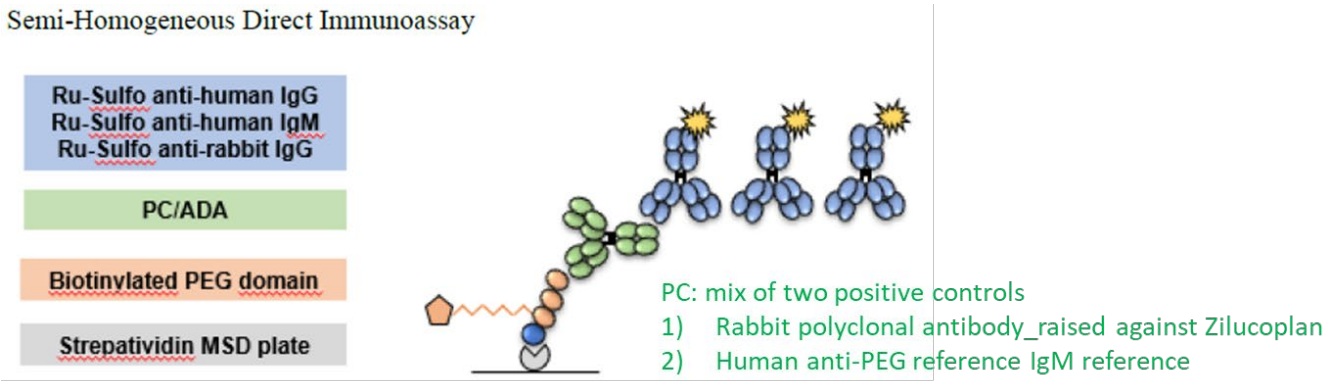
Method Principle

A brief description of each assay is given below and tables which detail the key assay parameters are given below for each assay.

Drug product:
ADA against Zilucoplan were measured using a direct immune binding assay. Samples were pre-treated with 300mM glycine (pH2.0) for acid dissociation. ADA were captured with immobilized biotinylated Zilucoplan (0.05µg/ml). The presence of ADA was detected using specific secondary antibodies for human IgG and IgM. The read out is ECL. The MRD of the assay is 1:100



PEG specific:
ADA against the PEG portion of Zilucoplan (PEG_Zilucoplan) were measured using a direct immune binding assay. Samples were pre-treated with 300mM glycine (pH2.0) for acid dissociation. ADA were captured with immobilized $dPEG_{24}$-Biotin acid (0.1µg/ml). The presence of ADA was detected using specific secondary antibodies for human IgG and IgM. The read out is ECL. The MRD of the assay is 1:100



Validation Exercises

Critical assay parameters are summarized below for each assay.

Validation Parameter	**Validation of an analytical method for the determination of anti-Zilucoplan antibodies (ADA) in human serum by LBA** VAM-ADA-LBA-Zilucoplan-Human Serum-v.1.0 Used in studies: MG0011, MG0011 (on-going)	Assessor Comment
Contract Research Org	UCB Biopharma	
Assay principle	A direct semi-homogeneous immunoassay on the MESO Quickplex SQ120 platform (ECL)	*Will detect both human IgG and IgM in human serum samples*
Sample Pretreatment (Acid dissociation)	Samples were diluted at 1:10 in 300mM Glycine (pH2.0) for 1hr.	
Positive control (PC)	Rabbit polyclonal antibody raised against Zilucoplan Antibodies diluted in a human serum matrix pool.	*A human PC would be more appropriate as a rabbit Ab cannot be detected by the same 2ry Abs.,*
PC Dose Curve and Hook Effect	No hook effect was observed up to 188000ng/mL. PC dilution curve used to determine the sensitivity	*Acceptable since zilucoplan plasma concentrations over time do not exceed 188000 ng/mL*
LPC	19.4 ng/ml	*1% failure rate in the screening and confirmatory assays, so acceptable*
MPC	2000 ng/ml	
HPC	188000 ng/ml	
Matrix and NC	human serum matrix pool.	
MRD	1:100 - 1:10 dilution with acid - 1:10 dilution with capture solution which is composed of 1.5M Tris pH9.5/5% rat serum	
Screening cut- point (SCP) (non-parametric, multiplicative, 95% upper limit)	Floating cut-point 1.81 Robust Parametric method using log-transformed normalized data	*5% FPR* *In-study FPR: 13.78% (after exclusion of outliers, 9.52%)* *Acceptable*
Confirmatory cut-point (CCP) (% inhibition, Fixed, 99% upper limit)	Fixed cut-point 35.2% Parametric approach using % inhibition data in drug displacement assay	*1% FPR.* *In-study FPR: 0.65% (after exclusion of outliers, 0.33%)* *There is difference in the means and variance of % inhibition across the runs, but no biological relevance associated with these differences* *Acceptable*
Titer Cut Point (TCP)	1.81	*95% upper limit*

		TCP factor obtained with the highest FPR yielding MSR<2.5 is selected
Assay Drug tolerance	Screening assay: HPC (188000ng/mL): 25µg/mL MPC (2000ng/mL): 25µg/mL PC (250ng/mL): 25µg/mL PC (100ng/mL): 25µg/mL LPC (19.4ng/mL): 0µg/mL PC (5.00ng/mL): 0µg/mL Confirmatory assay: HPC (188000ng/mL): 25µg/mL MPC (2000ng/mL): 25µg/mL PC (250ng/mL): 25µg/mL PC (100ng/mL): 25µg/mL LPC (19.4ng/mL): 5µg/mL PC (5.00ng/mL): 0µg/mL (C_{trough} levels expected around 10 to 14 ug/mL ZLP)	
Sensitivity (95% CI)	Screening 15.4ng/ml Confirmatory 8.34ng/ml	
Repeatability/Intra-assay variability	Screening (signal) NC 6.35 %CV LoPC 9.16 %CV MePC 5.51 %CV HiPC 7.01 %CV Confirmatory (% inhibition) NC N/A LoPC 8.01 %CV MePC 0.41 %CV HiPC 1.28 %CV	*Lower than 20% so acceptable*
Intermediate Precision (IP)/inter-assay variability	Screening (signal) NC 12.2 %CV LoPC 16.1 %CV MePC 14.8 %CV HiPC 14.9 %CV Confirmatory (% inhibition) NC N/A LoPC 10.9 %CV MePC 0.42 %CV HiPC 1.40 %CV	*Lower than 20% so acceptable*

