# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761388Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Division of Risk Management (DRM)**
**Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)**
**Office of Medication Error Prevention and Risk Management (OMEPRM)**
**Office of Surveillance and Epidemiology (OSE)**
**Center for Drug Evaluation and Research (CDER)**

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| **Application Type** | BLA |
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| **Division Director** | Cynthia LaCivita, PharmD (DRM) |
| **Review Completion Date** | June 20, 2024 |
| **Subject** | Evaluation of Need for a REMS |
| **Established Name** | Crovalimab-akkz |
| **Trade Name** | Piasky |
| **Name of Applicant** | Genentech, Inc |
| **Therapeutic Class** | Complement inhibitor |
| **Formulation(s)** | Injection, 340 mg (2mL) single-dose vial |
| **Dosing Regimen** | **PIASKY Dosing Regimen Based on Body Weight** |

| **Body Weight** | **≥ 40 kg to < 100 kg** | **≥ 100 kg** |
|---|---|---|
| **Loading Dose** | | |
| Day 1 | 1,000 mg (IV) | 1,500 mg (IV) |
| Day 2, 8, 15, 22 | 340 mg (SC) | 340 mg (SC) |
| **Maintenance Dose** | | |
| Day 29 and Q4W[a] thereafter | 680 mg (SC) | 1,020 mg (SC) |

IV = intravenous, SC = subcutaneous

a Q4W=every 4 weeks

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## EXECUTIVE SUMMARY

This review provides the Division of Risk Management (DRM) evaluation of whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Piasky (crovalimab-akkz) is necessary to ensure the benefits outweigh its risks and DRM's evaluation of the Applicant's proposed REMS (last amended on June 17, 2024 and Supporting Document submitted on June 20, 2024). This review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan (last submitted on June 20, 2024).

Genentech, Inc submitted a Biologics Licensing Application (BLA) 761388 for crovalimab-akkz with the proposed indication for treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). During the course of the review, the Agency revised the indication to: for treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg.

The benefits of crovalimab-akkz as a treatment for PNH were demonstrated in a phase 3, randomized, open-label, active-controlled, multicenter study which showed that crovalimab-akkz was non-inferior to eculizumab on transfusion avoidance and hemolysis control. These findings were further supported by confirmatory pharmacodynamic/mechanistic data.

The risks associated with crovalimab-akkz are serious meningococcal infections and Type III hypersensitivity reactions. The risk of Type III hypersensitivity reactions which may occur in patients switching to and from a different C5 inhibitor will be communicated in labeling as a (b) (4) warnings and precautions in the Prescribing Information and summarized in the Medication Guide for patients.

Serious meningococcal infections are a known risk associated with the use of complement C5 inhibitors approved for the treatment of PNH, such as Ultomiris and Soliris. Ultomiris and Soliris are subject to a REMS to mitigate this risk. The risks of serious meningococcal infections for crovalimab-akkz will be communicated in labeling as a boxed warning, warnings and precautions in the Prescribing Information and summarized in the Medication Guide for patients. DRM and DNH agree that a REMS is necessary to ensure the benefits of crovalimab-akkz outweigh the risk of serious meningococcal infections.

The goal of the PIASKY REMS is to mitigate the risk of serious meningococcal infections.

1. Patients are vaccinated against meningococcal infections caused by Neisseria meningitidis serogroups A, C, W, Y, and B prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving complement inhibitors and receive antibacterial drug prophylaxis if needed.
2. Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.
3. Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

The Piasky REMS includes: ETASU A (healthcare providers who prescribe crovalimab-akkz are specially certified), ETASU B (pharmacies that dispense crovalimab-akkz are specially certified), and ETASU D (dispensing of crovalimab-akkz may be done only with the documentation of safe-use conditions). Prescriber certification ensures that each prescriber is trained about the risk of serious meningococcal infections associated with crovalimab-akkz, the need to provide the appropriate meningococcal vaccines for serotypes A, C, W, Y, and B two weeks prior to crovalimab-akkz initiation, and the need for antibacterial drug prophylaxis if crovalimab-akkz is initiated prior to the patient being up to date on vaccines. Prescribers must attest to comply with the requirements of the REMS, and counsel patients about the risk of serious meningococcal infections, the need for vaccination and antibacterial drug prophylaxis if needed, the signs and symptoms of serious meningococcal infections, and the need to seek immediate medical evaluation if these symptoms occur. Pharmacies must certify to be able to dispense, verify prescribers are certified prior to dispensing, and establish processes and procedures to assess and document the patients' vaccination status including antibacterial drug prophylaxis prior to dispensing crovalimab.

Based on the risk of serious meningococcal infections, DRM and DNH agree that a REMS that includes ETASU A, B, and D is necessary to ensure that the benefits outweigh the risks of crovalimab-akkz. The timetable for submission of assessments is at 6 months and 18 months from the date of the initial approval of the REMS and every 12 months thereafter from the date of the 18 month submission.

DRM finds the proposed REMS submitted on June 20, 2023 and last amended on June 17, 2024 acceptable for approval. DMAMES found the REMS Assessment Plan as submitted on June 20, 2024 to be acceptable.

# 1. Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Piasky (crovalimab-akkz, hereafter referred to as crovalimab) is necessary to ensure the benefits outweigh its risks and includes DRM's evaluation of the proposed REMS. This review also includes the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluation of the proposed REMS Assessment Plan. Genentech, Inc (hereafter referred to as the Applicant) submitted a Biologics Licensing Application (BLA) 761388 for crovalimab with the proposed indication for treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH).[1] This application is under review in the Division of Nonmalignant Hematology (DNH). The applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.[2]

# 2. Background

## 2.1. Product Information

Crovalimab, a new molecular entity,[a] is a complement protein 5 (C5) inhibitor indicated for the treatment of adult and pediatric patients 13 years and older with PNH and body weight of at least 40 kg. Crovalimab binds to C5 of the complement system and inhibits its cleavage into C5a and C5b thus preventing formation of the membrane attack complex (MAC). In patients with PNH, crovalimab inhibits terminal complement-mediated intravascular hemolysis.[3]

Crovalimab is proposed to be supplied as a 340 mg/2 mL single-use vial for injection. The proposed dosing regimen consists of one loading dose administered by intravenous (IV) infusion (on Day 1), followed by four additional weekly loading doses administered by subcutaneous (SC) injection (on Days 2, 8, 15, and 22). The maintenance dose starts on Day 29 and is then administered every 4 weeks by subcutaneous injection, as PNH requires chronic treatment.[b] Doses are based on the patient's body weight (see table 1). The IV loading dose of crovalimab is to be administered by healthcare providers in outpatient and inpatient settings. Initially, the Applicant proposed that SC maintenance dosing of crovalimab could be self-administered by patients and caregivers. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors validation study report submitted by the Applicant and determined that the results from the human factors validation study do not support self-administration of the proposed product by adult and pediatric patients.[4]

Crovalimab is not currently approved in any jurisdiction.

**Table 1. Crovalimab dosing regimen based on body weight[3]**

| **Body Weight** | **≥ 40 kg to < 100 kg** | **≥ 100 kg** |
|---|---|---|
| **Loading Dose** | | |
| Day 1 | 1,000 mg IV | 1,500 mg IV |
| Day 2, 8, 15, 22 | 340 mg SC | 340 mg SC |
| **Maintenance Dose** | | |
| Day 29 and every 4 weeks thereafter | 680 mg SC | 1,020 mg SC |

IV = intravenous, SC = subcutaneous

## 2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761388 relevant to this review:

- 06/20/2023: BLA 761388 submission for crovalimab received for the treatment of adult and pediatric patients with PNH.[1]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 12/14/2023: Applicant informed at the mid-cycle meeting via teleconference that a REMS was necessary to ensure the benefits outweigh the risks of serious meningococcal infections.
- 04/03/2024: Agency issued an information request (IR) to clarify the Applicant's distribution model, their proposed authorization to dispense, and the REMS website.
- 04/08/2024: Applicant submitted a response to the Agency's IR issued on 04/03/2024.[5]
- 04/22/2024: Agency issued an IR to clarify the Applicant's proposed file transfer option for pharmacy verification of prescriber certification.
- 04/24/2024: Applicant submitted a response to the Agency's IR issued on 04/22/2024.[6]
- 04/30/2024: Applicant submitted an additional response to the Agency's IR issued on 04/22/24 that included a revised Supporting Document with details regarding the REMS authorization to dispense and their distribution model.[7]
- 05/15/2024: Agency issued interim comments to align the REMS goals and objectives and the REMS materials with revised labeling, align the REMS materials with the changes to the REMS Document, rename the Healthcare Provider Brochure to the Healthcare Provider Safety Brochure, propose Key Risk Messages (KRM) based on REMS goals and objectives, propose Key Performance Indicators (KPI), and revise the REMS Assessment Plan.
- 05/22/2024: Applicant submitted a REMS amendment in response to the interim comments issued on 05/15/2024.[8]
- 06/05/2024: Applicant submitted an additional response to the Agency's interim comments issued on 05/15/24 that included revised REMS Materials and supporting document.[9]
- 06/11/2024: Agency issued interim comments to revise the audit language in the REMS Document, align the REMS materials with revised labeling and with the changes to the REMS Document, revise Key Performance Indicators (KPI), and revise the REMS Assessment Plan.
- 06/13/2024: Applicant submitted a REMS amendment in response to the interim comments issued on 05/15/2024.[2]
- 06/14/2024: Agency issued an information request to revise the REMS Document to align with the REMS Document Technical Conformance Guide.[10]
- 06/17/2024: Applicant submitted a REMS amendment in response to the information request issued on 06/14/2024.[11]
- 06/18/2024: Agency issued an information request to revise the REMS Assessment Plan.[12] The Applicant responded in an email and submitted a REMS Supporting Document with the revised REMS Assessment Plan.[13] (b) (4) See Section 7.1.1 for additional details.
- 06/19/2024: Agency issued an information request to revise the REMS Assessment Plan.[15]
- 06/20/2024: Agency issued an information request revising the Supporting Document to align with the labeling and to update the REMS Assessment Plan. The Applicant submitted an updated Supporting Document and accepted all Agency changes. changes were accepted by the

Applicant.[16] The Applicant submitted an updated Supporting Document and accepted all Agency changes. The changes were accepted by the Applicant.[17]

# 3. Therapeutic Context and Treatment Options

## 3.1. Description of the Medical Condition

PNH is a rare, chronic, life-threatening hematologic disorder characterized by uncontrolled activation of the terminal complement pathway leading to hemolytic anemia, bone marrow failure, and increased risk of thrombosis.[18,19,c] Hemolysis can result in symptoms including fatigue, chest pain, transfusion dependence, and organ damage.[19,20] If untreated, PNH is associated with risk of hospitalization, poor health-related quality of life, and increased risk of mortality, with thrombotic events accounting for approximately two-thirds of PNH-related deaths.[18] PNH primarily impacts adults with a median age of onset in the 30s, however cases in children have been reported.[19] There is no difference in PNH incidence by sex, geographic location, race, or ethnicity.[19] The incidence of PNH is estimated at 0.1-1/100,000 persons per year. [19] The incidence of PNH is estimated at 0.1-1/100,000 persons per year. PNH primarily impacts adults with a median age of onset in the 30s, however cases in children have been reported. There is no difference in PNH incidence by sex, geographic location, race, or ethnicity. The incidence of PNH is estimated at 0.1-1/100,000 persons per year.[19,21,d]

## 3.2. Description of Current Treatment Options

FDA-approved products for the treatment of PNH in adults includes Soliris(eculizumab), Bkemv (eculizumab-aeeb),[e] Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan).[22-26] Ultomiris (ravulizumab) is the only FDA-approved product that is indicated for both adults and pediatric patients one month of age and older.[27] All of the complement inhibitors approved for PNH are subject to a REMS for the risk of serious meningococcal infections (complement C5 inhibitors) or the risk of serious infections caused by encapsulated bacteria (alternative pathway inhibitors and complement C3 inhibitor).[28-31]

Eculizumab reduces intravascular hemolysis (IVH) through inhibition of complement C5.[23,26,27] Extravascular hemolysis may occur in patients taking complement C5 inhibitors due to accumulation of complement C3 fragments on red blood cells that are not hemolyzed due to terminal complement inhibition.[32] Pegcetacoplan (complement C3 inhibitor) and Iptacopan (Factor B inhibitor) act proximally in the complement system controlling both C3b-mediated extravascular hemolysis (EVH) and terminal complement-mediated IVH.[22,24] Danicopan acts proximally in the alternative pathway of the complement system to preferentially control C3 fragment-mediated EVH, while co-administered ravulizumab or eculizumab is anticipated to maintain control over MAC-mediated IVH.[25] All of the

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[e] Bkemv (eculizumab-aeeb) is biosimilar to Soliris (eculizumab).

complement inhibitors that are subject to a REMS include prescriber certification (ETASU A), pharmacy certification (ETASU B), and evidence of safe use conditions (ETASU D).

See Appendix 10.2 for a summary of the FDA-approved therapies for the treatment of PNH.

# 4. Benefit Assessment

The pivotal clinical trial supporting this application is study BO42162, also known as COMMODORE2 (NCT04434092), a phase 3, randomized, open-label, active-controlled, multicenter study. The study evaluated crovalimab in 135 adults (≥ 18 years of age) versus eculizumab in 69 adults with paroxysmal nocturnal hemoglobinuria (PNH) not previously treated with complement inhibitors for 24 weeks. Following the 24-week primary treatment period, patients could continue or switch to crovalimab treatment for a maximum of 5 years during the extension period. Crovalimab was also evaluated in 6 pediatric patients (<18 years old, body weight ≥ 40 kg) during the primary treatment period, in a descriptive, non-randomized study arm; and one additional pediatric patient that switched to crovalimab during the extension period.

The co-primary endpoints for the non-inferiority assessment include 1) proportion of patients who achieve transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment), and 2) proportion of patients with hemolysis control, measured by lactate dehydrogenase (LDH) ≤ 1.5 x upper limit of normal (ULN) from Week 5 through Week 25 (as measured at the central laboratory). The proportion of patients who achieved transfusion avoidance from baseline to Week 25 was 65.7% for crovalimab vs 68.1% for eculizumab, with a difference in proportions of -2.8% [95% CI: -15.7, 11.1]. The mean proportion of patients with hemolysis control from Week 5 through Week 25 in patients treated with crovalimab compared to eculizumab was 79.3% vs 79.0% respectively, resulting in an odds ratio of 1.02 [95% CI: 0.57, 1.82]. Results show that crovalimab was non-inferior to eculizumab on transfusion avoidance and hemolysis control.[1] The review team had concerns that the open-label nature of the trial may introduce bias particularly when determining the need for red blood cell transfusions.[33] The Agency also did not agree with the Applicant's prespecified non-inferiority margin (NIM) of -20% for the co-primary endpoint of TA or the prespecified NIM of 0.2 for the co-primary endpoint of hemolysis control during the IND stage.[33] However, the statistical review team determined that the non-inferiority was demonstrated for both co-primary endpoints based on the updated NIM of -18% for TA and 0.33 for hemolysis control.[33]

Additional data was provided from three clinical trials including COMMODORE3 (NCT04654468), COMMODORE1 (NCT04432584), and COMPOSER (NCT03157635) which provided confirmatory evidence of effectiveness for crovalimab based on the observed pharmacodynamic and mechanistic effects that would not be expected to occur spontaneously in this disease.[33]

The review team concluded that the Applicant provided SEE based on one adequate and controlled trial and confirmatory evidence that support the benefits of crovalimab in patients with PNH naïve to C5

inhibitor therapy including hemolysis control, as well as transfusion avoidance.[33, f] The findings from the pivotal trial are supported by confirmatory pharmacodynamic/mechanistic evidence.[33] See the integrated review for crovalimab for more details regarding the DNH's conclusions for evidence of effectiveness.

