Summary Table of Study Protocol

Title	Periodic Assessment Survey of Patients/Caregivers to Assess Understanding of the Risks with the BKEMV® Risk Evaluation and Mitigation Strategy (REMS)
Protocol version identifier	20240214 Version 1.0
Date of last version of the protocol	27 October 2025
EU Post Authorization Study (PAS) Register No	1000000368
Active Substance	Eculizumab-aeeb
Medicinal Product	BKEMV
Device	Not Applicable (N/A)
Product Reference	N/A
Procedure Number	N/A
Joint PASS	No

Research Question and Objectives	The objectives of the REMS Patient/Caregiver Knowledge Assessment Survey (hereinafter referred to as Patient/Caregiver REMS Knowledge Assessment Survey) are to conduct a survey with patients who are at least 18 years of age who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV. The following survey knowledge domains for patients have been developed based on the goal of the REMS as reviewed and approved by the Food and Drug Administration (FDA) (refer to Section 3.2.6 of the BKEMV REMS Supporting Document). For a complete list of the survey knowledge questions encompassing the domains, as outlined below, Section 4. Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early (Survey Knowledge Domain 1). Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed (Survey Knowledge Domain 2). Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation (Survey Knowledge Domain 3). The survey will begin with screening questions followed by survey knowledge questions. Additionally, the survey will collect data about patient/ caregiver awareness, reading, and use of the BKEMV educational materials followed by the collection of demographic information.
Country(ies) of Study	United States (US)

Author	[redacted] [redacted] Associate Director, Center for Observational Research (C*f*OR) Amgen Inc. [redacted] [redacted] Observational Research Senior Manager, Center for Observational Research (C*f*OR) Amgen Inc. [redacted]

Marketing Authorization Holder (MAH)

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	[redacted] Global Safety Medical Director, Safety TA & Combination Products, Amgen Inc. [redacted]

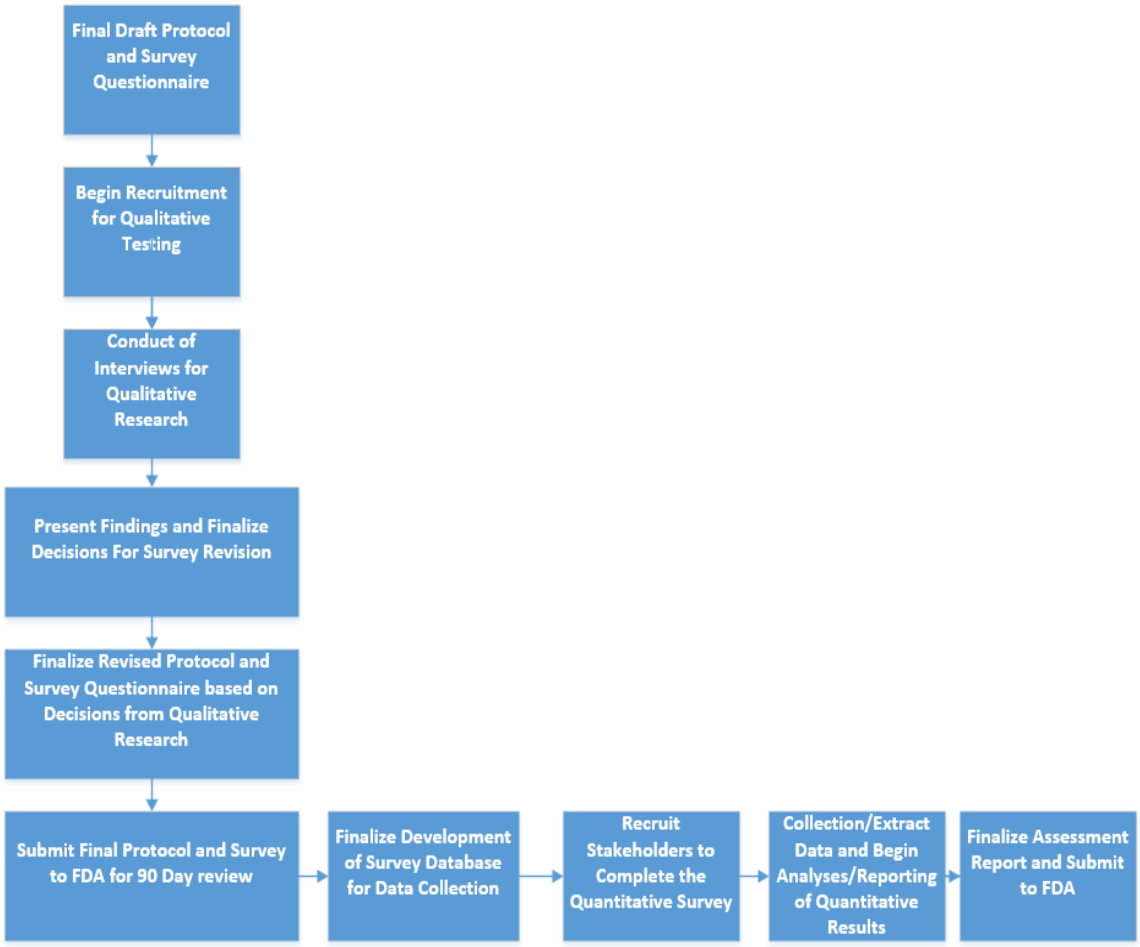
This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0	27 October 2025	27 October 2025

Confidentiality Notice

Study Design Schema

Wave 1 Patient/Caregiver REMS Knowledge Assessment Survey Projected Timeline



1. Table of Contents

List of Tables

List of Figures

N/A

List of Appendices

2. List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
aHUS	Atypical Hemolytic Uremic Syndrome
Amgen	Amgen Inc.
AR	Authorized Representative
CAPTCHA	Completely Automated Public Turing Test to Tell Computers and Humans Apart
CFR	Code of Federal Regulations
CI	Confidence Interval
DCT	Data Collection Tool
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
GCP	Good Clinical Practice
HCP	Healthcare Provider/Professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
N/A	Not Applicable
OSF	Other Safety Findings
Patient and/or Caregiver	Participant
PNH	Paroxysmal Nocturnal Hemoglobinuria
QC	Quality Control
QR	Qualitative Research