<table>
<tr><td>Selectivity</td><td><table>
<tr><th>Assay Type</th><th>Population</th><th>Cut-point</th><th>PC conc (ng/mL)</th><th>Sample Number Meeting Acceptance Criteria</th></tr>
<tr><td rowspan="2">Screen</td><td rowspan="2">Healthy</td><td rowspan="2">1.81</td><td>Blank</td><td>10/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
<tr><td rowspan="2">Confirm</td><td rowspan="2">Healthy</td><td rowspan="2">35.2</td><td>Blank</td><td>10/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
<tr><td rowspan="2">Screen</td><td rowspan="2">Myasthenia Gravis</td><td rowspan="2">1.81</td><td>Blank</td><td>8/10</td></tr>
<tr><td>LPC</td><td>9/10</td></tr>
<tr><td rowspan="2">Confirm</td><td rowspan="2">Myasthenia Gravis</td><td rowspan="2">35.2</td><td>Blank</td><td>10/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
</table></td><td>In screening assay, Ind 01 and 08 in mGV patients is tested positive in blank but the signal is increased when spiked. Ind05 in mGV patients is tested negative when assessed blank and spiked.
At least 80% of samples fulfill acceptance criteria, so acceptable.</td></tr>
<tr><td>Stability</td><td>Spiked PCs are stable up to 168 hours at RT
Spiked PCs are stable up to 6 freeze thaw cycles.</td><td></td></tr>
<tr><td>Lipemia</td><td>No effect up to 19.4 ng/ml of PC (LoPC) in screening and confirmatory assay</td><td>Spiked with 300mg/dL of triglycerides</td></tr>
<tr><td>Hemolysis</td><td>No effect up to 19.4 ng/ml of PC (LoPC) in screening and confirmatory assay</td><td>Spiked with 2% of whole blood. 1 out of 3 LoPC spiked with whole blood failed to meet the acceptance criteria (25.6 %CV) and tested negative, but it met the run acceptance criteria.</td></tr>
<tr><td>ADA Assay Assessment</td><td></td><td>Acceptable if ADA does not impact PK or PD.
In the labeling (section 12.6 Immunogenicity), the sponsor should include a statement indicating that “The sensitivity of the assay is not known although ADA was detectable in the tested samples.”</td></tr>
</table>

The cut point determination was carried out using 52 individual serum samples. Measurement for each sample were performed 3 times by two independent analysts. The sponsor removed outliers using the simple Turkey outlier detection method. Appropriate plate acceptance criteria are in place.

Additional Reviewer Comments:

The clinical studies evaluating the immunogenicity risk include one phase 1 study (UP0112) in healthy participants, one phase 2 study (MG0009) and two phase 3 studies (MG0010 and MG0011) in participants with gMG. In ISI, data from the phase 1 are not included due to limited sample no. and data from the phase 2 study are also not included as the drug tolerance of the supporting bioanalytic method was insufficient. Note that the data from the phase 1, 2 and 3 are generated using the different methodology. The methodology described in validation report is used for phase 3 studies only.

The assay is fit for purpose and can detect antibodies that bind to different domains of Zilucoplan. The biggest limitation of the assay is that the assay validation was performed using PC generated in rabbit and detection reagent was species-specific. Assay parameters established using non-human PC may not be representative of the ability of the assay to detect human antibodies. However, as ADA did not seem to have an impact on PK and PD, a PMC to develop a sensitive assay to detect human antibodies may not be needed. Instead, in the labeling (section 12.6 Immunogenicity), the sponsor should include a statement “The sensitivity of the assay is not known although ADA was detectable in the tested samples.”

The cut-points have been confirmed and are acceptable.

Validation Parameter	**Validation of an analytical method for the determination of anti-PEG_Zilucoplan antibodies (ADA) in human serum by LBA** VAM-ADA-LBA-PEG_Zilucoplan-Human Serum-v.1.0 Used in studies: MG0011, MG0011 (on-going)	Assessor Comment
Contract Research Org	UCB Biopharma	
Assay principle	A direct semi-homogeneous immunoassay on the MESO Quickplex SQ120 platform (ECL)	*Will detect human IgG/M*
Sample Pretreatment (Acid dissociation)	Samples were diluted at 1:10 in 300mM Glycine (pH2.0) for 1hr.	
Positive control (PC)	Mix of two PC: - Rabbit polyclonal antibody raised against PEG_Zilucoplan (stock: 1.45 mg/ml) - Human anti-PEG reference IgM standard (stock: 254 ug/ml)	*PC mixture was prepared in the ratio 1:1 by concentration*
PC Dose Curve and Hook Effect	No Hook effect observed up to 40000 ng/mL of PC. PC dilution curve used to determine the sensitivity and LoPC.	
LPC	282 ng/ml	
MPC	3350 ng/ml	
HPC	40000 ng/ml	
Matrix and NC	Human serum	
MRD	1:100	
Screening cut- point (SCP) (non-parametric, multiplicative, 95% upper limit)	1.31 *Non-parametric method using log-transformed normalized data*	*2 samples identified as biological outliers in the confirmatory data set, are considered indicative for pre-existing antibodies and thus were removed from the data set prior to determination of screening and titration cut points.*
Confirmatory cut-point (CCP) (% inhibition, Fixed, 99% upper limit)	Fixed cut point 17.8%	
Titer Cut Point (TCP)	1.31 95% upper limit	
Assay Drug tolerance	Screening assay: PC (20000ng/mL): 25µg/mL PC (3750ng/mL): 25µg/mL PC (750ng/mL): 25µg/mL PC (282ng/mL): 25µg/mL PC (250ng/mL): 0µg/mL PC (100.00ng/mL): 0µg/mL Confirmatory assay: PC (20000ng/mL): 25µg/mL	