Adolescents (ages 13-17) demonstrated similar benefits to adults treated with crovalimab. Efficacy in pediatric patients was evaluated in 10 pediatric patients between the ages 13-17 from the COMMODORE2 study (7 patients) and the other confirmatory clinical trials (3 patients). The review team concluded that the efficacy results of crovalimab in pediatric patients were consistent with those of the adult patients and recommends that the indication for treatment of patients with PNH include pediatric patients 13 years and older.[33]

# 5. Risk Assessment & Safe-Use Conditions

The safety of crovalimab was evaluated in the primary treatment period of the two active-controlled Phase 3 studies in patients with PNH, the COMMODORE2 and COMMODORE1 studies. The PNH safety population is comprised of crovalimab treated PNH patients that received at least 1 dose of crovalimab in the primary treatment period including 135 complement inhibitor naïve patients from the COMMODORE 2 study and 45 patients previously treated with a complement inhibitor (non-naïve) from the COMMODORE 1 study. Exposure included body weight-based dosing of one loading dose administered by intravenous (IV) infusion (on Day 1), followed by four additional weekly loading doses administered by subcutaneous (SC) injection (on Days 2, 8, 15, and 22). Body weight-based maintenance doses were administered by subcutaneous injection starting on Day 29 and every 4 weeks thereafter. The most commonly reported adverse reactions (≥ 10%) in treatment naïve PNH patients treated with crovalimab were leukopenia (49%), neutropenia (43%), hypokalemia (27%), thrombocytopenia, infusion related reaction (16%), nasopharyngitis (12%), and viral infection (11%).[3] The most commonly reported adverse reaction (≥ 10%) in non-naïve patients previously treated with a different complement inhibitor were neutropenia (39%), leukopenia (36%), respiratory tract infection (25%), viral infections (23%), hypokalemia (23%), pyrexia (18%), type III hypersensitivity reaction (16%), infusion related reaction (14%), COVID-19 (14%), peripheral edema (11%), thrombocytopenia (11%), nasopharyngitis (11%), and headache (11%).[3] The review team commented that the safety database is adequate for comprehensive safety assessment of crovalimab for the proposed indication, patient population, dosage regimen, and duration.[33]

## 5.1. Deaths

Three deaths (crovalimab naïve: 2 [1.5%], eculizumab naïve: 1 [1.4%]) occurred during the primary treatment period in COMMODORE2 and no deaths in the COMMODORE1 study. Of the two crovalimab treated patients, one died due to myocardial infarction and the other died of respiratory tract

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

hemorrhage. The review team concluded that neither of the deaths in patients treated with crovalimab were due to crovalimab.[33]

## 5.2. Serious Adverse Events

In the COMMODORE2 study, the incidence of serious adverse events (SAEs)[g] in patients who were complement inhibitor naïve was similar between the crovalimab treated patients (10.4%) and those treated with eculizumab (13.0%) during the primary treatment period. The reported SAEs in crovalimab treated patients included pneumonia, COVID-19, pyelonephritis, aplastic anemia, thrombocytopenia, epistaxis, respiratory tract hemorrhage, myocardial infarction, pyrexia, small intestinal hemorrhage, infusion related reaction, thyroid cancer, affective disorder Henoch-Schonlein purpura, and hypovolemic shock. The review team concluded that 6% of patients had SAEs due to crovalimab, which included events of infection, epistaxis, pyrexia, hypovolemic shock, and infusion reaction.[33]

In the COMMODORE1 study, the incidence of SAEs in patients who were previously treated with complement inhibitor was higher in crovalimab treated patients (13.6%) compared to those who continued eculizumab (2.4%) during the primary treatment period. The reported SAEs in crovalimab treated switch patients included pneumonia, nasopharyngitis, urinary tract infection, neutropenia, pyrexia, hyperbilirubinemia, skin laceration, and cervical dysplasia. The clinical review team concluded that 9.1% of patients had SAEs due to crovalimab, which included infectious events and pyrexia.[33]

## 5.3. Adverse Events of Special Interest

### 5.3.1. Serious Meningococcal Infections

Complement C5 inhibitors like crovalimab can increase a patient's susceptibility to serious, life threatening, or fatal infections caused by encapsulated organisms, most notably *Neisseria meningitidis* infections. The complement C5 inhibitor Soliris (eculizumab) has been associated with a 1,000 to 2,000 fold increased risk for meningococcal infections when compared to the general population in the United States due to terminal complement inhibition.[34] Serious meningococcal infections are bacterial infections that present as meningitis, bacteremia, or both and can become rapidly life-threatening and fatal if not treated immediately.[34,35] Serious meningococcal infections are bacterial infections that present as meningitis, bacteremia, or both and can become rapidly life-threatening and fatal if not treated immediately.[35] Life-threatening and fatal meningococcal infections have occurred in patients receiving Soliris and Ultomiris.[23,27]

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

No cases of infection with *Neisseria meningitidis* were reported in the crovalimab PNH development program. However, one case of grade 3 Meningococcal meningitis (*Neisseria meningitidis* serotype X) was reported on Day 430 in Study BO42354 (NCT04958265), a study evaluating the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of crovalimab in pediatric patients with atypical hemolytic uremic syndrome (aHUS). The aHUS patient was vaccinated against serotype ACWY. The event resolved after 4 days, with no change to crovalimab treatment.

Per the COMMODORE2 study protocol, all patients were required to be vaccinated against meningococcal infections for serotypes A, C, W, and Y at least 3 years prior to initiation of study treatment. Vaccination against serotype B was recommended to be administered in accordance with the most current local guidelines. If vaccination was completed less than 2 weeks prior to initiation of treatment with crovalimab or after the start of study treatment, antibiotic prophylaxis was recommended from first study drug administration, continuing for at least 2 weeks after completion of vaccination.

The Advisory Committee on Immunization Practices (ACIP) recommends vaccinating persons receiving a complement inhibitor with meningococcal vaccines for serogroups A, C, W, and Y and serogroup B due to the substantially increased risk for meningococcal infections in these patients.[35] Vaccinated patients receiving a complement C5 inhibitor may be still at risk for meningococcal infections, as the vaccines may not completely protect patients against meningococcal disease due to the C5 inhibition despite development of antibodies with the vaccines and due to non-groupable strains of *N. meningitidis* which the vaccines do not target.[36]

Given the increased susceptibility to serious meningococcal infections associated with other C5 inhibitors used in the treatment of PNH, the review team recommends a REMS that includes ETASU to mitigate the risk of *Neisseria meningitidis* infections. The risk of serious meningococcal infections will be communicated in the prescribing information (PI) in a Boxed Warning, included in Section 5: Warnings and Precautions and summarized in the Medication Guide.[33] The recommended vaccination and prophylaxis for meningococcal infections is summarized in Section 2.1 and patient counseling information is summarized in Section 17.[3] To further assess the long-term risk of serious infections, the review team recommends a post-marketing requirement (PMR) to establish or participate in a registry for up to 5 years of follow-up and to submit reports summarizing meningococcal infections and other infections with encapsulated bacteria.[33]

### 5.3.2. Type III Hypersensitivity Reactions

Crovalimab is C5 inhibitor that binds to a different C5 epitope than the previously approved C5 inhibitors (i.e., eculizumab and ravulizumab). When both crovalimab and eculizumab (or ravulizumab) are present in the circulation, drug-target-drug complexes (DTDCs) comprised of the two antibodies bridged by C5 are formed.[37] Therefore, patients who previously received a different C5 inhibitor and switch to crovalimab (or vice versa) are at risk for type III hypersensitivity reactions due to the transient formation of DTDCs made of eculizumab or ravulizumab, crovalimab, and complement C5.

In the crovalimab switch population in Studies COMMODORE2 and COMMODORE1, a total of 39 out of 201 (19.4%) patients experienced transient immune complex reactions (reported as Type III immune complex mediated reaction). The median time to onset of transient immune complex reaction in patients who switched treatment from eculizumab or ravulizumab to crovalimab was 1.6 weeks (range: 0.7 – 4.4 weeks) and the median duration of transient immune complex reactions was 1.9 weeks (range 0.4 – 34.1 weeks). The majority of events were Grade 1-2. Grade 3 transient immune complex reaction occurred in 8% of patients who switched from eculizumab or ravulizumab to crovalimab. A total of two patients experienced two events of transient immune complex reaction. Both patients experienced the first event when switching from eculizumab/ravulizumab to crovalimab in the study and the second event after they discontinued crovalimab treatment and switched to ravulizumab. Two patients also had symptoms of axonal neuropathy, in the context of transient immune complex reactions but also sepsis, administration of fluoroquinolone in one patient and bacterial respiratory tract infection in the other patient.

During the course of the review, DNH consulted the Division of Pulmonology, Allergy, and Critical Care (DPACC) for their expertise in hypersensitivity reactions. The consult team agreed with the Applicant's conclusion that drug-target-drug complexes (DTDCs) lead to Type III hypersensitivity reactions and agreed with the description of these reactions in the warnings and precautions section in the PI.[38] The review team recommends to include transient immune complex reactions in the PI as a (b) (4) in the Warning and Precaution section. To further understand the long-term risk of Type III Hypersensitivity reactions, the review team also recommends a PMR to establish a registry to characterize the long-term safety of crovalimab in adult and pediatric patients 13 years and older with PNH with up to 5 years of follow-up with reports summarizing Type III Hypersensitivity reactions and axonal neuropathy.[33]

# 6. Expected Postmarket Use

If approved, crovalimab will be a chronic therapy option for patients with PNH. Dosing includes an initial intravenous loading dose followed by subcutaneous loading doses and maintenance subcutaneous dosing likely to occur primarily in the outpatient healthcare settings.

The likely prescribing population for crovalimab includes hematologists and oncologists. This prescribing population is similar to other complement C5 inhibitors approved for this indication and may be familiar with the approved REMS for other complement C5 inhibitors. Healthcare providers who prescribe crovalimab will need to understand the risk of meningococcal infections and actions to take to mitigate this risk.

# 7. Risk Management Activities Proposed by the Applicant

## 7.1. Review of Applicant's Proposed REMS

The amendments received on June 17, 2024 and the Supporting Document received on June 20, 2024, are the subjects of this review. The Applicant proposed a REMS which includes the certification of

Healthcare Providers who prescribe Piasky (ETASU A), certification of Pharmacies that dispense Piasky (ETASU B), and assessment and documentation of patient's vaccination history/antibiotic prophylaxis by pharmacies prior to dispensing Piasky (ETASU D).

### 7.1.1. REMS Goal

The goal of the PIASKY REMS is to mitigate the risk of serious meningococcal infections.

1. Patients are vaccinated against meningococcal infections caused by *Neisseria meningitidis* serogroups A, C, W, Y, and B prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving complement inhibitors and receive antibacterial drug prophylaxis if needed.
2. Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.
3. Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

***Reviewer's Comments:*** (b) (4)

*The REMS goals and objectives in the REMS Document as submitted on June 17, 2024 are acceptable. Throughout the course of the review, the REMS goal and objectives were revised to align with the class labeling related to the risk of meningococcal infections and vaccination. The REMS objectives align with public health prevention aims of 1) primary prevention: to prevent an event from occurring, and 2) secondary prevention: to identify early signs and symptoms of meningococcal infection and the need for prompt evaluation to mitigate the morbidity of infection should infection occur. In addition, the REMS objectives should allow for an objective assessment of the REMS.*

### 7.1.2. REMS Participants and Materials

#### 7.1.2.1. Prescriber Requirements

The Applicant proposed that the prescriber must certify in the Piasky REMS prior to prescribing Piasky. To become certified, prescribers must review the PI, the Healthcare Provider Safety Brochure, Patient Safety Brochure, and Patient Safety Card. The prescriber must complete and submit the Prescriber Enrollment Form to the REMS.

Prior to initiating treatment with Piasky, prescribers must: 1) assess the patient for unresolved serious meningococcal infections, 2) assess the patient's meningococcal vaccination status and vaccinate as

needed according to current ACIP recommendations, 3) provide the patient with a prescription for antibacterial drug prophylaxis if the patient is not up to date with vaccines and must start Piasky immediately, and 4) counsel the patient using the Patient Guide and Patient Safety Card.

During treatment, prescribers must: 1) assess the patient for early signs of serious meningococcal infections and evaluate immediately if infection is suspected, 2) not initiate Piasky in patients being treated for serious meningococcal infection, and 3) revaccinate patients according to current ACIP recommendations.

***Reviewer Comments:*** *We agree that prescriber training and certification as summarized above and described in the REMS document is necessary. It ensures that prescribers are educated on the risks of serious meningococcal infections associated with crovalimab, the need for meningococcal vaccines and antibacterial drug prophylaxis, the need for monitoring and early evaluation, and the need for patient counseling on the risks of serious meningococcal infections.*

### Prescriber Enrollment Form

The Prescriber Enrollment Form provides a mechanism for the HCP to enroll in the REMS and to attest that they understand the requirements of the REMS.

### Healthcare Provider Safety Brochure

The Healthcare Provider Safety Brochure serves to inform prescribers and pharmacies of the serious risks of meningococcal infections associated with crovalimab, the REMS requirements, and the corresponding responsibilities of the prescriber and pharmacy.

### Vaccination Reminder Letter

The annual Vaccination Reminder Letter is to be issued to all REMS certified prescribers of crovalimab to ensure prescriber awareness of the importance of verifying that patients' vaccination status is up to date according to the Advisory Committee on Immunization Practices recommendations including the need for vaccine boosters.

***Reviewer Comment:*** *The Prescriber Enrollment Form, Healthcare Provider Safety Brochure, and Vaccination Reminder Letter are acceptable. These REMS materials will provide education for the prescriber and support the goal and objectives of the REMS. Refer to section 7.1.1.3 for the review of the Patient Safety Brochure, and Patient Safety Card.*

## 7.1.2.2. Pharmacy Requirements

Prior to dispensing crovalimab, pharmacies must certify in the Piasky REMS (ETASU B). Certified pharmacies will be required to verify that prescribers are certified by obtaining a REMS Dispense Authorization (RDA) code prior to dispensing crovalimab. In addition, pharmacies must document safe use conditions prior to dispensing the first dose of crovalimab and for up to 6 months thereafter by assessing the patient's vaccination status for up to 6 months thereafter for up to date meningococcal

vaccines for serotypes A, C, W, Y and B including antibacterial drug prophylaxis according to ACIP recommendations and document the findings (ETASU D).

Pharmacies become certified by designating an authorized representative to complete the certification process. The authorized representative must review the Healthcare Provider Safety Brochure and enroll in the REMS by completing and submitting the Healthcare Setting and Pharmacy Enrollment Form to the REMS. The authorized representative is responsible for overseeing implementation and compliance of the REMS requirements in their pharmacy. They agree to train all relevant staff involved in dispensing Piasky on the REMS requirements and are responsible for establishing processes and procedures to ensure the REMS requirements are met. This includes but is not limited to ensuring that the patient's vaccination status is assessed prior to dispensing the first dose and for up to 6 months thereafter for up to date meningococcal vaccines for serotypes A, C, W, Y and B including antibacterial drug prophylaxis according to ACIP recommendations and document the findings and serious adverse events suggestive of meningococcal infection.