Abbreviation	Definition
REMS	Risk Evaluation and Mitigation Strategy
SAS	Statistical Analysis System
SCC	Survey Coordinating Center
SOP	Standard Operating Procedure
TL	Tables and Listings
UAT	User Acceptance Testing
[redacted]	
URL	Uniform Resource Locator
US	United States

3. Responsible Parties

Name, Degree(s)	Job Title	Affiliation	Address
[redacted] MSc	Senior Manager, Observational Research, Clinical Program Operations	Amgen Limited	216 Cambridge Science Park Milton Road Cambridge CB4 0WA
[redacted]			

4. Abstract

Title: Periodic Assessment Survey of Patients/Caregivers to Assess Understanding of the Risks with the BKEMV® Risk Evaluation and Mitigation Strategy (REMS)

Study Rationale & Background: The BKEMV Risk Evaluation and Mitigation Strategy (REMS) was approved by the United States (US) Food and Drug Administration (FDA) on 28 May 2024. In accordance with section 505-1 of Federal Food, Drug, and

Cosmetic Act (FDCA), the FDA determined that a REMS is necessary for BKEMV to mitigate the risk of serious meningococcal infections and to educate healthcare providers/professionals (HCPs) and patients/caregivers regarding:

a. the need to ensure that patients are vaccinated against meningococcal infections,
b. the need to ensure that patients are aware of early signs and symptoms of meningococcal infections and the need for immediate medical evaluation; and,
c. the need to ensure that prescribers are aware of early signs and symptoms of meningococcal infections and the need for immediate medical evaluation.

The specific objectives to be achieved by the BKEMV REMS include the assessment of patients'/caregivers' knowledge of the following survey knowledge domains:

- Survey Knowledge Domain 1: Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early.
- Survey Knowledge Domain 2: Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.
- Survey Knowledge Domain 3: Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

The survey will begin with screening questions followed by survey knowledge questions. The survey will also collect data about patient awareness, reading, and use of the BKEMV educational materials followed by the collection of demographic information.

A component of the BKEMV REMS Assessment Plan is the conduct of a quantitative evaluation survey with patients/caregivers, to assess awareness of the REMS materials, knowledge of the risks associated with BKEMV, and knowledge of the requirements of the BKEMV REMS. Throughout this protocol, the quantitative evaluation survey will, hereinafter, be referred to as the "Patient/Caregiver REMS Knowledge Assessment Survey." Findings from the Patient/Caregiver REMS Knowledge Assessment Survey, together with other REMS evaluation metrics, will be used to assess the BKEMV REMS and determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the intended goal. Also hereinafter, a patient/caregiver may be referred to as "participant."

This protocol provides the procedures to be followed with patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1

dose of BKEMV, for inclusion in the BKEMV REMS Assessment Reports to be submitted to the FDA at 12 months post the approval of the REMS, and annually thereafter. This non-interventional study is part of the BKEMV REMS Assessment and is a commitment to the FDA.

Research Question(s) & Objective(s): The above survey knowledge domains identify the most critical information for stakeholders to know about the risk and safe use behaviors to mitigate the risks with BKEMV. The objectives of the Patient/Caregiver REMS Knowledge Assessment Survey are to conduct a survey with patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV to assess their awareness and understanding of the risk of serious meningococcal infections associated with the use of BKEMV, the BKEMV REMS requirements, and the REMS goals and materials. The survey knowledge questions have been grouped into the following survey knowledge domains:

- Survey Knowledge Domain 1: Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early.
- Survey Knowledge Domain 2: Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.
- Survey Knowledge Domain 3: Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

The survey questions associated with each survey knowledge domain have been developed as described above. A select number of questions will be pre-tested through qualitative research (QR) and finalized prior to implementation of the Patient/Caregiver REMS Knowledge Assessment Survey.

Study Design: This is a US-based, observational, cross-sectional survey of patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV. The survey can be self-administered by respondents via secure internet and telephone modalities utilizing a validated [redacted] Knowledge Survey System for data collection that is secure for receiving and storing survey data.

Because the REMS database does not collect the necessary contact information for patient outreach, the recruitment efforts will be attained via the Authorized Representative (AR) at each infusion site where a patient is receiving their treatment

with BKEMV. Each AR will receive a packet of invitation based on the number of patients identified as receiving BKEMV at their site. The AR will be asked to distribute the invitation letters to those targeted patients. Throughout the survey wave, reminder letters will be distributed to non-responders. Because patients are not enrolled in the REMS, no telephone numbers are available; therefore, outbound calling cannot be performed.

Population: Respondents must meet all the following inclusion criteria to be eligible for inclusion in the study:

- Patients of 18 years of age who have been dispensed at least 1 dose of BKEMV will be permitted to participate.
- Caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV will be permitted to participate.

Respondents meeting any of the following exclusion criteria will not be included in the study:

- Respondents who do not agree to participate in the survey.
- Respondents who are currently working for and/or whose immediate family members who are currently working for or consultants to Amgen, [redacted], or the FDA.
- Respondents who report having a conflict of interest.
- Respondents who have participated in QR.
- Respondents who have previously participated may be eligible to participate in future surveys. This eligibility criteria will be dependent upon the number of patients who have been dispensed at least 1 dose of BKEMV, prior to launch of subsequent survey waves.

Variables: The Patient/Caregiver REMS Knowledge Assessment Survey will document each patient/caregivers' knowledge of the important information as presented in the key domain messages communicated through the BKEMV REMS. Survey knowledge questions were pre-tested via QR and submitted for FDA review for review.

The Patient/Caregiver REMS Knowledge Assessment Survey will also collect demographic characteristics for patients and/or caregivers who complete all survey questions.

These include:

- Type of respondent (patient versus caregiver)
- Patient age
- Education Level
- Length of time being treated with BKEMV

- Past Completer versus Current Completer – if it is decided that prior survey completers are permitted to participate this analysis will be introduced. This decision will occur prior to Wave 2 and subsequent waves thereafter.
- Geographic location
- Survey completion status

Data Sources: The survey will be administered via a secure web-based internet connection, which will allow respondents who choose to participate to do so at a time and location that is convenient for them.

The structured survey comprises survey knowledge questions or statements written in several formats, which include specific survey knowledge domains:

- Questions or statements with a defined list of possible answers from which the respondent is required to choose one answer (ie, multiple-choice).
- Questions or statements with a defined list of possible answers from which the respondent is required to choose one or more answers (eg, “Select all that apply”).
- Questions or statements with response options of “yes” or “true,” “no” or “false,” and “I don’t know” that require the respondent to indicate agreement or disagreement.