<table>
<tr><td></td><td>PC (3750ng/mL): 25µg/mL
PC (750ng/mL): 25µg/mL
PC (282ng/mL): 25µg/mL
PC (250ng/mL): 5µg/m
PC (100.00ng/mL): 0µg/mL</td><td></td></tr>
<tr><td>Sensitivity (95 CI)</td><td>Screening 200 ng/ml
Confirmatory 134 ng/ml</td><td></td></tr>
<tr><td>Repeatability/Intra-assay variability</td><td>Screening (signal)
NC 6.08 %CV
LoPC 11.3 %CV
MePC 6.90 %CV
HiPC 12.4 %CV

Confirmatory (% inhibition)
NC N/A
LoPC 16.6 %CV
MePC 3.2 %CV
HiPC 1.4 %CV</td><td>The PC spiked at LoPC, MePC and HiPC showed an intra-assay precision of less than 20 %CV, so acceptable.</td></tr>
<tr><td>Intermediate Precision (IP)/inter-assay variability</td><td>Screening (signal)
NC 9.02 %CV
LoPC 16.0 %CV
MePC 20.3 %CV
HiPC 20.8 %CV

Confirmatory (% inhibition)
NC N/A
LoPC 18.6 %CV
MePC 4.7 %CV
HiPC 1.7 %CV</td><td>The % CV of signals for MePC and HiPC are greater than 20%, but that of normalized signal is 11.6% and 16.9%, respectively. Acceptable</td></tr>
<tr><td>Selectivity</td><td><table>
<tr><th>Assay Type</th><th>Population</th><th>Cut-point</th><th>PC conc (ng/mL)</th><th>Sample Number Meeting Acceptance Criteria</th></tr>
<tr><td rowspan="2">Screen</td><td rowspan="2">Healthy</td><td rowspan="2">1.31</td><td>Blank</td><td>10/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
<tr><td rowspan="2">Confirm</td><td rowspan="2">Healthy</td><td rowspan="2">17.8</td><td>Blank</td><td>10/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
<tr><td rowspan="2">Screen</td><td rowspan="2">Myasthenia Gravis</td><td rowspan="2">1.31</td><td>Blank</td><td>8/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
<tr><td rowspan="2">Confirm</td><td rowspan="2">Myasthenia Gravis</td><td rowspan="2">17.8</td><td>Blank</td><td>10/10</td></tr>
<tr><td>LPC</td><td>10/10</td></tr>
</table></td><td>In screening assay, Ind 05 and 08 in mGV patients is tested positive in blank but the signal is increased when spiked.
At least 80% of samples fulfill acceptance criteria, so acceptable.</td></tr>
<tr><td>Stability</td><td>Spiked PCs are stable up to 168 hours at RT
Spiked PCs are stable up to 12 freeze thaw cycles.</td><td></td></tr>
<tr><td>Lipemia</td><td>No effect up to 282 ng/ml of PC (LoPC) in screening and confirmatory assay</td><td>Spiked with 300mg/dL of triglycerides.</td></tr>
<tr><td>Hemolysis</td><td>No effect up to 282 ng/ml of PC (LoPC) in screening and confirmatory assay</td><td>Spiked with 2% of whole blood.</td></tr>
<tr><td>ADA Assay Assessment</td><td></td><td>Acceptable if ADA does not impact PK or PD.</td></tr>
</table>

		In the labeling (section 12.6 Immunogenicity), the sponsor should include a statement indicating that "The sensitivity of the assay is not known although ADA was detectable in the tested samples."

The cut point determination was carried out using 52 individual serum samples. Measurement for each sample were performed 3 times by two independent analysts. The sponsor removed outliers using the simple Turkey outlier detection method.

Additional Reviewer Comments:

The sponsor's assay to detect PEG should be able to detect anti-PEG antibodies (APA) in human serum, and the cut points have been confirmed in screening and confirmatory assays. However, the overall pre-APA positive rate is very low (1.2-8%) in-study groups (MG0010 and MG0011), indicating low sensitivity of the assay. Study participants in Zilucoplan treatment group showed higher APA positive rate (9.3% in MG0010 and 9.9% in MG0011) compared to placebo group (6.8% in MG0010 and 1.2% in MG0011), suggesting that Zilucoplan could induce APA responses. Assay parameters established using a mix of rabbit and human IgM PCs may not be representative of the ability of the assay to detect human antibodies. However, as APA did not seem to have an impact on PK and PD, a PMC to develop a sensitive assay to detect human antibodies may not be needed. Instead, in the labeling (section 12.6 Immunogenicity), the sponsor should include a statement "The sensitivity of the assay is not known although ADA was detectable in the tested samples."

Assessor Comments:

During the review process, we sent the following comments to the applicant and received sponsor's answers (highlighted in blue):

Information Request #1:

In the report NCD3824, you state that you used a rabbit polyclonal antibody raised against Zilucoplan as a Positive Control (PC). While you use a mix of 2ry reagents that recognize rabbit and human antibodies, it is not clear how the sensitivity of the one is related to the sensitivity of the other. Provide any additional data you have supporting the assay design, demonstrating that the anti-rabbit antibodies do not interfere with the anti-human antibodies. In addition, provide binding curves for the individual and combined 2ry antibodies and any other data that can help us understand the data produced by this assay.

Answer to the IR #1

Binding curves of biotinylated human IgG and IgM controls used as a surrogate for human antibody bound to drug over a concentration range of 1-100000 ng/mL detected with each of the following detection antibodies Ru_Anti-h-IgG + Ru_Anti-h-IgM (0.25 µg/mL each) and Ru_Anti-h-IgG + Ru_Anti-h-IgM + Ru_Anti-r-IgG (0.25 µg/mL each) are shown in Figures 1 and 2. Similar responses were obtained for the 2 detector systems for both human IgG and IgM control curves. This demonstrates that the presence of anti-rabbit antibodies does not impact the ability to sensitively detect human antibodies raised against Zilucoplan in clinical samples. It is confirmed that system suitability control samples, biotinylated hIgG and hIgM, with predefined acceptance limits for anti-human IgG and anti-human IgM control antibodies are included during sample analysis.