***Reviewer Comments:*** *Pharmacy certification is necessary to ensure that prescribers are certified, and the patient's vaccination status is assessed, including antibiotic prophylaxis, if needed. Contact with prescribers will also serve as a reminder to vaccinate patients if needed and documentation of vaccination and antibacterial drug prophylaxis will further inform if education and certification of prescribers results in appropriate vaccination of patients and therefore achieves the overall goal of the REMS.*

*It is expected that vaccine series for some meningococcal vaccines can take up to 6 months to complete; therefore, pharmacies are required to continue to assess the patient's vaccination status for up to 6 months if patients are not up to date at the time of the first dispense. We also agree with the requirements for certification listed above which support the goal and objectives of the REMS.*

## Pharmacy Enrollment Form

Pharmacy Enrollment Form provides a mechanism for pharmacies to enroll the in the REMS and attest that they understand and agree to the requirements of the REMS.

## Healthcare Provider Safety Brochure

The Healthcare Provider Safety Brochure serves to inform prescribers, healthcare settings, and pharmacies of the serious risks of meningococcal infections associated with crovalimab, the REMS requirements, and the corresponding responsibilities of the prescriber and pharmacy.

***Reviewer Comment:*** *The Pharmacy Enrollment Form and Healthcare Provider Safety Brochure are acceptable. These REMS materials will provide education for the pharmacy and support the goal and objectives of the REMS.*

### 7.1.2.3. Patients

The Applicant did not propose patient enrollment in the Piasky REMS; however, the REMS Document outlines what patients should do to minimize their risk of meningococcal infections if they are prescribed Piasky.

Before treatment initiation patients should 1) get vaccinated against meningococcal infections as directed by their prescriber, 2) take antibiotics as directed by their prescriber if they have to start Piasky right away, 3) receive counseling from their prescriber using the Patient Safety Card and Patient Safety Brochure, and 4) receive copies of these materials from their prescriber.

During treatment, patients should receive additional vaccines as directed by their prescriber. Additionally, patients should carry the Patient Safety Card at all times during treatment and for 11 months after the last dose of Piasky and inform their prescriber or seek emergency medical care immediately if signs and symptoms of serious bacterial infection occur.

***Reviewer Comments:*** *The actions a patient should take as proposed by the Applicant are acceptable.*

**Patient Safety Card**

The Patient Safety Card serves to inform patients on the serious risks of meningococcal infections associated with crovalimab, that these risks persist for several months after the last dose, when to seek medical attention and to present the card to healthcare professionals involved in their care including those in the emergency room.

**Patient Guide**

The Patient Guide serves to inform patients on the serious risks associated with crovalimab, meningococcal vaccines, antibacterial drug prophylaxis, when to seek immediate care, and how to use the patient safety card.

***Reviewer Comment:*** *The Patient Safety Card and Patient Guide are acceptable. These REMS materials will provide important safety information for the patient/caregiver and support the goal and objectives of the REMS.*

### 7.1.2.4. Wholesaler/Distributor

Applicant proposed to distribute Piasky to certified pharmacies via specialty distributors.

***Reviewer Comment:*** *The Applicant's proposal to distribute Piasky only to certified pharmacies via specialty distributors is acceptable.*

### 7.1.2.5. Key Risk Messages

This section includes the KRMs that identify the most critical safety information that stakeholders should know about the risk and safe use behaviors to mitigate the risk of serious meningococcal infections. The

KRMs are based on the REMS goals and objectives and guide the messaging throughout the REMS materials. The proposed KRMs are:

**Key Risk Messages for Healthcare Providers (HCPs):**

1. PIASKY, a complement inhibitor, increases a patient's risk of serious, life-threatening, or fatal infections caused by Neisseria meningitidis in any serogroup, including non-groupable strains.
2. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.
3. Serious meningococcal infections may become rapidly life-threatening or fatal if not recognized and treated early. Closely monitor patients for early signs and symptoms of serious meningococcal infections and evaluate patients immediately if an infection is suspected.
4. Complete or update meningococcal vaccination (for serogroups A, C, W, Y, and B) at least 2 weeks prior to administration of the first dose of PIASKY, according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor.
5. Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.
6. If PIASKY therapy is needed right away in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations for patients receiving a complement inhibitor, provide the patient with antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible.
7. During treatment with PIASKY, vaccinate patients as needed according to ACIP recommendations for patients receiving a complement inhibitor.
8. The initiation of PIASKY treatment is contraindicated in patients with unresolved serious meningococcal infections.
9. Counsel patients using the **Patient Safety Card** and the **Patient Guide**
    a) Counsel patients on the need to carry the **Patient Safety Card** at all times during treatment and for 11 months after the last dose of PIASKY.
    b) Counsel patient to show the card to any healthcare provider that provides treatment.
    c) Tell patients to seek immediate medical attention if they develop any of the following signs or symptoms of serious meningococcal infections: fever, headache, stiff neck or stiff back, confusion or irritability, nausea or vomiting, skin rashes or spots, muscle aches with flu-like symptoms, or sensitivity of eyes to light.

**Key Risk Messages for Patients:**

1. PIASKY increases your chance of getting serious and life-threatening meningococcal infections.
2. These serious meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.
3. Complete or update meningococcal vaccine(s) at least 2 weeks before your first dose of PIASKY or as soon as possible if you have not already received these vaccines.
4. If you have not completed or are not up to date with meningococcal vaccines at least 2 weeks before your first dose of PIASKY and PIASKY therapy must be started right away, take antibiotics as directed by your healthcare provider.

5. Call your healthcare provider or get emergency medical care right away if you get any of these signs or symptoms of a serious meningococcal infection:
    a) fever
    b) feeling sick (nausea or vomiting)
    c) headache, confusion, or irritability
    d) stiff neck or stiff back
    e) muscle aches with flu-like symptoms
    f) sensitivity to lights
    g) skin rashes or spots
6. Carry the **Patient Safety Card** with you at all times during treatment and for 11 months after your last dose of PIASKY.
7. Show the **Patient Safety Card** to any healthcare provider that treats you.

***Reviewer Comments:*** *The KRM's proposed by the Applicant are acceptable.*

### 7.1.3. REMS Applicant Requirements and Materials

#### 7.1.3.1. Implementation and Operations

As part of the implementation system to operationalize the REMS, the Applicant is proposing a REMS website, REMS Call Center, a REMS database and have developed a process for pharmacies to obtain a REMS Dispense Authorization (RDA) to ensure prescribers are certified.

**REMS Website**

The REMS Website serves as a resource for stakeholders and supports prescriber online enrollment and implementation of prescriber and pharmacy requirements. The REMS website will have the capability for the certified pharmacy to obtain REMS dispense authorizations (RDA) online. Designated pharmacy staff will be able to access an online database to review previously generated RDA codes and be able to access an online database of certified healthcare providers who prescribe crovalimab and certified pharmacies who dispense crovalimab. In addition, the website will include links to the Prescribing Information and Medication Guide which can be downloaded.

**REMS Call Center**

The REMS call center will provide REMS support to stakeholders by responding to questions about the Piasky REMS and will be able to provide pharmacies with an RDA code if the prescriber is certified.

**REMS Database**

The Applicant proposes a validated, secure REMS database comprised of all REMS participants certified in the Piasky REMS.

**REMS Dispense Authorization (RDA)**

The Applicant proposes to support pharmacy requirements to verify prescriber certification by providing pharmacy authorized representatives and designated pharmacy staff two different options for obtaining

an RDA code prior to dispensing including the REMS website and the call center. The proposed RDA codes are contingent on prescriber certification whereby an RDA code will not be generated or provided if the prescriber is not certified in the Piasky REMS. In addition, pharmacy authorized representatives and designed pharmacy staff will have access to previously generated RDA codes.

***Reviewer Comment:*** *The proposed public REMS Website, REMS Call Center, the process for obtaining the RDA, and the REMS database are acceptable.*

#### 7.1.3.2. Compliance

The REMS Supporting Document, last amended on June 20, 2024, did not include the Applicant's Non-Compliance Plan and Audit Plan.

***Reviewer Comments:*** *The Agency will recommend in the approval letter that the Applicant submit their audit plan and noncompliance plan as a REMS Assessment Methodology within 60 days of approval to be reviewed by DMAMES.*

### 7.1.4. REMS Assessment Timetable

The proposed REMS Document, last amended on June 17, 2024, in response to our comments, included an updated timetable for submission of assessments at 6 months and 18 months from the date of the initial approval of the REMS and every 12 months thereafter from the date of the 18 month submission.

***Reviewer Comments:*** *DMAMES found the Applicant's proposed REMS Assessment Timetable is acceptable.*

### 7.1.5. REMS Assessment Plan

The REMS assessment plan is included in the proposed REMS Supporting Document. The REMS assessment plan includes metrics within the following assessment categories: Program Outreach and Communication, Program Implementation and Operations, Safe Use Behaviors, Health Outcomes and/or Surrogates of Health Outcomes, Knowledge, and Overall Assessment of REMS Effectiveness. The REMS Assessment Plan also includes metrics to inform on the outcome and process key performance indicators that will aid in the determination if the REMS is meeting its goal and objectives and operating as intended.

**Reviewer's Comments:** *The Applicant's proposed REMS Assessment Plan received on June 20, 2024, included all our requested revisions and is acceptable. The Piasky REMS Assessment Plan is included in the Appendix of this review and will be included in the approval letter.*

## 7.2. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on May 23, 2024, to provide feedback on the content of the **Prescriber Enrollment Form, Outpatient Pharmacy Enrollment Form, Inpatient Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, Patient Guide**, and **REMS Website**. The OPDP review was completed by Melissa Khashei, Regulatory Review Officer on June 7, 2024.[40]

OPDP provided comments on the materials based on draft Prescribing Information and Medication Guide. Labeling discussions were ongoing; therefore, OPDP recommended to revise REMS materials, as appropriate, to reflect all changes in the final approved label.

OPDP recommendations are summarized below:

**REMS Website**

- Revise page four of the REMS Website to includes information from the Piasky PI necessary for the safe use of Piasky. Specifically, the PATIENT COUNSELING INFORMATION, Serious Meningococcal Infection, section of the draft PI states (in pertinent part): "Advise patients of the risk of serious meningococcal infection Inform patients of the need to complete or update their meningococcal vaccinations at least 2 weeks prior to receiving the first dose of PIASKY or receive antibacterial drug prophylaxis if PIASKY treatment must be initiated immediately and they have not previously been vaccinated. Inform patients of the requirement to be revaccinated according to current ACIP recommendations for meningococcal infection while on PIASKY therapy. Inform patients that vaccination may not prevent serious meningococcal infection."
- Revise page four of the Piasky REMS Website to include information from the draft Piasky PI necessary for the safe use of Piasky. Specifically, the PATIENT COUNSELING INFORMATION, *Serious Meningococcal Infection,* section of the draft PI which states: "Inform patients that they will be given a **Patient Safety Card** for PIASKY that they should carry with them at all times during and for 11 months after following treatment with PIASKY. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation."

***Reviewer Comments:*** *These statements were not added to the REMS Website as the information is already captured in other relevant REMS materials such as the Patient Safety Card and the Patient Guide. This approach is consistent with information included for other complement inhibitors. DRM corresponded with Melissa Khashei on June 12, 2024 and explained DRM's rationale for not accepting the OPDP comments listed above. OPDP accepted DRM's rationale for not including these changes.*

*Unless noted above, DRM agrees with OPDP's remaining recommendations and updated the REMS materials accordingly.*

# 8. Discussion

**Discussion of Need for a REMS**

The benefits of crovalimab for the treatment of PNH were demonstrated in one pivotal phase 3 trial (COMMODORE2), which showed improvement in the transfusion avoidance from baseline through Week 25 and mean change in hemoglobin from Week 5 through Week 25 compared to eculizumab. The proposed indication is for the treatment of adult and pediatric patients 13 years and older with PNH and body weight of at least 40 kg.

The risk of serious meningococcal infections is a known risk for complement C5 inhibitors such as Soliris and Ultomiris, which are subject to a REMS to mitigate this risk. Crovalimab is a C5 complement inhibitor which increases the risk of serious infections caused by *Neisseria meningitidis*. These infections may become life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors.

There were no deaths or serious adverse events related to infection caused by *Neisseria meningitidis* in the PNH development program. There was one case of grade 3 Meningococcal meningitis (*Neisseria meningitidis* serotype X) reported in a patient with atypical hemolytic uremic syndrome (aHUS) that was receiving crovalimab treatment in a study evaluating the use of crovalimab in patients with aHUS. During the COMMODORE2 trial, risk mitigation measures were in place to prevent meningococcal infections by requiring patients to be vaccinated against serotypes A, C, W, and Y. Vaccination against serotype B was also recommended and if vaccination was completed less than 2 weeks prior to initiation or after the start of study treatment, antibiotic prophylaxis was recommended.

The review team determined that a REMS is necessary to ensure the benefits of treatment with crovalimab outweigh the risks of serious meningococcal infection. The REMS is comprised of ETASU, an implementation system, and a timetable for submission of assessments. The ETASU include prescriber certification, pharmacy certification, and documentation of safe-use conditions (verification of prescriber certification and assessment of vaccination status and need for antibacterial drug prophylaxis). These REMS elements are necessary in combination to form a program that will mitigate the risks of serious meningococcal infection and provide data to assist in determining if the goals of the REMS are being met. The design of the REMS is similar to other approved complement inhibitors and aligns with the Agency's current thinking on the necessary elements to ensure safe use for these products.

The proposed REMS for crovalimab as well as other products that are complement inhibitors were shared with the REMS Oversight Committee (ROC)[h] on August 15, 2023. The members of the ROC did not raise any concerns about the planned strategy for crovalimab.

**Assessment of the REMS and Key Performance Indicators**

Key Performance Indicators (KPIs) are measures that are used to help determine if the REMS is functioning as designed and whether the REMS is achieving its goal of mitigating the risk serious meningococcal infections. Although mitigation of serious meningococcal infections is an overall goal of the REMS, life-threatening and fatal serious meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors; therefore, it may not be possible to prevent all cases of serious meningococcal infection. While the number of cases of serious meningococcal infections will be measured and assessed, this will not be a KPI used to assess the success of the REMS. The REMS provides training to prescribers and is intended to affect safe use behavior so that prescribers do not start treatment in patients with an unresolved serious meningococcal infection, patient vaccination status is assessed, and patients receive required vaccines prior to initiating treatment with crovalimab, and patients receive antibacterial drug prophylaxis if the patient must start therapy urgently before the vaccinations are up to date. To align the KPIs with the objectives of the REMS, the KPIs are related to meningococcal vaccination rates against serotypes A, B, C, W, and Y, and education of prescribers (achieved through prescriber certification).

The Applicant incorporated revisions and comments provided by the Agency to the Supporting Document. The KPIs and minimum target thresholds for crovalimab are described below.

Primary KPI: Percent (%) of patients dispensed Piasky who received at least one dose of Advisory Committee on Immunization Practices (ACIP) recommended meningococcal vaccines (against all of the following serogroups: A, B, C, W, Y) and antibacterial drug prophylaxis if needed before the first dispense.

- Numerator: Number of patients who received at least one dose of ACIP recommended meningococcal vaccines before the first Piasky dispense and antibacterial drug prophylaxis if the patient has not received a complete series or vaccination occurred <2 weeks before first dispense of Piasky
- Denominator: Number of patients who received a first dispense of Piasky
- Minimum target threshold: 80%

Secondary KPI: Percent (%) of Piasky dispenses corresponding to prescriptions written by REMS certified Healthcare Providers

- Numerator: Number of Piasky dispenses corresponding to prescriptions written by REMS certified Healthcare Providers

[h] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

- Denominator: Number of Piasky dispenses
- Minimum target threshold: 99%

These KPIs align with our approach to related products with an approved REMS in this therapeutic class and include both outcome and process measures for REMS program evaluation.