All answers for survey knowledge questions permitting multiple responses will be tallied to provide a broad picture of respondent’s knowledge, attitudes, and behavior.

The desired response for survey knowledge questions is generally “true” indicating knowledge of the objectives of the BKEMV REMS. However, some questions are formatted to have the respondent disagree with the statement as written (“false”) to avoid having the same affirmative answer for all desired responses. Whenever possible within a key domain message, there will be an equal balance of questions with a “true” and “false.”

The recruitment list for survey participation will be compiled via the REMS database. This list will include patients who have been dispensed at least 1 dose of BKEMV. Outreach will be conducted by targeting the Authorized Representative at the infusion center requesting that they distribute the number of letters to their patients who are receiving BKEMV. The respondent characteristics that are captured in this dataset to be used for survey execution include the patient’s first name, last name and mailing address.

Study Size: The survey will target the completion of at least 25 completed surveys in Wave 1.

Data Analysis: Statistical analyses will be primarily descriptive in nature. Survey administration data will be summarized using descriptive statistics.

In the primary analysis, descriptive analyses will be performed for each survey knowledge domain question. For each question/item, the number of individuals who selected each response will be reported. Additionally, the percentage and 95% confidence interval (CI) will be calculated for the correct response.

Milestones: The date of commercialization of BKEMV was not targeted to begin until March 2025. Data collection for Wave 1 was originally planned to begin on or about July 2025. However, following receipt of the FDA feedback in August 2025, the launch date was consequently pushed to begin in November 2025. The Wave 1 Patient/Caregiver REMS Knowledge Assessment Survey Report will be submitted to the FDA by May 2026. The annual Assessment Reports will continue each year with data collection ending on 28 March and the final assessment report submitted by 28 May until notified otherwise by the FDA.

Milestones

Milestones	**Planned Date[1]**
Final Study Protocol and Survey	18 November 2024
Start of Data Collection	~01 December 2025
Wave 1 Assessment Report due to FDA	28 May 2026
Wave 2 Assessment Report due to FDA	28 May 2027
Wave 3 Assessment Report due to FDA	28 May 2028
End of Data Collection	TBD[2]
Final Assessment Report	TBD[2]

FDA = Food and Drug Administration
[1] Dates are subject to change based on receipt of FDA feedback.
[2.] The Assessment Reports will continue until notified otherwise by the FDA.

Objectives	Endpoints
Primary	
To describe patient and/or caregiver knowledge of: • Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early (Survey Knowledge Domain 1). • Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed (Survey Knowledge Domain 2). • Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation (Survey Knowledge Domain 3). See Appendix ED for all question/options/answers to survey knowledge questions associated with each survey knowledge domain.	• The number of respondents who score 80% or greater in each survey knowledge domain
Secondary	
N/A	
Exploratory	
N/A	

N/A = not applicable

- Study Design/Type

This is a US-based, observational, cross-sectional survey of patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV. The survey can be self-administered by the respondents via secure internet and telephone modalities utilizing a validated [redacted] Knowledge Survey System for data collection that is secure for receiving and storing survey data.

- Study Population or Data Resource

Patients who have been dispensed at least 1 dose of BKEMV. Caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV will also be permitted to participate.

- Summary of Respondent Eligibility Criteria

Respondents must meet all the following inclusion criteria to be eligible for inclusion in the study:

  - Patients who have been dispensed at least 1 dose of BKEMV.
  - Caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV.

Respondents meeting any of the following criteria will not be included in the study:

  - Respondents who do not agree to participate in the study.
  - Respondents who are currently working for and/or whose immediate family members are currently working for are consultants to Amgen, [redacted], or the FDA.
  - Respondents who have participated in QR.
  - Respondents who reported having a conflict of interest.
  - Respondents who have previously participated may be eligible to participate in future surveys. This eligibility criteria will be dependent upon the number of patients being treated with BKEMV, prior to launch of subsequent survey waves.

- Follow-up

N/A

- Variables

The survey knowledge concepts, which will be evaluated in this survey, include the following:

  - Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early.
  - Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.
  - Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

- Exposure Variable(s)

N/A

- Other Covariate(s)

N/A

- Study Sample Size

The goal for the Wave 1 Patient/Caregiver REMS Knowledge Assessment Survey is a sample of at least 25 completed surveys. The survey enrollment window will remain open for the planned duration of the survey even if the target of 25 completed surveys is reached. Recruitment may exceed the minimum target sample size since the recruitment window will continue until the pre-specified survey end date, with a data cut-off no sooner than 60 days +/- 2 weeks prior to REMS assessments submitted to the FDA.

As of 27 October 2025, the population of patients is 49 at the time of launch of the Wave 1 survey; therefore, no random sampling will be performed. To reduce the margin of error, all patients who have been dispensed at least 1 dose of BKEMV will receive an invitation for survey completion. Caregivers for patients under the age of 18 will be targeted to receive the invitation on behalf of this patient. Prior to each survey wave, the population will be evaluated to determine if sampling can be performed. For more information regarding sampling see Section 9.7.13.1.1. If the Patient/Caregiver Survey sample size is not achieved, the following measures will be considered to increase the response rate, if applicable, for future waves:

- Changes in Survey Field Time – Extend the period during which Patients/Caregivers can complete the survey, allowing more time for participation. Allowing extra time may improve the likelihood of reaching the target sample size by increasing opportunities for Patients/Caregivers who may have scheduling conflicts or require reminders to respond.
- Study Timelines – If the target sample size is not met at the 60-day data cut, the survey enrollment window may be extended to collect additional surveys for the first wave due to the limited sample size. In such cases, notification will be provided to the FDA in the annual assessment, including a statement that a supplemental report will be delivered. The submission date for the supplemental report will be determined according to the number of completed surveys received and the estimated time needed to collect remaining responses to reach the target; however, this extension will not exceed four months from the original survey end date.
- Recruitment Alternatives – To enhance Patient/Caregiver participation in the REMS Knowledge Assessment Survey, alternative recruitment strategies—such as pre-registration—should be considered. If implemented, these strategies must be available year-round, ensuring that all patients have an equal opportunity to participate. Patient engagement should be triggered by their visits to the facility, thereby increasing awareness of the survey opportunity. Pre-registration and other recruitment alternatives should be initiated prior to the survey enrollment window for each wave, and no later than three months before the start of enrollment, to optimize response rates. Early implementation allows time for Patients/Caregivers to pre-register, potentially aiding in meeting the target sample size within the planned period.