Figure 1:
Biotinylated Human IgG control curves with 2 detector systems

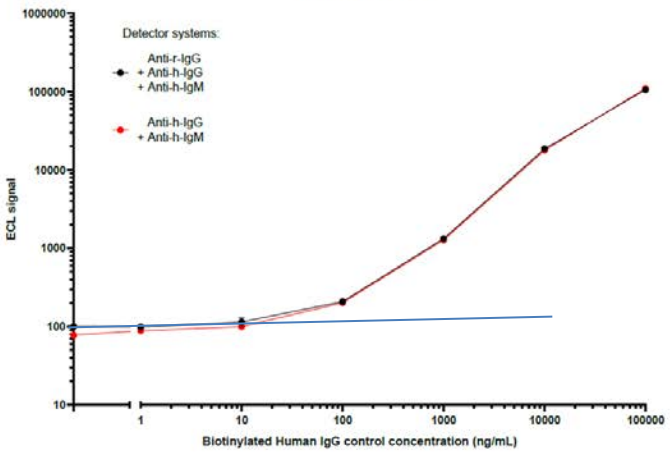
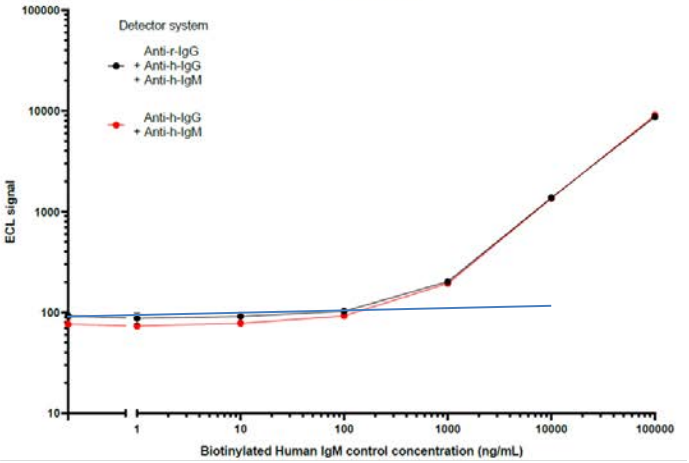


Figure 2:
Biotinylated Human IgM control curves with 2 detector systems



Information Request #2:
Your proposed confirmatory cut-point is based on inhibition of your rabbit PC antibodies. Provide the data that supports the use of this cut point for confirming the presence of ADA. Demonstrate competition using an alternative target to confirm that the competition inhibition is performing as expected.

Answer to the request #2
The confirmatory cut-point (CCP) was defined during validation using un-spiked and spiked drug-naïve individual human serum samples and therefore the calculated CCP is independent of the rabbit PC response. The CCP was calculated from a dataset comprised 24 plates, details of which are included in Appendix 2 of validation report NCD3824. Post-validation the CCP was subsequently reassessed using patient pre-dose samples from MG0010 and was confirmed unchanged at 35.2%. It was not feasible to assess the impact of an alternative target on competition binding as a suitable peptide analogous to Zilucoplan of similar size and charge and in the same chemical class was not available. Multiple different IgG isotypes and other matrix components are present in human serum at high concentrations. Despite the presence of these multiple proteins highly sensitive detection of the positive control in the screening assay was observed with significant reduction only observed in presence of additional ZLP indicating clear specificity of the assay. In addition, as the confirmatory cut-point is being determined on drug naïve individual serum samples, any irrelevant inhibition is accounted for in the calculation of the CCP. Therefore, the presence of a potential alternative target is not anticipated to produce an inhibitory response or to impact the assay. Any samples that demonstrate inhibition above the CCP in the confirmatory assay will be considered truly ADA positive.

Information Request #3:
In your drug tolerance assessment (table 11-13), 5 ug/ml of drug resulted in 32% while 2 ug/ml of resulted in 85.3-90.9% inhibition of the same amount of PC (18800ng/ml) in the confirmatory assay. Please explain why there was less inhibition observed with higher drug concentration in the confirmatory assay.

Answer to the request #3
The apparent disparity in % inhibition values noted between the drug tolerance data shown in Table 11-3 (confirmatory assay) and Table 11-13 (screening assay) in NCD3824 is attributed to differences in the assay step when drug is added to the sample in the methodology impacting the final drug concentration in the plate. Drug concentrations as shown in the drug tolerance assessment (table 11-13) are expressed as the concentration in the neat sample, i.e., before applying the minimum required dilution (MRD). Therefore, a

concentration of 5 µg/mL in the sample leads to a concentration of 0.05 µg/mL at the plate level after applying the MRD (1:100). In contrast, the drug concentration (2 µg/mL) used to deplete the drug-specific antibody response in the confirmatory assay is expressed at the plate level. Thus, at the plate level the drug is present at a concentration 40 times lower in the drug tolerance assessment in comparison to the confirmatory assay and hence a lower depletion of the antibody response is seen that is in keeping with expectation.

Information Request #4:
In the report NCD2825, you used a mix of rabbit polyclonal antibody raised against PEG-Zilucoplan and human anti-PEG reference IgM standard (stock: 254 ug/ml) as PC, but do not detail on how this control is prepared. Please provide the method how to prepare PC (1:1 ratio of conc or vol?) and justify the selection for your assay.

Answer to the request #4
The positive control comprising rabbit polyclonal antibody raised against PEG_Zilucoplan and human anti-PEG reference IgM standard was prepared in the ratio 1:1 by concentration, i.e., the Low PC with a nominal concentration of 282 ng/mL was made up of 141 ng/mL rabbit PC and 141 ng/mL human IgM PC. This ratio was deemed most appropriate to assess assay performance.