The patient vaccination KPI for meningococcal vaccines is an outcome indicator which aligns with the primary objectives of the REMS. The minimum target thresholds (80%) for vaccination were derived based on the following considerations: vaccinations are not required before dispensing crovalimab, data collection by the pharmacy and the potential for missing data at the time of the first dispense, the Agency's experience with related approved REMS in this therapeutic class, and national rates of compliance for other vaccine schedules.[41,42] Based on these factors, we consider 80% a reasonable minimum target threshold for this KPI.

The KPI on prescriber certification is a process indicator and includes pharmacy dispenses. The KPI threshold (99%) for this KPI is based on the pharmacy verification of prescriber certification being a closed system and compliance rates with closed systems in other REMS. Although the REMS is a closed system, there is still opportunity for human error as these actions are not integrated into the pharmacy system and pharmacists must step outside their typical workflow to obtain authorization to dispense crovalimab. Therefore, the proposed REMS relies on the pharmacy authorized representative to ensure that training and processes and procedures are developed and there is good compliance. As described in the "Improving the Reliability of Health Care" white paper from the Institute of Healthcare Improvements (IHI), the expected failure rate in a system that has a process in place, which includes an identification trigger to help identify and mitigate failure such as a pharmacy identifying patients that are not vaccinated per ACIP recommendations, will help move the reliability of the care process to $10^{-2}$.[43] Therefore, the expected failure rate is very low and a high threshold of 99% is achievable, appropriate, and in line with the expected reliability of $10^{-2}$. We consider 99% a reasonable minimum target threshold for this KPI.

The Applicant's REMS Assessment Plan, which will include data reporting on the metrics for the KPI as well as additional metrics, will aid in determining the extent to which the approved strategies are meeting the goal of mitigating the risk of serious meningococcal infections.

DRM concludes the proposed REMS last submitted on June 17, 2023 will support actions that will mitigate the risk of serious meningococcal infections.

# 9. Conclusion & Recommendations

The risk of serious meningococcal infections associated with complement C5 inhibitors, such as crovalimab, is significant and can be life-threatening and fatal. DRM and DNH agree that a REMS consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions (pharmacy assessment and documentation of meningococcal vaccination and antibacterial drug prophylaxis prior to dispensing) is necessary to ensure the benefits of crovalimab outweigh the risks. The REMS will also include an implementation system and timetable for submission of assessments. These

elements along with the assessment metrics are intended to form a REMS program to mitigate the risk of serious meningococcal infections and assess if the program is meeting its intended goals.

The timetable for submission of assessments is 6 months and 18 months from the date of the initial approval of the REMS, and every 12 months thereafter from the date of the 18 month submission. DMAMES finds the REMS Assessment Plan as submitted on June 20, 2024, to be acceptable. DRM finds the Applicant's proposed Piasky REMS received on June 20, 2023 and last amended on June 17, 2024, to be acceptable and it is appended to this review.

# 10. Appendices

## 10.1. References


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## 10.2. Summary of FDA-Approved Therapies for PNH[22-27]

| **Drug (Approval Date)** | **Indication** | **Dosing and Administration** | **Important Safety and Tolerability Issues** | **Risk Management Approaches** |
|---|---|---|---|---|
| Soliris-eculizumab (2007)<br>Bkemv-eculizumab-aeeb (2024)[i] | PNH to reduce hemolysis | IV infusion: 600 mg weekly for first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter | Meningococcal infection, other infections, infusion-related reactions | REMS-ETASU<br>Labeling- boxed warning, warnings and precautions |
| Ultomiris-ravulizumab (2018) | Adult and pediatric patients one month of age and older with PNH | IV infusion: weight based, maintenance dose every 4 or 8 weeks, starting 2 weeks after loading dose | Meningococcal infections, other infections, infusion-related reactions | REMS-ETASU<br>Labeling- boxed warning, warnings and precautions |

[i] Bkemv (eculizumab-aeeb) is biosimilar* to Soliris (eculizumab).

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of BKEMV has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

| | | | | |
|---|---|---|---|---|
| | | Maintenance subcutaneous injection (on-body delivery system, adults only): 490 mg once weekly | | |
| Empaveli-pegcetacoplan (2021) | Adult patients with PNH | Subcutaneous infusion: 1,080 mg twice weekly | Serious infections caused by encapsulated bacteria, infusion-related reactions | REMS-ETASU<br>Labeling- boxed warning, warnings and precautions |
| Fabhalta-iptacopan (2023) | Adults with PNH | 200 mg orally twice daily | Serious infections caused by encapsulated bacteria, signs of hemolysis after discontinuation, and hyperlipidemia | REMS-ETASU<br>Labeling- boxed warning, warnings and precautions |
| Voydeya – danicopan (2024) | Add-on therapy to ravulizumab or eculizumab for the treatment of EVH in adults with PNH | 150 mg orally three times a day | Serious infections caused by encapsulated bacteria, hepatic enzyme increases, signs of hemolysis after discontinuation, and hyperlipidemia | REMS-ETASU<br>Labeling- boxed warning, warnings and precautions |

## 10.3. REMS

Assessment Plan
REMS Document
Prescriber Enrollment Form
Pharmacy Enrollment Form
Healthcare Provider Safety Brochure
Patient Guide
Patient Safety Card
REMS Letter: Vaccination Reminder Letter
REMS Website

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06/20/2024 04:30:01 PM

KATHRYN K MARWITZ
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JACQUELINE E SHEPPARD
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U.S. FOOD & DRUG ADMINISTRATION

# Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**OFFICE OF CARDIOLOGY, HEMATOLOGY, ENDOCRINOLOGY, AND NEPHROLOGY**
**DIVISION OF NON-MALIGNANT HEMATOLOGY**

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| | |
|---|---|
| **BLA#:** | 761388 |
| **Product:** | Piasky (crovalimab-akkz) injection |
| **APPLICANT:** | Genentech, Inc |
| **FROM:** | Rosanna Setse, MD, MPH, PhD<br>Deputy Director of Safety |
| **DATE:** | June 20, 2024 |

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Piasky (crovalimab-akkz) to ensure that the benefits of the drug outweigh the risk of serious meningococcal infections. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with paroxysmal nocturnal hemoglobinuria (PNH) is 15.9 per million (Hill 2006).

B. PNH is a rare, progressive, chronic, and life-threatening disease characterized by uncontrolled complement activation leading to hemolytic anemia (both intravascular and extravascular), peripheral cytopenias, increased susceptibility to thrombosis, and bone marrow dysfunction (Brodsky 2014). PNH leads to significant morbidity and mortality with ongoing hemolysis and the disease is considered life-threatening. Morbidities for patients with PNH include thromboembolism, pulmonary hypertension, renal and cardiac failure, infection, myelodysplastic syndrome, and aplastic anemia. The reported median survival prior to available therapies was 10 to 22 years.

C. The efficacy of Piasky in patients with PNH was evaluated in COMMODORE 2, a randomized, active-controlled, open-label non-inferiority study in patients with PNH not previously treated with a complement inhibitor. Efficacy was based on hemolysis control, as measured by the mean proportion of patients with LDH $\leq$ 1.5x ULN from Week 5 to Week 25; and the proportion of patients who achieved transfusion avoidance, defined as patients who are transfusion-free, from baseline through Week 25. COMMODORE 2 demonstrated that Piasky was non-inferior compared to eculizumab across all endpoints. The efficacy of Piasky in patients with PNH was also supported by the results of COMMODORE 1, a randomized active-controlled, open-label study in patients with PNH switching from another complement C5 inhibitor therapy. Overall, the results of COMMODORE 1 showed that patients switching to Piasky from eculizumab maintained disease control.

D. The expected use of Piasky is for the treatment of adult and pediatric patients 13 years and older with PNH and body weight of at least 40 kg. Piasky is to be administered intravenously on a chronic basis. The recommended dosage regimen is body weight based and consists of one loading dose administered by intravenous infusion (on Day 1), followed by four additional weekly loading doses administered subcutaneously on Days 2, 8, 15, and 22; and a maintenance dose administered every 4 weeks by subcutaneous injection from Day 29.

E. Crovalimab-akkz is a monoclonal antibody that specifically binds to the complement protein C5 inhibiting its cleavage into C5a and C5b preventing the formation of the membrane attack complex (MAC). Crovalimab-akkz inhibits terminal complement-mediated intravascular hemolysis in patients with PNH. An important risk associated with C5 inhibition is increased susceptibility to serious infections caused by meningococcal bacteria (septicemia and/or meningitis). These infections are serious, life-threatening, and often require hospitalization and significant medical management. Use of eculizumab, another C5 complement inhibitor product, has been associated with a 1000-fold to 2000-fold increased incidence of meningococcal disease (Applegate et al. 2015). Because

crovalimab-akkz and eculizumab are both C5 complement inhibitors indicated for the same PNH patient populations, the increased incidence of meningococcal disease will likely be the same.

F. Piasky is a new molecular entity.

The elements of the REMS will be Elements To Assure Safe Use (ETASU) including that healthcare providers who prescribe Piasky are specially certified (ETASU A); pharmacies that dispense Piasky are specially certified (ETASU B); the drug is dispensed to patients with evidence or other documentation of safe use conditions (meningococcal vaccination history including antibiotic prophylaxis will be assessed and documented by pharmacies that dispense Piasky) (ETASU D), an implementation system, and a timetable for submission of assessments of the REMS.

**References**

Applegate AO, Fong VC, Tardivel K, Lippold SA, Zarate S. Notes from the Field: Meningococcal Disease in an International Traveler on Eculizumab Therapy - United States, 2015. MMWR Morb Mortal Wkly Rep. 2016 Jul 15;65(27):696-7.

Brodsky, RA, 2014, Paroxysmal nocturnal hemoglobinuria, Blood, 124(18):2804-2811.

Hill, A, PJ Platts, A Smith, SJ Richards, MJ Cullen, QA Hill, E Roman, and P Hillmen, 2006, The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire, Blood, 108(11):985-985.

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ROSANNA W SETSE
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**MEMORANDUM**

**Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)**
**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 | June 19, 2024 |
| Application Type and Number | BLA 761388 |
| REMS TTT | 2023-6271 |
| DMAMES Team Lead | Barbara Bergquist, PharmD (DMAMES) |
| DMAMES Designee | Jo Wyeth, PharmD (OMEPRM) |
| Established Name | crovalimab-akkz |
| Trade Name | Piasky |
| Name of Applicant | Genentech Inc. |

**1. Purpose of the Memorandum**

We determined further edits were needed on the Applicant's REMS Assessment Plan included in their June 18, 2024 REMS Supporting Document. The purpose of this memorandum is to advise the Applicant of the changes that are needed to the REMS Assessment Plan.

**2. Conclusion**

The Agency does not agree with the Applicant's inclusion of the following language footnoted in the most recent submission of their REMS Assessment Plan:

(b) (4)

We do not agree with this language as certified pharmacies are required to assess and document vaccination information. The REMS Assessment Plan needs to be revised to remove this language. See our comments and recommendations in Section 3 (Comment to the Applicant). The revised REMS Assessment Plan is in Section 4 (Appendix).

**3. Comment to the Applicant**

Send the following comment along with the revised Piasky REMS Assessment Plan to the Applicant:

We refer to our Information Request dated June 18, 2024 to revise your Piasky REMS Assessment Plan. We also refer to your email response to our Information Request and your proposed Piasky REMS Assessment Plan in the REMS Supporting Document submitted on June 18, 2024.

We note your request to retain (b) (4) " in the REMS Assessment Plan.

We acknowledge your concerns; however, documentation of safe use conditions (assessment and documentation of meningococcal vaccination and antibacterial drug prophylaxis prior to dispensing) is necessary to ensure the benefits of crovalimab-akkz outweigh the risks. Per the REMS, pharmacies are required, before dispensing the first dose, and before dispensing, up to 6 months after the first dose, to assess the patient's vaccination status by contacting the prescriber if needed and document the findings. We expect pharmacies to make every attempt to obtain and document vaccination information before dispensing. If the information cannot be initially obtained, pharmacies may dispense and continue to follow-up with the prescriber to collect these data to avoid treatment delays.

Furthermore, as you indicated in your comments in the June 13, 2024 submission of the REMS Supporting Document, the Key Performance Indicator takes into consideration:

- Meningococcal vaccination is not an absolute requirement for receipt of the first dose, as there are cases where the risks of delaying treatment outweighs the risk of developing a serious infection.
- Data collection by specialty pharmacies may be incomplete or missing at the time of first dispense.
- National vaccination rates for the meningococcal vaccine in the general population and other vaccinations (Pingali et al. 2022).

We attached the REMS Assessment Plan that, if crovalimab-akkz is approved, will be included in the Approval Letter. It is unacceptable for the REMS Assessment Plan to state that (b) (4)

You do not need to submit a revised REMS Supporting Document at this time.

If in the future you want to include a statement referencing (b) (4), we recommend submitting a revised REMS Supporting Document post approval that includes the language below in Section 4 (Piasky REMS Requirements) of the REMS Supporting Document.

"(b) (4)."

**4. Appendix: Revised Piasky REMS Assessment Plan (June 19, 2024)**

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**MEMORANDUM**

**Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)**
**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 | June 18, 2024 |
| Application Type and Number | BLA 761388 |
| REMS TTT | 2023-6271 |
| Reviewer Name | Kathryn Marwitz, PharmD, MPH (DMAMES) |
| DMAMES Team Lead | Barbara Bergquist, PharmD (DMAMES) |
| DMAMES Designee | Jo Wyeth, PharmD (OMEPRM) |
| Established Name | crovalimab-akkz |
| Trade Name | Piasky |
| Name of Applicant | Genentech Inc. |

**1. Purpose of the Memorandum**

We determined further edits were needed on the Applicant's REMS Assessment Plan included in their June 17, 2024 REMS Supporting Document. The purpose of this memorandum is to revise the Applicant's REMS Assessment Plan.

**2. Conclusion**

We revised the REMS Assessment Plan and will send a communication to the Applicant describing our comments and edits.

**3. Comment to Applicant**

Send the following comment along with the revised Piasky REMS Assessment Plan to the Applicant:

See the attached redlined Piasky REMS Assessment Plan with our comments and edits. Submit your revised REMS Supporting Document including the updated REMS Assessment Plan by close of business today. Include a redlined and clean version in your submission.