- Assess compensation options equivalent to fair market value.

Re-evaluation of these approaches should occur before each wave, alongside the review of sampling strategy and population assessment, to ensure recruitment methods remain suitable and responsive to changes in the Patients/Caregivers population.

If the Patients/Caregivers population changes significantly (defined as an increase or decrease of 10% or more from the previous survey wave), the target sample size will be recalculated to maintain clarity and statistical appropriateness.

- Data Analysis

Statistical analyses will focus on descriptive summaries, with formal hypothesis testing used to determine if pre-defined knowledge rate thresholds are met. The primary criterion is the lower bound of the 95% confidence interval (CI) for each knowledge rate rather than point estimates. Hypergeometric two-sided 95% CIs (Berkopec 2007) will be calculated; meeting or exceeding the CI's lower bound threshold will indicate that the prescriber knowledge objective has been achieved.

Analyses will be performed at the respondent level; therefore, within-respondent variation is not relevant.

5. Amendments and Updates

This amendment outlines substantial modifications to the REMS Knowledge Assessment Study Protocol, specifically concerning statistical methodologies, recruitment strategies, compensation for respondents who choose to participate in the survey, and the recalculation of the target sample size. These updates are intended to enhance the study’s methodological rigor and operational feasibility in response to evolving study needs and participant populations.

5.1 Recruitment Strategy Evolution

The recruitment strategy has undergone significant refinement throughout the study's development. Initially, specialty pharmacy data was considered as a means to identify eligible patients; however, this approach proved infeasible due to the direct distribution of the product to infusion sites, which resulted in the absence of patient information within that data source. Subsequent data analysis suggested the potential utility of direct letter outreach and the engagement of a third-party vendor to expand patient identification efforts, especially since patient addresses were not available in the REMS database. Upon further review, it was determined that the REMS database lacked patient names, which are essential for accurate identification by external vendors. As a result, the revised recruitment approach now focuses on targeting Authorized

Representatives (ARs) at infusion sites. Participating ARs will be sent a packet including an introductory letter and the number of invitation letters to share with eligible patients under their care, thereby promoting direct patient engagement and maximizing survey participation rates.

5.1.1 AR Compensation For Patient Recruitment

To recognize their role in the recruitment process, participating ARs will receive a stipend of $50. Compensation will be provided following confirmation that at least 1 patient from their site has completed the survey, or they contact the REMS SCC via e-mail attesting that they distributed the letters to their patients, ensuring alignment of incentives with study objectives and data collection milestones.

5.2 Survey Questions

In accordance with feedback and requests from the FDA modification to select survey questions were reviewed and adjusted to better align with regulatory expectations and study objectives.

Amendment or Update Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Substantial** << *state Yes or No* >>	**Reason**
1	*21 November 2025*	*9.4 – Recruitment Strategy*	*Update*	*Yes*	*Program Requirement*
2	*21 November 2025*	*9.3.2 – Survey Questions*	*Update*	*Yes*	*FDA Request*
3	*21 November 2025*	*9.7.2 – Planned Analyses*	*Update*	*Yes*	*FDA Request*
4	*21 November 2025*	*9.7.13.1.1 – Sample Size Adjustment*	*Update*	*Yes*	*Program Requirement*

5.3 Statistical Approach

The statistical analysis plan has been revised to replace the previously used Clopper-Pearson method for confidence interval (CI) calculation with the hypergeometric method. This change provides improved accuracy for the calculation of 95% CIs, particularly in small or finite populations, thereby strengthening the reliability of the knowledge rate

estimates. The primary analytic criterion remains the lower bound of the 95% CI for each knowledge rate, which will be used to determine whether pre-defined thresholds are met.

5.4 Sample Size Adjustment

The target sample size has been recalculated based on the total number of known patients as of 27 October 2025 (N=49). Accordingly, the new target sample size for the study is at least N=25. This adjustment ensures that the study remains statistically appropriate and reflective of the current patient population.

6. Milestones

The initiation of BKEMV commercialization was not scheduled to begin until March 2025. Initially, data collection for Wave 1 of the REMS assessment was planned for approximately July 2025. However, following receipt of the FDA feedback in August 2025, the data collection start date was rescheduled to November 2025. The Wave 1 Patient/Caregiver REMS Knowledge Assessment Survey Report is planned for submission to the FDA by May 2026. Subsequent annual assessment reports will be submitted each year, with data collection concluding on March 28 and the final assessment report due by May 28, unless the FDA provides further direction.

Milestone	Planned date
Final Study Protocol and Survey	21 November 2024
Start of Data Collection	~01 December 2025
Wave 1 Assessment Report due to FDA	28 May 2026
Wave 2 Assessment Report due to FDA	28 May 2027
Wave 3 Assessment Report due to FDA	28 May 2028
End of Data Collection	TBD[2]
Final Assessment Report	TBD[2]

FDA = Food and Drug Administration
[1] Dates are subject to change based on receipt of FDA feedback.
[2.] The Assessment Reports will continue until notified otherwise by the FDA.

7. Rationale and Background

The BKEMV® (eculizumab-aeeb) Risk Evaluation and Mitigation Strategy (REMS) was approved by the United States (US) Food and Drug Administration (FDA) on 28 May 2024. In accordance with section 505-1 of Federal Food, Drug, and Cosmetic Act (FDCA), the FDA determined that a REMS is necessary for BKEMV to mitigate the risk of serious meningococcal infections and to educate healthcare providers (HCPs) and patients and/or caregivers regarding the need to:

a. The need to ensure that patients are vaccinated against meningococcal infections,
b. The need to ensure that patients are aware of early signs and symptoms of meningococcal infections and the need for immediate medical evaluation; and,
c. The need to ensure that prescribers are aware of early signs and symptoms of meningococcal infections and the need for immediate medical evaluation.