Information Request #5:
We note that the mean absorbance of negative Control (NC) in Zilucoplan ADA assay (approximately 150 in the report NCD3824) is higher than that in PEG ADA assay (approximately 45 in the report NCD3825). Please justify why the background signal is higher in Zilucoplan ADA assay compared to PEG ADA assay.

Answer to the request #5
UCB agrees that there is a difference between the low-level signals of the negative controls of the two assays. This degree of variation is to be expected given the inherent differing physicochemical properties of the capture reagents, hence some variation in background signal of negative control samples is to be anticipated between the two methods. However, the signals are low and close to instrument background noise for both assays.

Information Request #6:
Lastly, while your intermediate precision studies show acceptable profile, some of your other studies show some differences between runs raising concern regarding the reproducibility of the results. Provide an analysis across runs of your suitability controls.

Answer to the request #6
Precision of the PEG ADA screening assay at high, mid and low PC calculated from 12 precision runs on the normalized signal as reported in NCD3825 Table 1-2 is reproduced below.

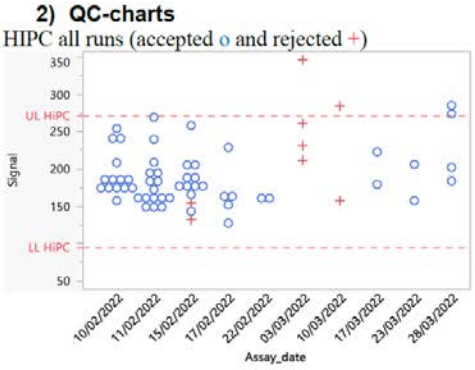
QC Level	N result	Overall Intra Run Variability CV (%) (assay signals)	Overall Inter Run Variability CV (%) (normalized S/N)
HiPC	36	12.4	16.1
MePC	36	6.90	16.9
LoPC	36	11.3	11.6

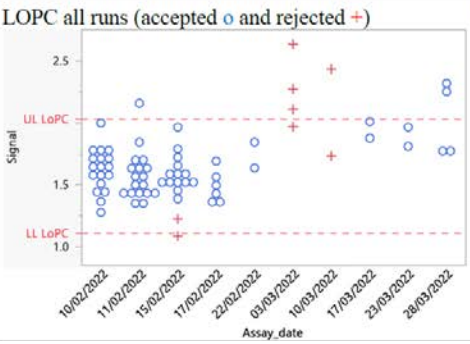
Further analysis across runs of the suitability controls was performed by 1) calculation of the inter-run precision over all the validation runs and the accepted validation runs and 2) by QC charts / visualization of the suitability controls (normalized HiPC and LoPC and NC) across all validation runs (both accepted and rejected) as provided below:

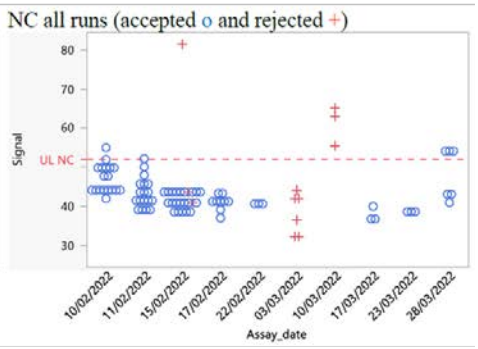
1) Inter-run precision

	All validation runs (accepted and rejected)			Accepted validation runs		
QC Level	N result	Overall Intra Run Variability CV (%) (assay signals)	Overall Inter Run Variability CV (%) (normalized S/N)	N result	Overall Intra Run Variability CV (%) (assay signals)	Overall Inter Run Variability CV (%) (normalized S/N)
HiPC	62	14.4	16.7	54	13.6	11.3
LoPC	74	12.2	13.4	64	10.6	5.7

2) QC-charts







In conclusion, the level of precision is similar when including all validation batches in comparison to the data from the 12 precision batches, for both of which were <20% CV at all PC levels. This is indicative of the assay performing reproducibly.

Additional accessor comments:

In response to information request sent on 04-03-2023, the sponsor provided the answers and the supporting data. For IR #1, the sponsor provided the additional data to support the anti-rabbit Abs do not interfere with the anti-human Abs, but it is still unclear how the sensitivity of this assay can be translated to human samples. Assay parameters established using non-human PC are not representative of the ability of the assay to detect human antibodies. The secondary reagent to detect antibodies in clinical samples should ideally be used to detect positive control antibodies and quality control samples as well. However, the sponsor has demonstrated that their assay is capable of detecting human antibodies based on their system suitability controls, and the specificity of the assay can be assessed by measuring the levels of anti-Zilucoplan antibodies at baseline and different times post-treatment. Although PCs used in the assay are not acceptable, Zilucoplan might have the low immunogenicity risk, and the data from studies MG0011 and MG0012 show that ADA titers detected in ADA positive samples were low and ADA did not have an impact on PK and PD. As such, the sponsor will be asked to include the statement in the labeling (section 12.6 Immunogenicity) that "The sensitivity of the assay is not known although ADA was detectable in the tested samples." This also applies to the anti-PEG ADA assay as the anti-PEG Ab controls used were a mix of rabbit polyclonal antibody raised against PEG-Zilucoplan and human anti-PEG reference IgM standard (See IR #4). For other IRs, the sponsor promptly responded with additional information and clarification.

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DANIELA I VERTHELYI
05/04/2023 01:31:06 PM

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 20, 2022

To: Teresa Buracchio, MD, Director, Division of Neurology I

Through: Dominic Chiapperino, PhD, Director, Controlled Substance Staff
Chad Reissig, PhD, Supervisory Pharmacologist, Controlled Substance Staff

From: Neil Varshneya, PhD, Pharmacologist, Controlled Substance Staff

Subject: NDA 216834 for Zilucoplan subcutaneous injection
Indication: generalized Myasthenia gravis (gMG)
Dosages: 16.6 mg, 23.0 mg, 32.4 mg, SC, QD
Sponsor: UCB, Inc.