Appendix: Revised Piasky REMS Assessment Plan (June 18, 2024)

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JO H WYETH
06/18/2024 01:42:13 PM

**Division of Risk Management (DRM)**
**Office of Medication Error Prevention and Risk Management (OMEPRM)**
**Office of Surveillance and Epidemiology (OSE)**
**Center for Drug Evaluation and Research (CDER)**

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| | |
|---|---|
| **Application Type** | BLA |
| **Application Number** | 761388 |
| **PDUFA Goal Date** | June 20, 2024 |
| **Nexus TTT#** | 2023-5218 |
| **Reviewer Name(s)** | Carla Darling, Pharm.D., BCPS, Risk Management Analyst (DRM)<br>Anahita Tavakoli, MA, Health Communication Analyst (DRM)<br>Kathryn Marwitz, Pharm.D., MPH, REMS Assessment Analyst (Division of Mitigation Assessment and Medication Error Surveillance [DMAMES]) |
| **Team Leader** | Jacqueline Sheppard, Pharm.D., Risk Management Team Leader (DRM)<br>Barbara Bergquist, Pharm.D., REMS Assessment Team Leader (DMAMES) |
| **Division Director** | Cynthia LaCivita, Pharm.D. |
| **Review Completion Date** | June 11, 2024 |
| **Subject** | Interim Review of Proposed REMS |
| **Established Name** | crovalimab-akkz |
| **Trade Name** | Piasky |
| **Name of Applicant** | Genentech Inc. |
| **Therapeutic Class** | Complement Inhibitor |
| **Formulation(s)** | 340 mg (2 mL) single-dose vial for intravenous or subcutaneous use |
| **Dosing Regimen** | **PIASKY Dosing Regimen Based on Body Weight** |

| **Body Weight** | **≥ 40 kg to < 100 kg** | **≥ 100 kg** |
|---|---|---|
| **Loading Dose** | | |
| Day 1 | 1,000 mg (IV) | 1,500 mg (IV) |
| Day 2, 8, 15, 22 | 340 mg (SC) | 340 mg (SC) |
| **Maintenance Dose** | | |
| Day 29 and Q4W[a] thereafter | 680 mg (SC) | 1,020 mg (SC) |

IV = intravenous, SC = subcutaneous

a Q4W=every 4 weeks

# TABLE OF CONTENTS

# 1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Piasky (crovalimab-akkz), Biologics License Application (BLA) 761388, submitted by Genentech Inc. (hereafter referred to as the Applicant) on June 20, 2023 and last amended on June 5, 2024.[1,2]

Piasky is a complement C5 inhibitor proposed for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Nonmalignant Hematology (DNH).[3]

This interim review provides DRM's comments on the REMS proposal last amended on June 5, 2024.

# 2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 05/15/2024: Agency issued interim comments to align the REMS goals and objectives and the REMS materials with revised labeling, align the REMS materials with the changes to the REMS Document, rename the Healthcare Provider Brochure to the Healthcare Provider Safety Brochure, propose Key Risk Messages (KRM) based on REMS goals and objectives, propose Key Performance Indicators (KPI), and revise the REMS Assessment Plan.
- 05/22/2024: Applicant submitted a REMS amendment in response to the interim comments issued on 05/15/2024.[4]
- 06/05/2024: Applicant submitted an additional response to the Agency's interim comments issued on 05/15/24 that included revised REMS Materials and supporting document.[2]

# 3. Review of Applicant's Proposed REMS

In response to the Agency's interim comments issued on May 15, 2024, the Applicant incorporated our comments in the REMS and proposed additional changes described below.

## 3.1. REMS Requirements

### 3.1.1. REMS Participant Requirements and Materials

The Applicant incorporated revisions and comments provided by the Agency on May 15, 2024. In addition, the Applicant proposed to add "Piasky" immediately before "REMS" to describe the Piasky REMS throughout the Prescriber Enrollment Form, Healthcare Provider Safety Brochure, and the Pharmacy Enrollment Form.

***Reviewer Comment:*** *We do not agree with adding "Piasky" immediately before "REMS" to describe the Piasky REMS throughout these REMS materials. Given that the REMS materials are specific to the Piasky REMS, it is implicit that the REMS in the REMS materials refers to the Piasky REMS; therefore, the addition of "Piasky" before REMS is not necessary. The REMS materials should be revised to remove "Piasky" before REMS as appropriate throughout the materials to align with the REMS Document. See the attached redlined Prescriber Enrollment Form, Healthcare Provider Safety Brochure, and Pharmacy Enrollment Form for additional edits and comments.*

#### 3.1.1.1. Prescriber

No further changes to the prescriber requirements were proposed.

**Prescriber Enrollment Form**

The Applicant added a statement to address follow up that may be needed regarding incomplete information provided in the Prescriber Enrollment form.

**Healthcare Provider Safety Brochure**

The Applicant added a statement regarding revaccinations under the heading titled "Risk of Serious Meningococcal Infections."

***Reviewer Comment:*** *The Prescriber Enrollment Form and Healthcare Provider Safety Brochure are not acceptable and need further revisions. The additional statement to the Healthcare Provider Safety Brochure related to revaccinations is not needed under the "Risk of Serious Meningococcal Infections" section as a similar statement is already included under the Prescriber Requirements section titled "During Piasky treatment, prescribers must."*

#### 3.1.1.2. Patient

No new patient requirements were proposed by the Applicant and no additional changes were proposed to the Patient Safety Card or the Patient Guide.

***Reviewer Comment:*** *The Patient Safety Card and Patient Guide are not acceptable and need further revisions. The following sentence should be underlined "Call your healthcare provider or get emergency medical care right away if you have any of these signs and symptoms." Additional edits are needed to Patient Safety Card and Patient Guide to align with labeling. Clarification is also needed regarding how the Patient Safety Card will be provided to patients, specifically if the card will be provided as a sheet of paper for the patient to cut and fold or if it will be provided as a card. See the attached redlined Patient Guide for additional comments and edits.*

#### 3.1.1.3. Pharmacy

No further changes to the pharmacy requirements were proposed by the Applicant.

**Pharmacy Enrollment Form**

No additional changes were proposed by the Applicant.

***Reviewer Comment:*** *The Pharmacy Enrollment Form needs further revisions. See the attached redlined Pharmacy Enrollment Form for additional edits and comments.*

### 3.1.2. REMS Applicant Requirements and Materials

#### 3.1.2.1. Operations

**REMS Website (Public)**

The Applicant incorporated revisions provided by the Agency on May 15, 2024. The Applicant's proposed website provides information for prescribers and pharmacies. Prescribers can also enroll in the REMS online. In response to the comments provided by the Agency on May 15, 2024, the Applicant

proposed a pharmacy landing page that includes instructions for how pharmacies can enroll in the REMS as well as a description of some of the pharmacy requirements.

***Reviewer Comment:*** *The public REMS website screenshots are not acceptable. The following edits to the REMS website are needed:*

- *Home landing page:*
  - *The following information was omitted from the previous submission and needs to be added back: "What is the PIASKY REMS? A Risk Evaluation and Mitigation Strategy (REMS) is a safety program require by the Food and Drug Administration (FDA) to help ensure that the benefits associated with a medication outweigh its risks. Because of the risk of serious meningococcal infections, PIASKY is available only through the PIASKY REMS, a restricted distribution program."*
  - *Rename the section titled "Key Piasky REMS Requirements" to "REMS Requirements."*
  - *Add a new section titled "Indication" that includes "PIASKY (crovalimab-akkz) is a complement inhibitor indicated for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH)."*
  - *Change the formatting of the "Reporting Adverse Events" section to a footer.*
- *Prescriber landing page:*
  - *Revise the instructions under "Step 2" for clarity as follows: "Enroll in the PIASKY REMS by completing and submitting the* ***Prescriber Enrollment Form:***
    - *Online*
    - *Fax*
      - *Fax the completed form to PIASKY REMS at 1-833-670-4840"*
- *Online prescriber enrollment page:*
  - *Edits are needed to the "Prescriber Agreement" section to align with changes to the Prescriber Enrollment Form.*
- *Pharmacy landing page:*
  - *In the section titled "To become certified to dispense PIASKY, pharmacies must,"*
    - *Revise the first sentence to align with the Pharmacy Enrollment Form "Have the Authorized Representative enroll by completing and submitting the Pharmacy Enrollment Form to the REMS by fax."*
    - *Revise the second sentence to add the method for how to contact the REMS for example "Pharmacies interested in getting certified in the PIASKY REMS should contact the PIASKY REMS Call Center at 1-866-4MY-Skyy (1-866-469-7599). "*
    - *The "Pharmacy Enrollment Form" should be an active link to the Pharmacy Enrollment Form. We acknowledge that pharmacies must contract with Genentech; however, the Pharmacy Enrollment Form is a REMS material that needs to be publicly available.*
  - *We do not agree with providing an incomplete list of the pharmacy requirements. The section titled "* (b) (4) *:" needs to be deleted and replaced with the following statement: "Steps pharmacy staff should take prior to dispensing PIASKY, and at all times, are included in the Healthcare Provider Safety Brochure."*
  - *Additional edits are needed for clarity and to align with the Agency's comments in the REMS Document and the Pharmacy Enrollment Form. See the attached redlined REMS website for additional edits and comments.*
- *Forms and Resources page:*

- *Add the "Pharmacy Enrollment Form" under the column titled "Forms." We acknowledge that pharmacies must contract with Genentech; however, the Pharmacy Enrollment Form is a REMS material that must be publicly available.*

#### 3.1.2.2. Compliance

The Applicant previously described that pharmacies would be asked to (b) (4) The Applicant did not provide a response to the Agency's questions issued on May 15, 2024, related to how the Applicant proposed to monitor compliance for the pharmacy requirement to (b) (4)

The Applicant also proposed edits for clarification to the audit language in the REMS Document.
***Reviewer Comment:*** *The Applicant did not provide clarification* (b) (4) *as requested by the Agency in the comments issued on May 15, 2024. The Applicant's next submission of the Supporting Document should include a detailed description* (b) (4) *We do not agree with the Applicant's grammatical revisions to the audit language, and have proposed additional revisions for clarity and readability.*

### 3.1.1. Implementation System

Applicant proposed to change the requirement for pharmacies to enroll via fax and online to enroll via fax only. The Applicant also proposed two different options for pharmacies to verify prescriber certification including: option 1) to obtain a REMS dispense authorization (RDA) code via the REMS portal and option 2) to obtain a RDA code via the call center, whereby the call center would provide the pharmacy with a RDA code if the prescriber is certified. The Applicant further explained that a RDA code would not be generated on their REMS Website or provided by their Call Center if the prescriber is not certified.

***Reviewer Comment:*** *The Applicant's proposed updates to the Implementation System as summarized above are acceptable.*

### 3.1.2. REMS Assessment Timetable

The Applicant did not agree with our revised REMS Document which included a REMS assessment timetable of at 6 months, 12 months and annually thereafter from the date of the initial approval of the REMS. Their June 5, 2024 revised REMS Document proposed an assessment timetable of REMS Assessments submission at 12 months and annually thereafter. The rationale provided for not including a 6 month submission was that (b) (4) PNH is an ultra rare disease.

***Reviewer Comment:*** *The Applicant's proposed timeline is not acceptable. Additional assessment submissions are needed to inform if the REMS is meeting its goal and functioning as intended and with fidelity. The REMS assessment timetable will be revised to submit assessments at 6 months, and 18 months from the date of initial approval of the REMS and every 12 months thereafter from the date of the 18 month submission. We are recommending submission of a 6-month assessment report, but*

*recognize per the Applicant's response that the data available may be limited. We are also recommending submission of an assessment report at 18 months instead of at 12 months as previously proposed. The reason for this is to allow sufficient time for the Applicant to develop methodologies (e.g., knowledge surveys, audit plans) used to assess the REMS and for the Agency to provide feedback on the methodology protocols if submitted for our review.*

# 4. Supporting Document

The Applicant incorporated revisions provided by the Agency on May 15, 2024, including edits to the non-public website, proposed KRM and KPI, and provided additional details regarding the RDA process. The Applicant also proposed additional changes to their non-public REMS website as described below.

***Reviewer Comments:*** *The REMS Supporting Document is still under review. Overall, the REMS Supporting Document must align with REMS Document and final FDA approved labeling.*

## 4.1. REMS Website (Non-Public)

The Applicant submitted revised screenshots of their secure REMS Website (non-public) attached to the revised Supporting Document. (b) (4)

***Reviewer Comment:*** *The non-public REMS website screenshots proposed by the Applicant are not acceptable. Clarification is needed regarding the pharmacy staff as follows:*

- *The Applicant's next submission of the Supporting Document should include a detailed description of the expected role of the pharmacy staff, for example "Pharmacy staff: include pharmacists or pharmacy technicians, who are designated by the Authorized Representative to manage REMS Dispense Authorization (RDAs) on behalf of the Authorized Representative."*
- *The "Add Pharmacy Staff User" screenshot should include a statement describing the role of the pharmacy staff, for example "I, the pharmacy Authorized Representative, grant administrative rights to the pharmacy staff user listed below to manage REMS Dispense Authorization (RDAs) on my behalf.*

## 4.2. Key Performance Indicator

The Applicant proposed the following key performance indicators for the Piasky REMS:

**Primary Indicator**

Percentage of PIASKY dispenses corresponding to prescriptions written by REMS certified Healthcare Providers

1. Numerator: Number of PIASKY dispenses corresponding to prescriptions written by REMS certified healthcare providers
2. Denominator: Number of PIASKY dispenses
3. Minimum target threshold: 99%

**Secondary Indicator**

Percentage of patients dispensed PIASKY who received at least one dose of Advisory Committee on Immunization Practices (ACIP) recommended meningococcal vaccines (against all of the following serogroups: A, B, C, W, Y) and antibacterial drug prophylaxis if needed before receiving the first dose of PIASKY.

1. Numerator: Number of patients who received at least one dose of ACIP recommended meningococcal vaccines before the first receiving the first dose of PIASKY or antibacterial drug prophylaxis if the patient has not received a complete series or vaccination occurred <2 weeks before first dose of PIASKY
2. Denominator: Number of patients who received a first dose of PIASKY and for whom the vaccination / drug prophylaxis status is known by the pharmacy
3. Minimum target threshold: 80%

***Reviewer's Comments:*** *The Applicant did not provide rationale or any data that supports their proposed target thresholds as requested by the Agency in the comments issued on May 15, 2024. The Applicant's next submission of the Supporting Document should include their rationale and any data to support their proposed target thresholds.*

*In addition, the Applicant's proposed secondary indicator is an outcome indicator, which aligns with the primary objective of the REMS and corresponds with the strategy to directly affect safe use behavior; therefore, should be the primary indicator. Edits to the Applicant's secondary KPI are needed. Below is the primary KPI as revised by the Agency, additions are noted by underline and deletions are noted by ~~strikethrough~~:*

*Primary KPI: Percentage of patients dispensed Piasky who received at least one dose of Advisory Committee on Immunization Practices (ACIP) recommended meningococcal vaccines (against all of the following serogroups: A, B, C, W, Y) and antibacterial drug prophylaxis if needed before the first dispense* (b) (4)

- *Numerator: Number of patients who received at least one dose of ACIP recommended meningococcal vaccines before the first* (b) (4) *Piasky dispense and* (b) (4) *antibacterial drug prophylaxis if the patient has not received a complete series or vaccination occurred <2 weeks before first dispense of Piasky*
- *Denominator: Number of patients who received a first dispense of Piasky* (b) (4)
- *Minimum target threshold: 80%*

*The primary indicator proposed by the Applicant is acceptable; however, this is a process indicator which aligns with all the objectives of the REMS and corresponds to the strategy to directly affect knowledge; therefore, should be the secondary indicator.*

## 4.3. REMS Assessment Plan

The Applicant proposed a REMS Assessment Plan in the REMS Supporting Document submitted on June 5, 2024.

***Reviewer's Comments:*** *The REMS Assessment Plan requires revisions to inform if the REMS is meeting its goal and functioning as intended. The revised redlined Assessment Plan provides our recommended edits and revisions and is included in section 8 of this review.*

# 5. Conclusions and Recommendations

DRM does not find the proposed REMS for Piasky (crovalimab-akkz) as submitted on June 20, 2023, and amended on June 5, 2024, to be acceptable, as described in this review. Send the comments in Section 6 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment by Thursday 11:00am EST on June 13, 2024.

# 6. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on June 5, 2024. Review of the REMS proposal is ongoing; these comments should not be considered final.