The specific objectives to be achieved by the BKEMV REMS include the assessment of patients'/caregivers' knowledge of the following survey knowledge domains:

- Survey Knowledge Domain 1: Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early.
- Survey Knowledge Domain 2: Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.
- Survey Knowledge Domain 3: Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

A component of the BKEMV REMS Assessment Plan is the conduct of a quantitative evaluation survey with patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV, to assess awareness of the REMS materials, knowledge of the risks associated with BKEMV, and knowledge of the requirements of the BKEMV REMS.

Findings from the Patient/Caregiver REMS Knowledge Assessment Survey, together with other REMS evaluation metrics, will be used to assess the BKEMV REMS and determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the intended goal.

7.1 Diseases and Therapeutic Area

BKEMV® (eculizumab-aeeb) is indicated for the treatment of adults with Paroxysmal Nocturnal Hemoglobinuria (PNH) to reduce hemolysis and for the treatment of adult and pediatric patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Eculizumab-aeeb binds to human C5 in the region of the protein that becomes C5b and blocks cleavage, thereby inhibiting the complement cascade and ultimately blocking terminal complement-mediated intravascular hemolysis.

The use of eculizumab products, (complement inhibitors), increases a patient's susceptibility to serious, life threatening, or fatal meningococcal infections (septicemia

and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. There were no adverse events (AE) of meningococcal infections reported in the BKEMV clinical development program. The initiation of BKEMV treatment is contraindicated in patients with unresolved serious Neisseria meningitidis infection.

Risk groups or risk factors for meningococcal infections include:

- Genetic deficiency or therapeutic inhibition of terminal complement
- Lack of commercially available vaccine against certain meningococcus serogroup
- (Partial) resistance of meningococcal strain to prophylactic antibiotics
- Professionals who are exposed to environments of greater risk for meningococcal disease
- Research, industrial, and clinical laboratory personnel who are routinely exposed to Neisseria meningitidis
- Military personnel during recruit training (military personnel may be at increased risk of meningococcal infections when accommodated in close quarters)
- Day-care center workers
- Living on a college or university campus
- Travelling to endemic areas for meningococcal meningitis (eg, India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj)
    - Meningococcal infections may resolve with appropriate treatment. However, fatal outcomes have been reported in patients treated with eculizumab products. Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination; therefore, patients should be closely monitored for early signs and symptoms of the disease.

7.2 Rationale

In accordance with Section 505 (1)(f)(3)(A) of the FDCA, the FDA determined that a REMS is necessary for BKEMV to ensure the benefits of the drug outweigh the potential risk of meningococcal infections.

A component of the BKEMV REMS Assessment Plan is the conduct of a quantitative evaluation survey with patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV to assess awareness of the REMS materials, knowledge of the risks associated with BKEMV, and knowledge of the requirements of the BKEMV REMS.

Findings from the Patient/Caregiver REMS Knowledge Assessment Survey, together with other REMS evaluation metrics, will be used to assess the BKEMV REMS and determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the intended goal.

This combined protocol/statistical analysis plan provides the procedures to be followed, for inclusion in the BKEMV REMS Assessment Reports. This noninterventional study is part of the BKEMV REMS Assessment and is a commitment to the FDA.

7.3 Feasibility and Futility Considerations

To effectively evaluate the Patient/Caregiver REMS Knowledge Assessment Survey, Qualitative Research (QR) was conducted on a subset of questions from the draft Wave 1 Patient/Caregiver REMS Knowledge Assessment Survey. QR was conducted with a general population of patients who are being treated for a blood disorder, excluding those with human immunodeficiency virus (HIV).

7.4 Statistical Inference (Estimation or Hypothesis[es])

Statistical analyses will be primarily descriptive in nature. Formal hypothesis testing will be conducted to evaluate whether pre-defined knowledge rate thresholds regarding survey knowledge domains have been met. The primary criterion is the lower bound of the 95% confidence interval (CI) for each knowledge rate rather than point estimates. Hypergeometric two-sided 95% CIs (Berkopec 2007) will be calculated; meeting or exceeding the CI's lower bound threshold will indicate that the knowledge objective for this survey has been achieved. This method ensures that knowledge rates are assessed with appropriate statistical rigor, accounting for uncertainty and providing a robust metric for threshold attainment.

8. Research Question and Objectives

The survey knowledge domain questions and statements in the survey address the goal and objectives of the BKEMV REMS and are written in several formats, which include:

- Questions or statements with a defined list of possible answers from which the respondent is required to choose one answer (ie, multiple-choice).
- Questions or statements with a defined list of possible answers from which the respondent is required to choose 1 or more answers (ie, Select all that apply).
- Questions or statements with response options of “yes” or “true,” or “false,” and “I don’t know” that require the respondent to indicate agreement or disagreement.

All answers for questions or statements will be tallied to provide a broad picture of the respondent's knowledge.

The desired response for survey knowledge domain questions is generally "true" or "yes," indicating knowledge of the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written ("false") to avoid having the same affirmative answer for all desired responses.

8.1 Primary

The objectives of the Patient/Caregiver REMS Knowledge Assessment Survey are to conduct a survey with patients who have been dispensed and caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV to assess their awareness and understanding of the risks of BKEMV, the BKEMV REMS requirements, and the REMS goals and materials:

- Survey Knowledge Domain 1: Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early.
- Survey Knowledge Domain 2: Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.
- Survey Knowledge Domain 3: Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

8.2 Secondary

Not Applicable (N/A)

8.3 Exploratory

N/A

9. Research Methods

This is a US-based, observational, cross-sectional survey of patients, identified via the REMS database and who have been dispensed at least 1 dose of BKEMV. Caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV will also be permitted to participate. The survey can be self-administered by the respondents via secure internet and telephone modalities utilizing a validated [redacted] Knowledge Survey System for data collection that is secure for receiving and storing survey data.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for patients in the US.

9.1 Study Design

Comprehension Pre-Testing of the Survey (Qualitative Research)

To effectively evaluate the Patient/Caregiver REMS Knowledge Assessment Survey, QR was conducted on questions associated with the survey knowledge domains from the draft Wave 1 survey. QR was conducted with a general population targeting 12 patients who were diagnosed with a blood disorder excluding HIV. The conduct of QR occurred through 1:1 interviews with an experienced Moderator.

The purpose of QR of select survey questions was to identify potential terms, questions, or topics for clarification or revision based on respondent feedback. Furthermore, the research assessed comprehension among participants regarding the words and phrases used in select survey questions and response options.