Materials Reviewed: Assessment of the Abuse Potential of Zilucoplan (August 11, 2022)

I. Background

This memorandum is in response to a consult request dated September 19, 2022 from the Division of Neurology I (DNI) pertaining to NDA 216834 for Zilucoplan. DNI requested that the Controlled Substance Staff (CSS) review the Applicant's NDA from an abuse potential perspective. Zilucoplan is a complement component 5 (C5) inhibitor in development by UCB, Inc. (Applicant) for the treatment of generalized Myasthenia gravis (gMG). The Applicant submitted a NDA for Zilucoplan dated August 31, 2022 with an assessment of the abuse potential of Zilucoplan. CSS previously reviewed Zilucoplan (RA-101495) for abuse liability under IND 134340 and responded to a question in a memorandum dated April 28, 2022 about the Sponsor's proposed plan for assessing the abuse potential of Zilucoplan.

Zilucoplan is a 15-amino acid macrocyclic peptide and is not similar in chemical structure to any other drugs scheduled under the Controlled Substances Act (CSA). Zilucoplan was evaluated for its primary pharmacology in vitro using direct binding assays, functional inhibition of complement assays, and enzyme-linked immunosorbent assays (ELISAs), and was determined to be a potent, selective, C5 inhibitor. Zilucoplan was also evaluated in an in vitro screening along with its major metabolites, RA102758 and RA103488, against a comprehensive package of abuse-related targets. Zilucoplan was determined to bind to the GABA transporter (K_i=11 μM) and OX_1 receptor (IC_{50} = 44 μM) in these tests. However, Zilucoplan, given its molecular size (mw = 3562.23 g/mol), is lowly BBB-penetrant and does not achieve CNS concentrations

sufficient to elicit abuse related-effects at these abuse-related receptor targets in doses within the therapeutic range or exceeding it by 3x (see the pharmacology subsection of Section 4 [Discussion of Abuse and Dependence-Related Data] of this memorandum for rationale). Moreover, there were no reports of abuse-related TEAEs (e.g., euphoria, high, feeling drunk, floating, rush, perceptual disturbances, hallucination, or dissociation). Although the in vitro studies demonstrate that Zilucoplan binds to receptors associated with abuse-related effects, Zilucoplan does not achieve CNS concentrations sufficient to elicit psychoactive or intoxicating effects, and does not produce TEAEs associated with abuse potential. Therefore, additional studies including non-clinical abuse potential assessments and a human abuse potential study are not needed.

Overall, CSS has not identified any additional abuse- or dependence-related concerns with Zilucoplan and has determined that it would not achieve CNS concentrations sufficient to elicit psychoactive or intoxicating effects. A review of TEAEs in the clinical studies did not reveal any evidence to suggest that Zilucoplan poses risks of addiction liability in humans. CSS concludes that Zilucoplan is unlikely to be abused and therefore should not be controlled under the Controlled Substance Act (CSA). The proposed drug product, if approved under this NDA, will not require Section 9 (Drug Abuse and Dependence section) in its label.

II. Conclusions

- Zilucoplan is a potent, selective, C5 inhibitor indicated for Myasthenia gravis (MG).
- There currently are no C5 inhibitors scheduled under the Controlled Substances Act (CSA).
- Zilucoplan was determined to bind to the GABA transporter and OX_1 receptor, binding sites that may be associated with abuse potential . However, Zilucoplan does not achieve CNS concentrations sufficient to elicit psychoactive or intoxicating effects, even at doses equivalent to or substantially exceeding (e.g., 3x) the therapeutic dose.
- A review of TEAEs in the clinical studies did not reveal any evidence to suggest that Zilucoplan poses risks of addiction liability in humans.
- Additional studies including non-clinical abuse potential assessments and a human drug abuse potential study were not requested or necessary.
- The proposed drug product, if approved under this NDA, will not require a Drug Abuse and Dependence section in its label.

III. Recommendations (to the Division)

- Zilucoplan does not appear to have a potential for abuse, and does not require scheduling under the Controlled Substance Act.
- Zilucoplan does not require a section 9 (Drug Abuse and Dependence section) in its label.

IV. Discussion of Abuse and Dependence-Related Data

Chemistry

Drug Substance. The chemical structure of Zilucoplan is shown in **Figure 1**. Zilucoplan has a molecular formula of $C_{172}H_{278}N_{24}O_{55}$ and a molecular weight of 3562.23 g/mol. The chemical properties and structural identifiers of Zilucoplan including the IUPAC Name, PubChem ID, CASRN, Molecular Formula, Molecular Weight, Canonical SMILES, Isomeric SMILES, InChI, and InChIKey are shown in **Table 1**.