**Global Comments:**

1. The following REMS materials have edits. Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features. See attached redlined documents for details:
   - REMS Document
   - Prescriber Enrollment Form
   - Pharmacy Enrollment Form
   - Healthcare Provider Safety Brochure
   - Patient Safety Card
   - Patient Guide
   - REMS Website
2. Remove "Piasky" immediately before "REMS" as appropriate throughout the Prescriber Enrollment Form, Healthcare Provider Safety Form, and Pharmacy Enrollment Form to align with the REMS Document. Given that these REMS materials are specific to the Piasky REMS, it is implicit that the REMS in the REMS materials refers to the Piasky REMS; therefore, the addition of "Piasky" before REMS is not needed.

**REMS Document:**

REMS Operations Section

- For bullet #8, add method of reporting "via phone or email" to align with other REMS materials.
- For bullet #20, revise the statement to clarify when you are auditing each pharmacy. See revisions in redlined REMS document.
- For bullet #21, revise the statement to clarify when you are auditing each wholesaler-distributor. See revisions in redlined REMS document.

In Section IV, revise your REMS Assessment Timetable to submit REMS Assessments at 6 months and 18 months from the date of the initial approval of the REMS, and every 12 months thereafter from the date of the 18 month submission to inform on whether the REMS is meeting its goal and is functioning as intended and with fidelity.

**Healthcare Provider Safety Brochure:**

- Remove the statement related to revaccinations under the “Risk of Serious Meningococcal Infections” section as a similar statement is already included under the Prescriber Requirements section titled “During Piasky treatment, prescribers must.”

**Patient Safety Card:**

Underline the following sentence: "Call your healthcare provider or get emergency medical care right away if you have any of these signs and symptoms.” Additional edits are needed to align with labeling. In your next submission of the Supporting Document, include how the Patient Safety Card will be provided to patients, specifically if the card will be provided as a sheet of paper for the patients to cut and fold or if it will be provided as a card.

**REMS Website (public):**

The public REMS website screenshots are not acceptable. Edits to the REMS website are needed as follows:

- Home landing page:
    - The following information was omitted from the previous submission and needs to be added back: "What is the PIASKY REMS? A Risk Evaluation and Mitigation Strategy (REMS) is a safety program require by the Food and Drug Administration (FDA) to help ensure that the benefits associated with a medication outweigh its risks. Because of the risk of serious meningococcal infections, PIASKY is available only through the PIASKY REMS, a restricted distribution program.”
    - Rename the section titled "Key Piasky REMS Requirements" to "REMS Requirements."
    - Add the following new section "Indication: PIASKY (crovalimab-akkz) is a complement inhibitor indicated for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH)."
    - Change the formatting of the "Reporting Adverse Events" section to a footer.
- Prescriber landing page:
    - Revise the instructions under “Step 2” for clarity as follows: “Enroll in the PIASKY REMS by completing and submitting the **Prescriber Enrollment Form:**
        - Online
        - Fax
            - Fax the completed form to PIASKY REMS at 1-833-670-4840”
- Online prescriber enrollment page:
    - Align the Prescriber Agreements section with changes made to the Prescriber Enrollment Form.
- Pharmacy landing page:
    - In the section titled “To become certified to dispense PIASKY, pharmacies must:”
        - Revise the first sentence to align with the Pharmacy Enrollment Form as follows "Have the Authorized Representative enroll by completing and submitting the Pharmacy Enrollment Form to the REMS by fax."
        - Revise the second sentence to add the method for how to contact the REMS for example "Pharmacies interested in getting certified in the PIASKY REMS should contact the PIASKY REMS Call Center at 1-866-4MY-Skyy (1-866-469-7599). "
        - The "Pharmacy Enrollment Form" should be an active link to the Pharmacy Enrollment Form. We acknowledge that pharmacies must contract with Genentech; however, the Pharmacy Enrollment Form is a REMS material that needs to be publicly available.

    - We do not agree with providing an incomplete list of the pharmacy requirements. The section titled "(b) (4) " needs to be deleted and replaced with the following statement: "Steps pharmacy staff should take prior to dispensing PIASKY, and at all times, are included in the Healthcare Provider Safety Brochure."
    - Additional edits are needed for clarity and to align with the Agency's comments in the REMS Document and the Pharmacy Enrollment Form.
- Forms and Resources page:
    - Add the "Pharmacy Enrollment Form" under the column titled "Forms." We acknowledge that pharmacies must contract with Genentech; however, the Pharmacy Enrollment Form is a REMS material that must be publicly available.

**Supporting Document:**

The REMS Supporting Document is still under review. Overall, the REMS Supporting Document must align with REMS Document and final FDA approved labeling.

REMS Website (non-public)

The proposed non-public REMS website screenshots are not acceptable. Clarification is needed regarding the pharmacy staff.

- Your next submission of the Supporting Document should include a detailed description of the expected role of the pharmacy staff, for example "Pharmacy staff: include pharmacists or pharmacy technicians, who are designated by the Authorized Representative to manage REMS Dispense Authorization (RDAs) on behalf of the Authorized Representative."
- The "Add Pharmacy Staff User" screenshot should include a statement describing the role of the pharmacy staff, for example "I, the pharmacy Authorized Representative, grant administrative rights to the pharmacy staff user listed below to manage REMS Dispense Authorization (RDAs) on my behalf.

Key Performance Indicators (KPI):

We note that you did not provide rationale or any data that supports your proposed target thresholds as requested by the Agency in the comments issued on May 15, 2024. Your next submission of the Supporting Document should include rationale and any data to support your proposed target thresholds.

In addition, your proposed secondary indicator is an outcome indicator, which aligns with the primary objective of the REMS and corresponds with the strategy to directly affect safe use behavior; therefore, should be the primary indicator. Edits to your proposed secondary KPI are needed. Below is the primary KPI as revised by the Agency, additions are noted by underline and deletions are noted by ~~strikethrough~~:

Primary KPI: Percentage of patients dispensed Piasky who received at least one dose of Advisory Committee on Immunization Practices (ACIP) recommended meningococcal vaccines (against all of the following serogroups: A, B, C, W, Y) and antibacterial drug prophylaxis if needed before the first dispense (b) (4)

- Numerator: Number of patients who received at least one dose of ACIP recommended meningococcal vaccines before the first (b) (4) Piasky dispense and (b) (4) antibacterial drug prophylaxis if the patient has not received a complete series or vaccination occurred <2 weeks before first dispense of Piasky

- Denominator: Number of patients who received a first dispense of Piasky (b) (4)
- Minimum target threshold: 80%

The primary indicator proposed by the Applicant is acceptable; however, this is a process indicator which aligns with all the objectives of the REMS and corresponds to the strategy to directly affect knowledge; therefore, should be the secondary indicator.

**Compliance:**

We noted that you did not provide clarification (b) (4) as requested by the Agency in the comments issued on May 15, 2024. Your next submission of the Supporting Document should include a detailed description (b) (4)

**REMS Assessment Plan**

The proposed Piasky REMS Assessment Plan, included in your REMS Supporting Document submitted on June 5, 2024 requires revisions. See the attached redlined Piasky REMS Assessment Plan with our recommended revisions, edits and comments.

**Resubmission Instructions**

Submit a REMS amendment by Thursday 11:00am EST on June 13, 2024, that addresses these comments.

The following REMS materials contain revisions. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous).

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Safety Card
- Patient Guide
- REMS Website

Your complete REMS proposal should be submitted as separate documents in the same submission, should include a Word tracked changes version, a Word clean version, and a .pdf version of the following documents:

| Material | Required Format |
|---|---|
| REMS Document | Tracked MS Word, Clean MS Word, Clean PDF version |
| Prescriber Enrollment Form | Tracked MS Word, Clean MS Word, Clean PDF version |
| Pharmacy Enrollment Form | Tracked MS Word, Clean MS Word, Clean PDF version |
| Healthcare Provider Safety Brochure | Tracked MS Word, Clean MS Word, Clean PDF version |
| Patient Safety Card | Tracked MS Word, Clean MS Word, Clean PDF version |
| Patient Guide | Tracked MS Word, Clean MS Word, Clean PDF version |
| REMS Website | Tracked MS Word, Clean MS Word, Clean PDF version |
| Vaccination Reminder Letter | Tracked MS Word, Clean MS Word, Clean PDF version |
| REMS Supporting Document | Tracked MS Word, Clean MS Word, Clean PDF version |
| Compiled PDF file that includes the REMS Document and all REMS materials in their final, clean format | PDF version |

# 7. References


1. Genentech Inc. Prior Approval Supplement Submission - crovalimab. *BLA 761388*. June 20, 2023 (sequence 001).

2. Genentech Inc. REMS Amendment - crovalimab. *BLA 761388*. June 05, 2024 (sequence 070).

3. Genentech Inc. DRAFT Piasky (crovalimab) Prescribing Information. *BLA 761388*. May 21, 2024 (sequence 064).

4. Genentech Inc. REMS Amendment - crovalimab. *BLA 761388*. May 22, 2024 (sequence 066).


# 8. Attachments

1. REMS Document
2. Prescriber Enrollment Form
3. Pharmacy Enrollment Form
4. Healthcare Provider Safety Brochure
5. Patient Safety Card
6. Patient Guide
7. REMS Website
8. Assessment Plan

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CARLA C DARLING
06/11/2024 08:57:06 AM

ANAHITA TAVAKOLI
06/11/2024 09:01:32 AM

KATHRYN K MARWITZ
06/11/2024 09:07:06 AM

BARBARA A BERGQUIST
06/11/2024 09:21:50 AM

JACQUELINE E SHEPPARD
06/11/2024 09:29:41 AM

CYNTHIA L LACIVITA
06/11/2024 10:18:57 AM

Office of Prescription Drug Promotion

# Internal Consult

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

**Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.**

To: Ana Tavakoli, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Melissa Khashei, Regulatory Review Officer, OPDP

CC: Matthew Falter, Deputy Division Director, OPDP
Jina Kwak, Team Leader, OPDP
Cristina Attinello, Safety Regulatory Project Manager, OSE
Jacqueline Sheppard, Team Leader, DRM
Carla S.C. Darling, Risk Management Analyst, DRM
Michael Wade, OPDP
CDER-OPDP-RPM

Date: June 7, 2024

Re: BLA 761388
PIASKY (crovalimab-akkz) injection, for intravenous or subcutaneous use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

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## Materials Reviewed

OPDP has reviewed the following proposed REMS materials for PIASKY (crovalimab-akkz) injection, for intravenous or subcutaneous use (Piasky):

- Healthcare Provider (HCP) REMS Materials:
  - PIASKY Prescriber Enrollment Form
  - PIASKY Pharmacy Enrollment Form
  - PIASKY Healthcare Provider Safety Brochure
  - PIASKY Vaccination Reminder Letter

- Direct-to-Consumer (Patient) REMS Materials:
  - PIASKY Patient Guide
  - PIASKY Patient Safety Card

- PIASKY REMS Website

The version of the draft REMS materials used in this review were sent from DRM (Ana Tavakoli) via email on May 23, 2024. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Piasky.

## General Comments

Please remind Genentech, Inc. that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.PIASKYREMS.com and toll-free numbers such as 1-866-4My-Skyy (469-7599). OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Genentech, Inc. that the REMS specific website should not be the sole source of approved REMS materials.

Comments are provided using the draft product labeling (PI) and Medication Guide (MG) for Piasky accessed from Sharepoint on May 24, 2024.

OPDP notes that the current Piasky PI and MG are still being reviewed by DNH. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for Piasky.

## REMS Materials

OPDP does not object to including the following materials in the REMS program (please see “Specific Comments” below):

- Healthcare Provider (HCP) REMS Materials:
  - PIASKY Prescriber Enrollment Form
  - PIASKY Pharmacy Enrollment Form
  - PIASKY Healthcare Provider Safety Brochure
  - PIASKY Vaccination Reminder Letter

- Direct-to-Consumer (Patient) REMS Materials:
  - PIASKY Patient Guide
  - PIASKY Patient Safety Card

- PIASKY REMS Website

**Specific Comments**

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:

(b) (4)

[redacted]

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We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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MELISSA KHASHEI
06/07/2024 03:32:54 PM

**MEMORANDUM**

**Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)**
**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** | May 15, 2024 |
| **Application Type and Number** | BLA 761388 |
| **REMS TTT** | 2023-6271 |
| **Reviewer Name** | Kathryn Marwitz, PharmD, MPH (DMAMES) |
| **DMAMES Designee** | Jo Wyeth, PharmD (OMEPRM) |
| **Established Name** | crovalimab-akkz |
| **Trade Name** | Piasky |
| **Name of Applicant** | Genentech Inc. |

## 1. PURPOSE OF MEMORANDUM

The purpose of this memorandum is to update the draft REMS Assessment Plan for Piasky (crovalimab-akkz).

On May 10, 2024, we finalized a joint review with the Division of Risk Management (DRM) to provide interim comments on the Applicant's proposed REMS Assessment Plan for Piasky.[a]

After finalizing our joint review, DRM requested we replace "Revaccination Reminder Letter" with "Vaccination Reminder Letter" in the REMS Assessment Plan to align with the Piasky REMS Document. This change was made. The updated draft REMS Assessment Plan is appended to this review.

## 2. CONCLUSIONS

We revised the draft REMS Assessment Plan per the request of DRM.

Appendix: Revised Piasky REMS Assessment Plan (May 14, 2024)

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[a] Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807437e7 .

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/s/

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KATHRYN K MARWITZ
05/14/2024 04:10:15 PM

JO H WYETH
05/14/2024 04:11:49 PM

**Division of Risk Management (DRM)**
**Office of Medication Error Prevention and Risk Management (OMEPRM)**
**Office of Surveillance and Epidemiology (OSE)**
**Center for Drug Evaluation and Research (CDER)**

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| | |
|---|---|
| **Application Type** | BLA |
| **Application Number** | 761388 |
| **PDUFA Goal Date** | June 20, 2024 |
| **Nexus TTT#** | 2023-5218 |
| **Reviewer Name(s)** | Carla Darling, Pharm.D., BCPS, Risk Management Analyst (DRM)<br>Anahita Tavakoli, MA, Health Communication Analyst (DRM)<br>Kathryn Marwitz, Pharm.D., MPH, REMS Assessment Analyst (Division of Mitigation Assessment and Medication Error Surveillance [DMAMES]) |
| **Team Leader** | Jacqueline Sheppard, Pharm.D., Risk Management Team Leader (DRM)<br>Barbara Bergquist, Pharm.D., REMS Assessment Team Leader (DMAMES) |
| **Division Director** | Cynthia LaCivita, Pharm.D. |
| **Review Completion Date** | May 10, 2024 |
| **Subject** | Interim Review of Proposed REMS |
| **Established Name** | crovalimab-akkz |
| **Trade Name** | Piasky |
| **Name of Applicant** | Genentech Inc. |
| **Therapeutic Class** | Complement Inhibitor |
| **Formulation(s)** | 340 mg (2 mL) single-dose vial for intravenous or subcutaneous use |
| **Dosing Regimen** | **PIASKY Dosing Regimen Based on Body Weight** |

| **Body Weight** | **≥ 40 kg to < 100 kg** | **≥ 100 kg** |
|---|---|---|
| **Loading Dose** | | |
| Day 1 | 1,000 mg (IV) | 1,500 mg (IV) |
| Day 2, 8, 15, 22 | 340 mg (SC) | 340 mg (SC) |
| **Maintenance Dose** | | |
| Day 29 and Q4W[a] thereafter | 680 mg (SC) | 1,020 mg (SC) |

IV = intravenous, SC = subcutaneous

a Q4W=every 4 weeks

# TABLE OF CONTENTS

# 1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed REMS for Piasky (crovalimab-akkz), Biologics License Application (BLA) 761388, submitted by Genentech Inc. (hereafter referred to as the Applicant) on June 20, 2023.[1]

Piasky is a complement C5 inhibitor proposed for the treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Nonmalignant Hematology (DNH).[2]

The Applicant's proposed REMS consists of elements to assure safe use (ETASU) that include prescriber certification (ETASU A), pharmacy certification (ETASU B) and documentation of safe use conditions (ETASU D); an implementation system; and a timetable for submission of assessments to ensure the benefits of Piasky outweigh the risk of serious meningococcal infections.[1]

This interim review provides DRM's initial comments on the REMS proposal.