QR was carried out in a double-blinded manner. Therefore, during QR, respondents did not know the identity of Amgen and the product under study and Amgen did not know the respondents who participated in the study. If during the interview, a potential event/report was identified, it was possible that Amgen received information related to the respondent, if the respondent consented to follow-up. For more information about potential reporting see Section 11.

Feedback elicited from the QR interviews was used to support the identification of terms, questions, or topics that require clarification or revision, based on areas of confusion or miscomprehension by interviewed participants.

Findings and recommendations from QR were reviewed and incorporated as appropriate to update the select survey questions and response options being tested, prior to the implementation of the Wave 1 Patient/Caregiver REMS Knowledge Assessment Survey. A copy of the Final Summary Report titled, Qualitative Research to Evaluate Healthcare Provider and Patient Knowledge, Attitudes, and Behavior (KAB)[1] Surveys for BKEMV along with the QR Discussion Guide used to conduct QR, redacted interview transcripts, and the findings presentation were included in Annex 5 of this document that was submitted to the FDA for review (See Table 1).

[1] The reference to Knowledge, Attitudes, and Behavior remains in this document when the reference is pointing to a document or activity that has occurred in the past.

9.2 Setting and Study Population

The Patient/Caregiver REMS Knowledge Assessment Survey will be administered via the internet or telephone and patients and/or caregivers will be able to choose the method that is preferred. The [redacted] Knowledge Survey System will be used for both methods of survey administration which has been validated and is secure for receiving and storing survey data. Details on data management are available in Section 9.6.

The projected timeline for program development, survey launch, recruitment, and reporting for Wave 1 is shown in Table 1 below.

Table 1: Projected Timeline for Wave 1 Survey Activities

Milestones	Planned Date[1]
Final Protocol and Survey for QR	24 July 2024
QR	31 July 2024 – 30 October 2024
Protocol and Survey Revision Post QR	02 October 2024 – 29 November 2024
Protocol and Survey Submission to FDA – 90-day review	28 November 2024 – 26 February 2025
[redacted] Knowledge Survey System Build	31 March 2025 – 14 November 2025[2]
Distribution of Pre-Notification Letter	~10 November 2025
[redacted] Knowledge Survey System in Production (Survey Launch)	17 November 2025
Start of Data Collection Period	01 December 2025
Distribution of Initial Survey Invitation	01 December 2025
First Reminder Mailing (alternating modalities such as email, fax, US Mail, as applicable)	~08 December 2025[3]
Second Reminder Mailing (alternating modalities such as email, fax, US Mail, as applicable)	~05 January 2026[3]
Outbound calling to nonresponders	Not Applicable[4]
Third Reminder Mailing (alternating modalities such as email, fax, US Mail, as applicable)	~02 February 2026[3]
Fourth Reminder Mailing (alternating modalities such as email, fax, US Mail, as applicable)	~23 February 2026[3]
End of Data Collection	28 March 2026
Data Processing and Report Development	29 March 2026 – 27 May 2026
Final Wave 1 Assessment Report to FDA	27 May 2026[5]

FDA = Food and Drug Administration; QR = Qualitative Research; [redacted].

[1] Dates are subject to change based on receipt of FDA comments.

[2] [redacted] Knowledge Survey System began building approximately 2 weeks following the completion of the FDA 90-day review cycle. However, due to commercialization as well as receipt of FDA feedback, the build was paused and restarted in the summary of 2025 aligning with FDA recommendations for a target launch as noted in this table.

[3] Distribution of letter campaigns may shift based on survey uptake.

[4] Because patients are not enrolled in the REMS, no outbound calling can be performed, at this time.

[5] Approval of the BKEMV REMS was on 28 May 2024. An assessment was to be submitted 12-months post approval. Due to the commercialization status of BKEMV, this is the first wave of the Patient/Caregiver REMS Knowledge Assessment Survey for inclusion as part of the Year 2 REMS Assessment Report.

9.2.1 Study Period

Data from the Patient/Caregiver REMS Knowledge Assessment Survey, together with other REMS evaluation metrics, will be used to assess the REMS and determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the BKEMV REMS. The results of this survey will be included in the 24-month assessment and will continue annually as required by the FDA.

9.2.2 Selection and Number of Sites

N/A

9.2.3 Respondent Eligibility

The Patient/Caregiver REMS Knowledge Assessment Survey will target patients who have been dispensed at least 1 dose of BKEMV with BKEMV identified via the REMS database.

Termination of the respondent's participation in the survey will occur if they do not meet the eligibility criteria below.

9.2.3.1 Inclusion Criteria

Respondents must meet all the following inclusion criteria to be eligible for inclusion in the study:

- Patients who are 18 years of age or older who have been dispensed at least 1 dose of BKEMV
- Caregivers 18 years of age or older who care for patients of all ages who are unable to take the survey for themselves

9.2.3.2 Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

- Respondents who do not agree to participate in the survey. *Patients and/or caregivers who respond 'no' to Question 1 that asks, "Do you agree to participate in this study about BKEMV?"*
- Respondents who are currently working for and/or whose immediate family members are currently working for or are consultants to Amgen, [redacted], or the FDA.
- Respondents who reported having a conflict of interest.
- Respondents who have participated in QR.
- Respondents who have previously participated in a prior survey wave may be eligible to participate in future surveys. This eligibility criteria will be dependent

upon the number of patients who have been dispensed at least 1 dose of BKEMV, prior to launch of subsequent survey waves.

Further details associated with respondents who do not meet the exclusion criteria established above will be addressed in the assessment report.

9.2.4 Matching - Comparison of the Survey Population to the BKEMV REMS Population Analysis

To assess the representativeness of the survey respondents, the survey completers will be compared to the Patient REMS Population (excluding the survey completers) at a given point in time. For this comparison, the patient data from the survey completers will be compared to the data utilized for recruitment, using Chi-Square tests; Fisher's exact test will be used if 20% or more of the expected cell counts in the table are less than 5. Geographic location will be the characteristic of interest for this comparison.

9.2.5 Baseline Period

Given that the survey questions can change periodically over time, there is no specific baseline period for this type of study.

9.2.6 Study Follow-up

N/A

9.3 Variables

9.3.1 Exposure Assessment

N/A

9.3.2 Outcome Assessment

The survey will assess each patient's and/or caregiver's knowledge of the important information as presented in the key domain messages communicated through the BKEMV REMS.