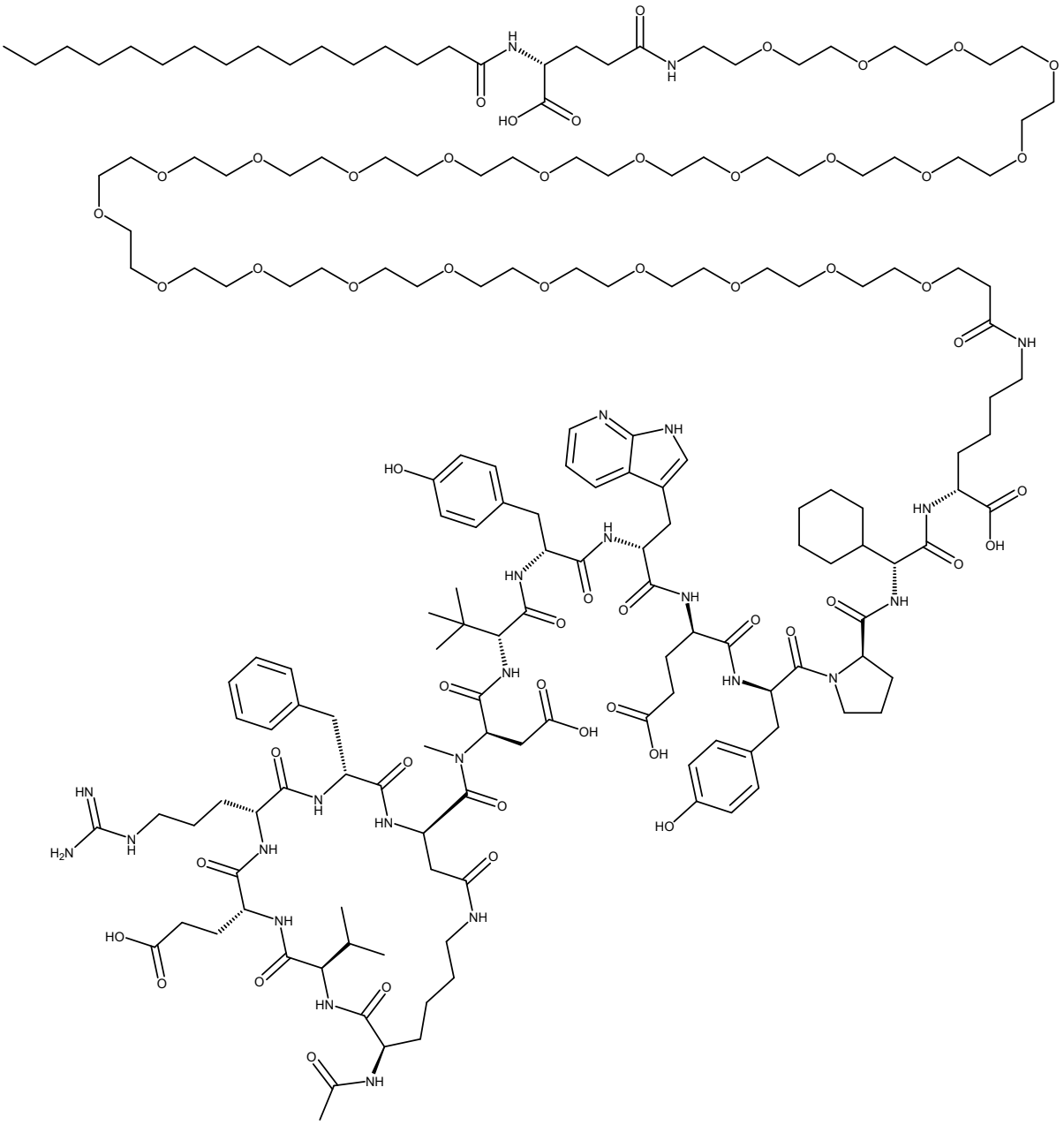

Figure 1. Chemical Structure of Zilucoplan.

Table 1. Chemical Properties and Structural Identifiers of Zilucoplan	
Property or Identifier	**Value**
Common Name	Zilucoplan
IUPAC Name	(2S)-2-[[(2S)-2-[[(2S)-1-[(2S)-2-[[(2S)-2-[[(2S)-2-[[(2S)-2-[[(2S)-2-[[(2S)-2-[[(2S,5S,8S,11S,14S,22S)-22-acetamido-11-benzyl-8-(3-carbamimidamidopropyl)-5-(2-carboxyethyl)-3,6,9,12,16,23-hexaoxo-2-propan-2-yl-1,4,7,10,13,17-hexazacyclotricosane-14-carbonyl]-methylamino]-3-carboxypropanoyl]amino]-3,3-dimethylbutanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)propanoyl]amino]-4-carboxybutanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]pyrrolidine-2-carbonyl]amino]-2-cyclohexylacetyl]amino]-6-[3-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[2-[[(4S)-4-carboxy-4-(hexadecanoylamino)butanoyl]amino]ethoxy]propanoylamino]hexanoic acid
PubChem ID	133083018
CASRN	1841136-73-9
Molecular Formula	$C_{172}H_{278}N_{24}O_{55}$
Molecular Weight	3562.23 g/mol
Canonical SMILES	CCCCCCCCCCCCCCCC(=O)NC(CCC(=O)NCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCC(=O)NCCCCC(C(=O)O)NC(=O)C(C1CCCCC1)NC(=O)C2CCCN2C(=O)C(CC3=CC=C(C=C3)O)NC(=O)C(CCC(=O)O)NC(=O)C(CC4=CNC5=C4C=CC=N5)NC(=O)C(CC6=CC=C(C=C6)O)NC(=O)C(C(C)(C)C)NC(=O)C(CC(=O)O)N(C)C(=O)C7CC(=O)NCCCCC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)N7)CC8=CC=CC=C8)CCCNC(=N)N)CCC(=O)O)C(C)C)NC(=O)C)C(=O)O
Isomeric SMILES	CCCCCCCCCCCCCCCC(=O)N[C@@H](CCC(=O)NCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCOCCC(=O)NCCCC[C@@H](C(=O)O)NC(=O)[C@H](C1CCCCC1)NC(=O)[C@@H]2CCCN2C(=O)[C@H](CC3=CC=C(C=C3)O)NC(=O)[C@H](CCC(=O)O)NC(=O)[C@H](CC4=CNC5=C4C=CC=N5)NC(=O)[C@H](CC6=CC=C(C=C6)O)NC(=O)[C@H](C(C)(C)C)NC(=O)[C@H](CC(=O)O)N(C)C(=O)[C@@H]7CC(=O)NCCCC[C@@H](C(=O)N[C@H](C(=O)N[C@H](C(=O)N[C@H](C(=O)N[C@H](C(=O)N7)CC8=CC=CC=C8)CCCNC(=N)N)CCC(=O)O)C(C)C)NC(=O)C)C(=O)O
InChI	InChI=1S/C172H278N24O55/c1-9-10-11-12-13-14-15-16-17-18-19-20-27-44-146(202)182-136(170(226)227)53-56-144(200)177-64-67-229-69-71-231-73-75-233-77-79-235-81-83-237-85-87-239-89-91-241-93-95-243-97-99-245-101-103-247-105-107-249-109-

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InChIKey	JDXCOXKBIGBZSK-PSNKNOTQSA-N
IUPAC = International Union of Pure and Applied Chemistry CASRN = Chemical Abstract Service Registry Number SMILES = Simplified Molecular-Input Line-Entry System InChI = International Chemical Identifier InChIKey = InChIKey is a hashed version of the full InChI (using the SHA-256 algorithm)	

Drug Product. Zilucoplan is administered by subcutaneous injection. From the Sponsor's submission, provided under Module 2 summary of chemistry, manufacturing, and controls:

"The drug product is supplied in a 1mL long (b) (4) glass pre-filled syringe. Each single-use syringe contains zilucoplan drug substance a inal injection (WFI). The finished product is a combination of the pre-filled syringe containing zilucoplan and the safety syringe components. It is a single-use pre-filled syringe with safety needle guard for selfadministration by subcutaneous injection, available in 3 dose presentations (16.6mg, 23.0mg and 32.4mg)."