# 2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 06/20/2023: BLA 761388 submission for crovalimab-akkz received for the treatment of adult and pediatric patients with PNH.[1]
- 12/14/2023: Applicant was informed at the mid-cycle meeting via teleconference that a REMS was necessary to ensure the benefits outweigh the risks of serious meningococcal infections.
- 04/03/2024: Agency issued an information request (IR) asking the Applicant to clarify their drug distribution model, their proposed authorization for pharmacies to allow dispensing, and the REMS website.
- 04/08/2024: Applicant submitted a response to the Agency's IR issued on 04/03/2024.[3]
- 04/22/2024: Agency issued an information request (IR) asking the Applicant to clarify their proposed file transfer option for pharmacy verification of prescriber certification.
- 04/24/2024: Applicant submitted a response to the Agency's IR issued on 04/22/2024.[4]
- 04/30/2024: Applicant submitted an additional response to the Agency's IR issued on 04/22/24 that included a revised Supporting Document with details regarding their proposed REMS dispense authorization process for pharmacies and their drug distribution model.[5]

# 3. Review of Applicant's Proposed REMS

## 3.1. REMS Goals

The Applicant proposed the following:

The goal of the Piasky REMS is to mitigate the occurrence and morbidity associated with meningococcal infections by educating healthcare providers and patients regarding:

(b) (4)

(b) (4)

***Reviewer Comment:*** *We do not agree with the Applicant's proposed REMS goal and objectives. The goal of this REMS should be to mitigate the risks of serious meningococcal infections. The applicant has focused on education and this REMS uses a combination of strategies to support that patients are vaccinated against meningococcal infections prior to starting treatment on Piasky and receive antibiotics as appropriate. In addition, our proposed changes to the goal and objectives, as described below, align with class safety labeling for other approved complement C5 inhibitors (Soliris (BLA 125166) and Ultomiris (BLA 761108)) and the Ultomiris and Soliris REMS that was modified March 22, 2024.*[6-8]

*We revised the REMS goals and objectives to the following:*

*The goal of the PIASKY REMS is to mitigate the risk of serious meningococcal infections.*

1. *Patients are vaccinated against meningococcal infections caused by Neisseria meningitidis serogroups A, C, W, Y, and B prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving complement inhibitors and receive antibacterial drug prophylaxis if needed.*
2. *Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.*
3. *Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.*

## 3.2. REMS Requirements

### 3.2.1. ETASU

The Applicant proposed a REMS with ETASU A, B, and D, which require the certification of Healthcare Providers who prescriber Piasky (ETASU A), certification of Pharmacies that dispense Piasky (ETASU B), and assessment and documentation of patient's vaccination history/antibiotic prophylaxis by pharmacies prior to dispensing Piasky (ETASU D).

***Reviewer Comments:*** *We agree with including prescriber certification (ETASU A), certification of pharmacies or other dispensers (ETASU B), and documentation of patient's vaccination history by pharmacies prior to dispensing (ETASU D); however, additional edits are needed. The applicant needs to clarify: 1) prescriber requirements and 2) pharmacy requirements. See sections 3.2.2.1 and 3.2.2.3 of this review and the attached redlined REMS Document appended to this review for additional comments and edits.*

### 3.2.2. REMS Participant Requirements and Materials

#### 3.2.2.1. Prescriber

The Applicant proposed that the prescriber must certify in the Piasky REMS prior to prescribing Piasky. To become certified, prescribers must review the prescribing information (PI), the Healthcare Provider Safety Brochure, Patient Safety Brochure, and Patient Safety Card. The prescriber must complete and submit the Prescriber Enrollment Form to the REMS.

Prior to initiating treatment with Piasky, prescribers must: 1) assess the patient for unresolved serious meningococcal infections, 2) assess the patient's meningococcal vaccination status and vaccinate as needed according to current ACIP recommendations, 3) provide the patient with two week course of antibacterial drug prophylaxis if the patient is not up to date with vaccines and must start Piasky immediately,4) document the patient's vaccination status and prophylactic antibiotic, and 5) counsel the patient using the Patient Guide and Patient Safety Card.

During treatment, prescribers must: 1) assess the patient for early signs of serious meningococcal infections and evaluate immediately if infection is suspected, 2) consider discontinuing Piasky in patients being treated for serious meningococcal infection, and 3) revaccinate patients according to current ACIP recommendations.

***Reviewer Comments:*** *We agree with the Applicant's proposal to certify healthcare providers that prescriber Piasky; however, we do not agree with requiring prescribers to document the patient's vaccination status. While we recognize that prescribers will be assessing patient vaccination status and should be able to provide this information to pharmacies as needed, requiring prescribers to document patient vaccination status would introduce additional burden. This requirement listed under Bullet number 8 in the REMS document should be removed. We do not object to encouraging prescribers to voluntarily provide this information to the REMS. Additional edits are also needed to the prescriber requirements to align with updated class labeling changes for complement C5 inhibitors. See the attached redlined REMS Document.*

## Prescriber Enrollment Form

The Applicant proposed a Prescriber Enrollment Form to enroll healthcare providers in the REMS and to attest that they understand the requirements of the REMS. This form includes information about how to become certified in the REMS, and prescriber agreements.

## Healthcare Provider Safety Brochure

The Applicant proposed a Healthcare Provider Safety Brochure to inform prescribers and pharmacies of the serious risks of meningococcal infections associated with Piasky, the REMS requirements, and the corresponding responsibilities of the prescriber and pharmacy.

***Reviewer Comment:*** *We agree the Prescriber Enrollment Form is necessary to enroll healthcare providers who want to prescriber Piasky in the REMS and a Healthcare Provider Safety Brochure is needed to inform prescribers and pharmacies about the risks of Piasky, appropriate safe use and the Piasky REMS requirements. Edits are needed to these REMS materials to align with the Agency's comments in the REMS Document. See the attached redlined Prescriber Enrollment Form and Healthcare Provider Safety Brochure for additional edits and comments.*

#### 3.2.2.2. Patient

## Patient Safety Card

The Patient Safety Card serves to inform patients on the serious risks of meningococcal infections associated with Piasky, that these risks persist for several months after the last dose of Piasky, when to seek immediate care, and instructs the patient to present the card to any healthcare professional involved in their care including those in the emergency room.

## Patient Guide

The Patient Safety Brochure serves to inform patients on the serious risks associated with Piasky, meningococcal vaccines, antibacterial drug prophylaxis, when to seek immediate care, and how to use the patient safety card.

***Reviewer Comment:*** *The Patient Safety Brochure should be renamed to Patient Guide to align with the Agency's current thinking on the names of patient and healthcare provider directed materials. Additional edits are needed to align with the Agency's comments in the REMS Document. See the attached redlined Patient Safety Card and Patient Guide for additional comments and edits.*

### 3.2.2.3. Pharmacy

The Applicant proposed that pharmacies must certify in the Piasky REMS prior to dispensing Piasky. Prior to dispensing Piasky, pharmacies will be required to verify that prescribers are certified by obtaining a REMS Dispense Authorization (RDA) code online via the REMS portal or by verifying via a file transfer received from the REMS administrator. In addition, pharmacies will be required to assess the patient's vaccination status prior to dispensing for up-to-date meningococcal vaccines for serotypes A, C, W, Y and B including antibacterial drug prophylaxis according to ACIP recommendations and document the findings.

Pharmacies become certified by designating an authorized representative to complete the certification process, who will oversee implementation and compliance with the REMS program. The authorized representative must : 1) review the Healthcare Provider Safety Brochure and enroll in the REMS by completing and submitting the Healthcare Setting and Pharmacy Enrollment Form to the REMS, 2) train all relevant staff involved in dispensing Piasky on the REMS requirements, 3) agree that all relevant staff involved in dispensing Piasky must assess the patient's vaccination status prior to dispensing for up-to-date meningococcal vaccines for serotypes A, C, W, Y and B including antibacterial drug prophylaxis according to ACIP recommendations and document the findings, and 4) agree that all relevant staff involved in dispensing Piasky must report serious adverse events suggestive of meningococcal infection to the Applicant.

***Reviewer Comment:*** *Vaccine series for some of meningococcal vaccines can take up to 6 months to complete; therefore, edits are needed to clarify that the pharmacy requirements to assess the patient's vaccination status continue for up to 6 months if patients are not up to date at the time of the first dispense. Additional edits are needed to pharmacy requirements to align with updated class labeling changes for complement C5 inhibitors. See the attached redlined REMS Document for additional edits and comments.*

## Pharmacy Enrollment Form

The Applicant proposed a Pharmacy Enrollment Form is to carry out the certification process. A designed authorized representative completes the form on behalf of the pharmacy and in doing so agrees to the conditions of the REMS.

## Healthcare Provider Safety Brochure

The Applicant proposed a Healthcare Provider Safety Brochure to inform prescribers and pharmacies of the serious risks of meningococcal infections associated with Piasky, the REMS requirements, and the corresponding responsibilities of the prescriber and pharmacy.

***Reviewer Comment:*** *We agree with the Pharmacy Enrollment Form to enroll pharmacies who want to dispense Piasky in the REMS and the Healthcare Provider Safety Brochure to inform prescribers and pharmacies about the Piasky REMS. However, edits are needed to align with the Agency's comments in the REMS Document. See the attached redlined Pharmacy Enrollment Form and Healthcare Provider Safety Brochure for additional edits and comments.*

#### 3.2.2.4. Wholesaler/Distributor

Applicant originally proposed to (b) (4). However, in a subsequent communication, the Applicant amended their proposal to only distribute Piasky to certified pharmacies via specialty distributors.

***Reviewer Comment:*** *Edits needed to the REMS Document to remove* (b) (4) *See the attached redlined REMS Document for additional edits and comments.*

### 3.2.3. REMS Applicant Requirements and Materials

#### 3.2.3.1. Operations

**REMS Website**

The Applicant proposes a REMS Website with information for stakeholders and includes the option for prescribers and pharmacies to enroll in the REMS online.

***Reviewer Comment:*** *The public REMS website screenshots included in your REMS Supporting Document submitted on April 30, 2024, are not acceptable. Remove the public REMS website screenshots appended to the Supporting Document in Appendix 1 and submit these in a separate document as the REMS Website is one of the appended REMS materials. Edits are needed to the public REMS website to align with the Agency's comments in the REMS Document and other REMS materials. See the attached redlined REMS website for additional edits and comments.*

#### 3.2.3.1. Implementation System

The Applicant proposed two different options for pharmacies to verify prescriber certification including: option 1) to obtain authorization via a look up tool in the REMS portal and option 2) (b) (4). The Applicant further explained that the file transfer with list of certified prescribers would be provided to pharmacies on a daily basis.

***Reviewer Comment:*** *We do not agree with the option for pharmacies to* (b) (4) *. Providing different ways to verify prescriber certification may create confusion to pharmacies regarding this requirement and potentially lead to non-compliance with REMS requirements. In addition,* (b) (4) *can become outdated, which may potentially contribute to non-compliance with the REMS requirements. Regarding the option for pharmacies to verify prescriber certification via the look up tool in the REMS portal, clarification is needed regarding the process for obtaining authorization. See section 4.1 of this review for additional comments regarding the REMS portal.*

#### 3.2.3.2. Compliance

As described in section 3.2.2.3 of this review, the Applicant proposed that pharmacies assess patient vaccination status and document the findings. (b) (4)

(b) (4)

***Reviewer Comment:*** *Clarification is needed* (b) (4)

### 3.3. REMS Assessment Timetable

The Applicant proposed a REMS assessment timetable of 12 months and every two years thereafter from date of the initial approval of the REMS.

***Reviewer Comment:*** *The Applicant's proposed timeline is not acceptable. Additional assessment submissions are needed to inform if the REMS is meeting its goal and functioning as intended and with fidelity. The REMS assessment timetable will be revised to submit assessments at 6 months, 12 months, and annually thereafter from the date of initial approval of the REMS.*

## 4. Supporting Document

The REMS Supporting Document includes the background of the REMS currently under review.

***Reviewer Comments:*** *The REMS Supporting Document is still under review. Overall, the REMS Supporting Document must align with REMS Document and final FDA approved labeling.*

### 4.1. REMS Portal

The Applicant proposes a secure REMS portal that requires the certified pharmacy to create an account so their staff can access a certified prescriber database to verify prescriber certification. The Applicant provided post-login website screenshots attached to the revised Supporting Document that show how pharmacies generate a REMS dispense authorization (RDA) code that is contingent on prescriber certification. In addition, the Applicant proposed that Authorized Representatives would be able to add office and pharmacy staff.

***Reviewer Comment:*** *The proposed post-login website screenshots are not acceptable. Clarification is needed regarding the process for obtaining a REMS dispense authorization code and the option to add office and pharmacy staff.*

- *The Applicant's next submission of the Supporting Document should include a detailed description of the REMS dispense authorization process.*
- *The Applicant's next submission of the Supporting Document should include a detailed description of the expected role of the office and pharmacy staff that includes:*
    - *Description of the role of the "pharmacy staff: in section 10.1 of the Supporting Document and "office staff" in section 10.2 of the Supporting Document.*
    - *Whether "pharmacy staff" and "office staff" will be able to generate a REMS dispense authorization code?*
    - *Description of who the expected office and pharmacy staff will be (e.g., pharmacist, technicians, clerks, etc.).*
    - *Description of the process for creating an account including who is responsible for providing access and creating accounts for office and pharmacy staff.*
- *The "Pharmacy Certification" screenshots of the online Pharmacy Enrollment Form were omitted in this submission. Ensure that all screenshots are included in your next submission.*

## 4.2. Key Risk Messages

The Applicant did not propose any key risk messages (KRM). KRMs should identify the most critical information for stakeholders to know about the risk and safe use behaviors to mitigate the risk of serious meningococcal infections. The KRMs should be based on the REMS goals and objectives and should guide the messaging throughout the REMS materials.