The survey knowledge domain questions, which will be evaluated in this Patient/Caregiver REMS Assessment Survey, include the following:

- Patients should understand that receiving treatment with BKEMV increases the chance of getting serious meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early (Survey Knowledge Domain 1).
- Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed (Survey Knowledge Domain 2).

- Patients should be able to recognize the signs and symptoms of meningococcal infection and the need for immediate medical evaluation (Survey Knowledge Domain 3).

The questions associated with survey knowledge domain questions messages were pre-tested via QR prior to submission for FDA review as noted in Table 1 above The survey knowledge domains and the corresponding questions/statements can be found in Table 2, Table 3, and Table 4.

Table 2: Survey Knowledge Domain 1

Patients should understand that receiving treatment with BKEMV increases the chance of getting serious and potentially life-threatening meningococcal infections, which may quickly become life-threatening and cause death if not recognized and treated early.		
Question Number	**Question**	**Desired Response**
9	[redacted]	
10	According to the BKEMV Patient Guide, indicate True, False, or I don't know for ***each statement*** about BKEMV.	
A	[redacted]	
12i	According to the BKEMV Patient Guide, indicate True, False, or I don't know for ***each statement*** about BKEMV.	
B	[redacted]	
13		
16		

To achieve the demonstrated understanding of 80%, 4 out of 5 questions are required to be answered correctly.

Table 3: Survey Knowledge Domain 2

Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.		
Question Number	**Question**	**Desired Response**
10i	According to the BKEMV Patient Guide, indicate True, False, or I don't know for ***each statement*** about BKEMV.	

Table 3: Survey Knowledge Domain 2

Patients should understand the need to be vaccinated against meningococcal infection and receive antibacterial drug prophylaxis if needed.		
Question Number	**Question**	**Desired Response**
B	[redacted]	
11		
12	According to the BKEMV Patient Guide, indicate True, False, or I don't know for ***each statement*** about BKEMV.	
A	[redacted]	
15		

To achieve the demonstrated understanding of 80%, all 4 questions are required to be answered correctly.

Table 4: Survey Knowledge Domain 3

Patients should be able to recognize the signs and symptoms of meningococcal infection and receive antibacterial drug prophylaxis if needed.		
Question Number	**Question**	**Desired Response**
12	According to the BKEMV Patient Guide, indicate True, False, or I don't know for ***each statement*** about BKEMV.	
A	[redacted]	
14		

Table 4: Survey Knowledge Domain 3

Patients should be able to recognize the signs and symptoms of meningococcal infection and receive antibacterial drug prophylaxis if needed.		
Question Number	**Question**	**Desired Response**
17	[redacted]	
18		
19		
21		

To achieve the demonstrated understanding of 80%, 12 out of 14 questions are required to be answered correctly.

The survey will also collect demographic characteristics for those who complete all survey questions. These include:

- Type of respondent (patient versus caregiver)
- Patient age
- Education level

- Length of time being treated with BKEMV
- Past Completer versus Current Completer – if it is decided that prior survey completers are permitted to participate this analysis will be introduced. This decision will occur prior to Wave 2 and subsequent waves thereafter.
- Geographic location
- Survey completion status

Eligibility and reasons for ineligibility will be presented by counts and percentages.

9.3.3 Covariate Assessment

N/A

9.3.4 Validity and Reliability

N/A

9.4 Data Sources

The survey will be administered via a secure web-based internet connection, which will allow respondents who choose to participate to do so at a time and location that is convenient for them. The survey is written to reflect wording for both methods of survey administration: internet and telephone.

The structured survey comprises questions or statements written in several formats, which include specific survey knowledge domains:

- Questions or statements with a defined list of possible answers from which the respondent is required to choose one answer (ie, multiple-choice).
- Questions or statements with a defined list of possible answers from which the respondent is required to choose one or more answers (eg, select all that apply).
- Questions or statements with response options of “yes” or “true,” “no” or “false,” and “I don’t know” that require the respondent to indicate agreement or disagreement.

All answers for questions permitting multiple responses will be tallied to provide a broad picture of respondents' knowledge.

The desired response for survey knowledge domain questions is generally “true” or “yes” indicating knowledge of the objectives of the BKEMV REMS. However, some questions are formatted to have the respondent disagree with the statement as written (“false” or “no”) to avoid having the same affirmative answer for all desired responses. Whenever possible within a survey knowledge domain, there will be an equal balance of questions with a “true” or “yes” and “false” or “no.”

Information from the REMS database will be used to identify all patients for recruitment. The total number of patients included in the REMS database are all patients who have been dispensed at least 1 dose of BKEMV.

9.4.1 Patient Recruitment via Authorized Representative

To enable targeted outreach for the REMS Knowledge Survey, patient recruitment will be conducted through direct letter correspondence with authorized representatives (ARs) at designated infusion centers where eligible patients are actively receiving infusions. Identification of eligible participants will be based on the inclusion criteria outlined in Section 9.2.3.1, and each facility will also receive a list of the electronic medical record numbers for each patient at their facility in order to establish a current roster of patients meeting these criteria. All patient-level data will be retained within the facility to maintain strict confidentiality.

The REMS Knowledge SCC will initiate contact with each facility's AR via the modality available from the REMS database (ie, email, fax, US mail). For each center, the AR will receive a packet containing an introductory letter and individual survey invitation letters. The quantity of invitation letters will match the number of eligible patients identified at the facility, at the time the letter outreach begins. The introductory letter will ask the AR to distribute one survey invitation to each eligible patient and will emphasize that the AR must not participate in survey completion or in any way influence patient responses. The packet will also include detailed distribution instructions and contact information for the REMS Knowledge SCC (see ANNEX 4).

To incentivize participation in the outreach process, each AR will be eligible for a $50 compensation, contingent upon confirmation of proper distribution. Confirmation may be provided in either of the following ways:

- The AR submits an attestation email to the REMS Knowledge Survey Project Manager confirming that all invitations were distributed according to protocol.

The total number patients who have been dispensed at least 1 dose of BKEMV as of 27 October 2025 is 49 unique patients. Given that the total number of patients is anticipated to be limited for this Wave 1 survey, all patients who meet the eligibility criteria (Section 9.2.3) will be invited to participate in this survey. Until the number of patients increase to >1,000, no random sampling will be completed. The patient characteristics that will be used for survey execution include first name, last name, and mailing address.