"Zilucoplan drug product is manufactured to provide an extractable volume of not less than:

- 0.416mL per syringe for 16.6mg dose;
- 0.574mL per syringe for 23.0mg dose;
- 0.810mL per syringe for 32.4mg dose."

Pharmacology

Zilucoplan was evaluated in vitro against a comprehensive suite of abuse-related targets. Zilucoplan was determined to bind to the rat GABA transporter (K_i = 11 μM) and human OX_1 receptor (IC_{50} = 44 μM) in these tests. In tissue distribution tests ((b) (4) Study Number: 16863;

(b) (4) Report Number: RPT04200 dated July 11, 2017) using Quantitative Whole-Body Autoradiography (QWBA) in male Long-Evans rats following a single subcutaneous dose (6 mg/kg, SC) of [^{14}C]RA101495, the observed peak brain (whole) tissue exposure concentration was C_{max} = 0.282 (µg equiv/g). Assuming brain tissue has the same density as water, the expected peak Zilucoplan concentration is 79.16 nM (0.282 µg / 1 ml * 1 mol / 3562.23 g). This concentration is 139x lower than the K_i value for the GABA transporter and 556x lower than the IC_{50} value for the OX_1 receptor. The therapeutic dose of Zilucoplan in humans is 0.3 mg/kg, SC.

In subsequent tissue distribution tests ((b) (4) Study Number: C18038; (b) (4) Report Number: RPTC18038 dated April 29, 2019) using QWBA in male Long-Evans rats following a single subcutaneous dose (6 mg/kg, SC) of [^{14}C]RA101495, the brain (whole) C_{max} was empirically determined to be 0.243 (µg equiv/g). Assuming brain tissue has the same density as water, the expected peak Zilucoplan concentration is 68.22 nM (0.243 µg / 1 ml * 1 mol / 3562.23 g). This concentration is 161x lower than the K_i value for the GABA transporter and 645x lower than the IC_{50} value for the OX_1 receptor. In these rat studies, a dose of 6 mg/kg, SC was used. This roughly equates to a 1 mg/kg human dose (6 mg/kg * 0.16 = 0.96 mg/kg or 3x the therapeutic dose).

In additional tests for CNS availability in cynomolgus monkeys (Study Report ECP-136 dated January 20, 2020), a single subcutaneous dose (1 mg/kg, SC) produced peak CSF concentrations of C_{max} = ~70 ng/ml, resulting in a CNS tissue exposure concentration of 19.6 nM (70 ng / 1 ml * 1 mol / 3562.23 g), 561x lower than the K_i value for the GABA transporter and 2245x lower than the IC_{50} value for the OX_1 receptor. In this monkey study, a dose of 1 mg/kg, SC was used. This roughly equates to a 0.32 mg/kg human dose (1 mg/kg * 0.32 = 0.32 mg/kg or ~1x the therapeutic dose).

The blood plasma concentrations observed were 27.2 µg equiv/g (rat), 31.4 µg equiv/g (rat), and ~17500 ng/ml (monkey), indicating that Zilucoplan is lowly BBB-penetrant. Although Zilucoplan binds to the GABA transporter and OX_1 receptor, it does not achieve CNS concentrations in rats and monkeys sufficient to elicit psychoactive or intoxicating effects, even at doses equivalent to or substantially exceeding (e.g., 3x) the therapeutic dose.

<u>The following are excerpts from the Applicant's Document titled Assessment of the Abuse Potential of Zilucoplan dated August 11, 2022. They are presented verbatim:</u>

3.1.2.2.1 Zilucoplan

As part of the assessment of the risk of abuse and/or dependence posed by zilucoplan, its affinity for 35 molecular targets (receptors, binding sites, ion channels, and transporters) that mediate the pharmacological effects of substances of abuse has been investigated in vitro (Study 100061456: abuse liability panel). Zilucoplan was screened at a concentration of 30 µM. The results reported in Table 3–4 show that with the exceptions of the orexin-1 (OX_1) receptor and the GABA transporter, zilucoplan had no affinity for any abuse-related molecular target (i.e., <50% displacement, inhibition or stimulation).

Further characterization revealed zilucoplan is a functional antagonist of OX_1 receptors (IC50 = 44 μM) and inhibits binding of radioligand at the GABA transporter (K_i = 11 μM) (Study 100062196). Zilucoplan is >99% protein bound in human plasma and to the plasma proteins in the species used in the nonclinical safety evaluation, i.e., monkey and rat. Therefore, these effects on OX_1 receptors or the GABA transporter are not pharmacologically or clinically relevant.

3.1.3.5 Summary of clinical studies

A comprehensive analysis of adverse events indicative of the potential for human abuse in the clinical safety database found that the incidence of TEAEs indicating potential for human abuse was lower in participants taking zilucoplan than in participants taking placebo. Although the number of abuse-related TEAEs was small, the incidence did not increase with the higher dose of ZLP (0.3mg/kg vs 0.1mg/kg). There were no reports of abuse-related TEAEs of particular concern, e.g., euphoria, high, feeling drunk, floating, rush, perceptual disturbances, hallucination, or dissociation. In summary, a review of TEAEs in the zilucoplan studies did not reveal any evidence to suggest that zilucoplan poses a human abuse risk.

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