***Reviewer Comments:*** *The Applicant must include KRM based on the REMS goal, objectives, and other relevant REMS educational materials and submit the KRM in the next included as a new section in the REMS Supporting Document. We will share the following KRMs that were used for other complement 5 inhibitors for the applicant to consider.*

***Key Risk Messages for Healthcare Providers (HCPs):***

1. *PIASKY, a complement inhibitor, increases a patient's risk of serious, life-threatening, or fatal infections caused by Neisseria meningitidis in any serogroup, including non-groupable strains.*
2. *Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.*
3. *Serious meningococcal infections may become rapidly life-threatening or fatal if not recognized and treated early. Closely monitor patients for early signs and symptoms of serious meningococcal infections and evaluate patients immediately if an infection is suspected.*
4. *Complete or update meningococcal vaccination (for serogroups A, C, W, Y, and B) at least 2 weeks prior to administration of the first dose of PIASKY, according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor.*
5. *Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.*
6. *If PIASKY therapy is needed right away in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations for patients receiving a complement inhibitor, provide the patient with antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible.*
7. *During treatment with PIASKY, vaccinate patients as needed according to ACIP recommendations for patients receiving a complement inhibitor.*
8. *The initiation of PIASKY treatment is contraindicated in patients with unresolved serious meningococcal infections.*
9. *Counsel patients using the* ***Patient Safety Card*** *and the* ***Patient Guide***
    a) *Counsel patients on the need to carry the* ***Patient Safety Card*** *at all times during treatment and for 11 months after the last dose of PIASKY.*
    b) *Counsel patient to show the card to any healthcare provider that provides treatment.*
    c) *Tell patients to seek immediate medical attention if they develop any of the following signs or symptoms of serious meningococcal infections: fever, headache, stiff neck or stiff back, confusion or irritability, nausea or vomiting, skin rashes or spots, muscle aches with flu-like symptoms, or sensitivity of eyes to light.*

***Key Risk Messages for Patients:***

1. *PIASKY increases your chance of getting serious and life-threatening meningococcal infections.*
2. *These serious meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.*

3. *Complete or update meningococcal vaccine(s) at least 2 weeks before your first dose of PIASKY or as soon as possible if you have not already received these vaccines.*
4. *If you have not completed or are not up to date with meningococcal vaccines at least 2 weeks before your first dose of PIASKY and PIASKY therapy must be started right away, take antibiotics as directed by your healthcare provider.*
5. *Call your healthcare provider or get emergency medical care right away if you get any of these signs or symptoms of a serious meningococcal infection:*
    a) *fever*
    b) *feeling sick (nausea or vomiting)*
    c) *headache, confusion or irritability*
    d) *stiff neck or stiff back*
    e) *muscle aches with flu-like symptoms*
    f) *sensitivity to lights*
    g) *skin rashes or spots*
6. *Carry the **Patient Safety Card** with you at all times during treatment and for 11 months after your last dose of PIASKY.*
7. *Show the **Patient Safety Card** to any healthcare provider that treats you.*

### 4.3. Key Performance Indicator

The Applicant has not proposed a key performance indicator for the Piasky REMS.

***Reviewer's Comments:***
*Key Performance Indicators (KPI):*
*KPI are measures that are used to help determine if the REMS is functioning as designed, and whether the Piasky REMS is achieving its goal of mitigating the risk of meningococcal infection. The REMS objectives were revised to align with the public health prevention aims (primary and secondary prevention) as described in section 3.1 of this review. The objectives of the REMS using the public health prevention aims inform the selection of the KPI. The KPI indicates whether the REMS is achieving its goal and may help to determine if modifications to the REMS are necessary. The Applicant should add a new section, titled "Key Performance Indicator (KPI)" to the Supporting Document which includes the KPI and the associated target threshold along with a supporting rationale and plans to evaluate the REMS if the KPI is not met. KPIs at or above the target threshold indicate the REMS is functioning as designed and is meeting its objective. The Applicant should propose a target threshold for the KPI considering the design of the REMS, how the data will be captured, and current vaccine climate. The Applicant should include a rationale and any data that supports the target threshold.*

### 4.4. REMS Assessment Plan

The Applicant proposed a REMS Assessment Plan in the REMS Supporting Document. The proposed Assessment plan includes metrics in the following assessment categories: Program Outreach and Communication, Program Implementation and Operations, Safe Use Behaviors, Health Outcomes and/or Surrogates of Health Outcomes and Knowledge.

***Reviewer's Comments:*** *The REMS Assessment Plan requires revisions to inform if the REMS is meeting its goal and functioning as intended. These revisions are necessary to align with the REMS document, add an additional assessment category, assess patient vaccination and antibacterial drug utilization, if*

*needed, assess REMS processes and REMS stakeholder compliance, and clarify Assessment Plan metrics. The revised redlined Assessment Plan provides our recommended edits and revisions and is included in section 8 of this review.*

# 5. Conclusions and Recommendations

DRM does not find the proposed REMS for Piasky (crovalimab-akkz) as submitted on June 20, 2023 to be acceptable, as described in this review. Send the comments in Section 6 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 5 business days.

# 6. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on June 20, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

**Global Comment:**

The following REMS materials have edits to align with the REMS Document and class safety labeling changes for complement C5 inhibitors. Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features. See attached redlined documents for details:

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Safety Card
- Patient Guide
- REMS Website

**REMS Document:**

- The goal and objectives require changes to align with class safety labeling for complement C5 inhibitors regarding the risk of serious meningococcal infections and vaccinations and to align with REMS for other approved complement C5 inhibitors. Please refer to the approved Prescribing Information for Soliris, BLA 125166 and Ultomiris, BLA 761108 (approved March 22, 2024) and the Ultomiris and Soliris REMS that was modified on March 22, 2024.

  Revise the REMS goals and objectives to the following:

  The goal of the PIASKY REMS is to mitigate the risk of serious meningococcal infections.

  1. Patients are vaccinated against meningococcal infections caused by *Neisseria meningitidis* serogroups A, C, W, Y, and B prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving complement inhibitors and receive antibacterial drug prophylaxis if needed.
  2. Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.
  3. Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

- Your proposal to certify healthcare providers that prescriber Piasky is acceptable; however, we do not agree with requiring prescribers to document patient's vaccination status. While we recognize that prescribers will be assessing patient vaccination status and should be able to provide this information to pharmacies as needed, requiring prescribers to document patient vaccination status would introduce additional burden. Remove the requirement listed under bullet number 8 in the REMS Document. We do not object to prescribers voluntarily providing e this information to the REMS.
- Vaccine series for some of meningococcal vaccines can take up to 6 months to complete; therefore, edits are needed to clarify that the pharmacy requirements to assess the patient's vaccination status continue for up to 6 months if patients are not up to date at the time of the first dispense.
- Remove (b) (4) from the wholesaler/distributor section.
- Revise your REMS Assessment Timetable to submit REMS Assessments at 6 months, 12, months, and annually thereafter from the date of the initial approval of the REMS to inform on whether the REMS is meeting its goal and is functioning as intended and with fidelity.

**Patient Guide:**

Rename the "Patient Safety Brochure" to "Patient Guide" to align with the Agency's current thinking on the names of patient and healthcare provider directed materials. Additional edits are needed to align with the Agency's comments in the REMS Document.

**REMS Website:**

The REMS public website screenshots included in your REMS Supporting Document submitted on April 30, 2024, are not acceptable. Remove the public REMS website screenshots appended to the Supporting Document in Appendix 1 and submit these in a separate document as the REMS Website is one of the appended REMS materials. Edits are needed to the public REMS website to align with the Agency's comments in the REMS Document and other REMS materials.

**Supporting Document:**

The REMS Supporting Document is still under review. Overall, the REMS Supporting Document must align with REMS Document and final FDA approved labeling.

REMS Portal

The proposed post-login website screenshots are not acceptable. Clarification is needed regarding the process for obtaining a REMS dispense authorization code and the option to add office and pharmacy staff.

- Include a detailed description of the REMS dispense authorization process in your next submission of the Supporting Document.
- In your next submission of the Supporting Document include a detailed description of the expected role of the office and pharmacy staff that includes:
    - Description of the role of the "pharmacy staff: in section 10.1 of the Supporting Document and "office staff" in section 10.2 of the Supporting Document.
    - Whether "pharmacy staff" and "office staff" will be able to generate a REMS dispense authorization code?

- Description of who the expected office and pharmacy staff will be (e.g., pharmacist, technicians, clerks, etc.).
- Description of the process for creating an account including who is responsible for providing access and creating accounts for office and pharmacy staff.

The "Pharmacy Certification" screenshots of the online Pharmacy Enrollment Form were omitted in this submission. Ensure that all screenshots are included in your next submission.

Key Risk Messages

KRMs should identify the most critical information for stakeholders to know about the risk and safe use behaviors to mitigate the risk of serious meningococcal infections. The KRMs should be based on the REMS goals and objectives and should guide the messaging throughout the REMS materials. Include KRMs in your next submission included as a new section in the REMS Supporting Document. We have included the following KRMs that were used for other complement 5 inhibitors for you to consider.

**Key Risk Messages for Healthcare Providers (HCPs):**

1. PIASKY, a complement inhibitor, increases a patient's risk of serious, life-threatening, or fatal infections caused by Neisseria meningitidis in any serogroup, including non-groupable strains.
2. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.
3. Serious meningococcal infections may become rapidly life-threatening or fatal if not recognized and treated early. Closely monitor patients for early signs and symptoms of serious meningococcal infections and evaluate patients immediately if an infection is suspected.
4. Complete or update meningococcal vaccination (for serogroups A, C, W, Y, and B) at least 2 weeks prior to administration of the first dose of PIASKY, according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor.
5. Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.
6. If PIASKY therapy is needed right away in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations for patients receiving a complement inhibitor, provide the patient with antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible.
7. During treatment with PIASKY, vaccinate patients as needed according to ACIP recommendations for patients receiving a complement inhibitor.
8. The initiation of PIASKY treatment is contraindicated in patients with unresolved serious meningococcal infections.
9. Counsel patients using the **Patient Safety Card** and the **Patient Guide**
    a) Counsel patients on the need to carry the **Patient Safety Card** at all times during treatment and for 11 months after the last dose of PIASKY.
    b) Counsel patient to show the card to any healthcare provider that provides treatment.
    c) Tell patients to seek immediate medical attention if they develop any of the following signs or symptoms of serious meningococcal infections: fever, headache, stiff neck or stiff back, confusion or irritability, nausea or vomiting, skin rashes or spots, muscle aches with flu-like symptoms, or sensitivity of eyes to light.

**Key Risk Messages for Patients:**

1. PIASKY increases your chance of getting serious and life-threatening meningococcal infections.
2. These serious meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.
3. Complete or update meningococcal vaccine(s) at least 2 weeks before your first dose of PIASKY or as soon as possible if you have not already received these vaccines.
4. If you have not completed or are not up to date with meningococcal vaccines at least 2 weeks before your first dose of PIASKY and PIASKY therapy must be started right away, take antibiotics as directed by your healthcare provider.
5. Call your healthcare provider or get emergency medical care right away if you get any of these signs or symptoms of a serious meningococcal infection:
    a) fever
    b) feeling sick (nausea or vomiting)
    c) headache, confusion or irritability
    d) stiff neck or stiff back
    e) muscle aches with flu-like symptoms
    f) sensitivity to lights
    g) skin rashes or spots
6. Carry the **Patient Safety Card** with you at all times during treatment and for 11 months after your last dose of PIASKY.
7. Show the **Patient Safety Card** to any healthcare provider that treats you.

Key Performance Indicators (KPI):

KPI are measures that are used to help determine if the REMS is functioning as designed, and whether the Piasky REMS is achieving its goal of mitigating the risk of meningococcal infection. The REMS objectives were revised to align with the public health prevention aims (primary and secondary prevention). The objectives of the REMS using the public health prevention aims inform the selection of the KPI. The KPI indicates whether the REMS is achieving its goal and may help to determine if modifications to the REMS are necessary. In your next submission, add a new section to the Supporting Document, titled "Key Performance Indicator (KPI)" which includes the KPI and the associated target threshold along with a supporting rationale and plans to evaluate the REMS if the KPI is not met. KPIs at or above the target threshold indicate the REMS is functioning as designed and is meeting its objective. In addition, propose a target threshold for the KPI considering the design of the REMS, how the data will be captured, and current vaccine climate. Include your rationale and any data that supports the target threshold.

**Implementation System:**

We do not agree with the option for pharmacies (b) (4) Providing different ways to verify prescriber certification may create confusion to pharmacies regarding this requirement and potentially lead to non-compliance with REMS requirements. In addition, (b) (4) can quickly become outdated, which may potentially contribute to non-compliance with the REMS requirements. Regarding the option for pharmacies to verify prescriber certification via the look up tool in the REMS portal, clarification is needed regarding the process for obtaining authorization. See the REMS portal comments above for additional details.

**Compliance:**

In your IR response submitted on April 24, 2024, you proposed that pharmacies will be expected to [redacted] (b) (4)

**REMS Assessment Plan**

The proposed Piasky REMS Assessment Plan, included in your REMS Supporting Document submitted on April 30, 2024, requires revisions. See the attached redlined Piasky REMS Assessment Plan with our recommended revisions, edits and comments.

**Resubmission Instructions**

Submit a REMS amendment in **5 business days** that addresses these comments.

The following REMS materials contain revisions. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous).

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Safety Card
- Patient Guide
- REMS Website

Your complete REMS proposal should be submitted as separate documents in the same submission, should include a Word tracked changes version, a Word clean version, and a .pdf version of the following documents:

| **Material** | **Required Format** |
|---|---|
| REMS Document | Tracked MS Word, Clean MS Word, Clean PDF version |
| Prescriber Enrollment Form | Tracked MS Word, Clean MS Word, Clean PDF version |
| Pharmacy Enrollment Form | Tracked MS Word, Clean MS Word, Clean PDF version |
| Healthcare Provider Safety Brochure | Tracked MS Word, Clean MS Word, Clean PDF version |
| Patient Safety Card | Tracked MS Word, Clean MS Word, Clean PDF version |
| Patient Guide | Tracked MS Word, Clean MS Word, Clean PDF version |
| REMS Website | Tracked MS Word, Clean MS Word, Clean PDF version |
| REMS Supporting Document | Tracked MS Word, Clean MS Word, Clean PDF version |
| Compiled PDF file that includes the REMS Document and all REMS materials in their final, clean format | PDF version |

# 7. References


1. Genentech Inc. Prior Approval Supplement Submission - crovalimab. *BLA 761388*. June 20, 2023 (sequence 001).

2. Genentech Inc. DRAFT Piasky (crovalimab) Prescribing Information. *BLA 761388*. June 20, 2023 (sequence 001).

3. Genentech Inc. REMS/Response to IR. *BLA 761388*. April 08, 2024 (sequence 046).

4. Genentech Inc. REMS/Response to IR. *BLA 761388*. April 24, 2024 (sequence 052).

5. Genentech Inc. REMS/Response to IR. *BLA 761388*. April 30, 2024 (sequence 056).

6. Alexion Pharmaceuticals Inc. Ultomiris (ravulizumab-cwvz) Prescribing Information. *Boston, MA*. 03/2024. Accessed April 18, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761108s026s031lbl.pdf

7. Alexion Pharmaceuticals Inc. Soliris (eculizumab) Prescribing Information. *Boston, MA*. 03/2024. Accessed April 18, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125166s443lbl.pdf

8. Ultomiris and Soliris REMS. *Approved Risk Evaluation and Mitigation Strategies (REMS)*. Accessed May 10, 2024. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=429


# 8. Attachments

1. REMS Document
2. Prescriber Enrollment Form
3. Pharmacy Enrollment Form
4. Healthcare Provider Safety Brochure
5. Patient Safety Card
6. Patient Guide
7. REMS Website
8. Revaccination Reminder Letter
9. Assessment Plan

60 Page(s) of Draft REMS 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.**

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/s/

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CARLA C DARLING
05/10/2024 03:02:00 PM

JACQUELINE E SHEPPARD on behalf of ANAHITA TAVAKOLI
05/10/2024 03:14:02 PM

KATHRYN K MARWITZ
05/10/2024 03:17:07 PM

JO H WYETH on behalf of BARBARA A BERGQUIST
05/10/2024 03:19:11 PM

JACQUELINE E SHEPPARD
05/10/2024 03:30:49 PM

CYNTHIA L LACIVITA
05/10/2024 04:33:33 PM