9.5 Study Size

Wave 1 will aim to reach, at a minimum, 25 completed surveys for patients and/or caregivers. Each survey will remain open for the entire scheduled fielding time but will close no earlier than 60 days +/- 2 weeks prior to assessment report submission.

Personalized invitations sent to the AR requesting their participation in distributing the letters to each of their patients via the modality available from the REMS database (ie, email, fax, US mail) for the AR outreach communication Table 1.

Because the REMS does not collect the necessary contact information for patient outreach, the recruitment efforts will be attained via the AR at each infusion site where patient are receiving their treatment with BKEMV. Each AR will receive a packet including an introductory letter providing directions to them on inviting their patients as well as a stipend for their participation. The packet will also include a number of invitation letters based on the number of patients identified as receiving BKEMV at their site. The AR's will be asked to distribute the invitation letters to those targeted patients. The Invitation Letter will include:

- Two methods (internet or telephone) for accessing the survey: a QR code for quick access, via a mobile device, to the secure website and a Uniform Resource Locator (URL) for the internet survey and a toll-free number to the SCC for the telephone interview.
- A unique code that the respondent must provide when accessing the survey via the internet or telephone.
- Notification that the survey should take approximately 20 minutes to complete depending on method chosen to complete it.
- Notification that participation in the survey or their choice to note participate in the survey will not affect their ability to receive treatment with BKEMV.
- Notification that payment meeting a fair market value amount will be provided to thank them for their participation will be made and or elect to receive the compensation.
- Notification that eligible patients/caregivers will receive compensation (if the respondent is able or chooses to receive compensation) for completing the survey. Additionally, potential patients and/or caregivers who are not eligible for compensation will be informed that, while they will not receive compensation for their participation, they may still participate in the survey but will not be compensated.

All targeted AR's, whose patients/caregivers do not respond to the survey, regardless of the response rate, will be sent Reminder Letters that will assist in informing non-responders that others have completed the survey and letting them know that their help is needed to encourage them to respond to the survey (social validation). The

intervals for sending Reminder Letters to non-responders will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date and but will close no earlier than 60 days no earlier than +/- 2 weeks prior to assessment report submission. Reminder letters will be flagged with terms associated with social validation, for example, Reminder 1 - "Friendly Reminder," Reminder 2 - "We need your help," Reminder 3 – "Please respond," and Reminder 4 - "Final Reminder" will be implemented. Additional reminder outreach may be conducted based on the time period in which the survey is being conducted and survey uptake (Table 1). Based on the population size of patients, at this time, no random sampling will be performed. Furthermore, to minimize sampling error and bias, if the data becomes available (Section 9.4) outbound calling may occur depending upon survey uptake.

9.6 Data Management

A secure, web-based, proprietary Knowledge Survey System designed and built by [redacted] will be used for the Patient/Caregiver REMS Knowledge Assessment Survey. The system meets Title 21 Code of Federal Regulations (CFR) Part 11, the Health Insurance Portability and Accountability Act (HIPAA) and the California Consumer Privacy Act guidelines for information systems. Respondent-identifying information will be stored separately from the survey responses.

Title 21 CFR Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations; the application must provide protection, security, and dependability. Protection of the data requires that audit trails be under application control for all updates and deletions, and that date and time stamps are available. The [redacted] Knowledge Survey System maintains an audit trail containing date and time stamps.

The security of the application requires physical and logical security. The [redacted] Knowledge Survey System maintains user and group-level permissions, so that only relevant project team members will have appropriate access to the system.

Dependability of the application requires that the database be validated and documented evidence that the application does what it is purported to do and will continue to do so. [redacted] will thoroughly validate and document the testing of the [redacted] Knowledge Survey System. The validation of this system begins with the development

of a Project Strategy Document. The document details the strategy for testing. Product Backlog Items are created, and test scripts are written and executed.

All associated Title 21 CFR Part 11 requirements, including requirements for data entry, audit trails, date and time stamps, and security, are tested at baseline.

When survey respondents access the survey website to complete an online survey, they will be asked to enter the unique code from the invitation letter and pass the CAPTCHA (Completely Automated Public Turing test to tell Computers and Humans Apart) robot check shown on the screen. After the respondent has correctly entered the code and passed the CAPTCHA test, the system will advance to the survey welcome page from which the respondent can access the actual survey.

After the [redacted] end users, who can facilitate completion of a survey with a respondent via telephone, access the survey website for entry of survey information collected from respondents over the telephone, they will click "[redacted] Login" and enter their [redacted] network credentials. They will then access the survey assigned to the respondent by matching the code provided to the respondent code in the system.

All data entered will be single data entered by either the respondent or a designated [redacted] resource who has been trained to enter data for this program. Data will be checked in real time to ensure it is being entered according to acceptable parameters and requirements. This process will include a data extract, at a time point during survey execution where the data collected is a reasonable number (ie, more than 25 completed surveys). This data extract will then follow the process in which it will be mapped to Statistical Analysis System (SAS®) datasets and evaluated for any parameters that were not planned (ie, skip pattern errors).

At the end of each survey cycle, the same process as outlined above will be followed which includes having all data extracted from the [redacted] Knowledge Survey System and mapped to SAS datasets (SAS V9.4 or higher). The mapping of raw data will be validated, as will the programming of the analysis tables created from the SAS datasets.

9.6.1 Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term data collection tool (DCT) (the survey) should be understood to refer to either a paper form or an electronic data record.

A completed DCT (the survey) is required for each included respondent. As defined (Section 9.7.1), a Completed Survey (Primary Population) is the population for a majority

of the analyses includes only those respondents who completed all eligibility questions, met all inclusion criteria and none of the exclusion criteria, and answered all questions associated with at least 1 survey knowledge domain. The completed original DCTs (the surveys) are the sole property of Amgen and should not be made available in any form to third parties, except for authorized representatives of Amgen or appropriate regulatory authorities, without written permission from Amgen. [redacted] shall ensure that the DCTs (the surveys) are securely stored at [redacted] on a secure server to prevent access by unauthorized third parties.

[redacted] has ultimate responsibility for the collection and reporting of all data entered on the DCTs (the surveys) as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT (the survey) serves as the source document. Any corrections to entries made in the DCTs (the surveys) must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.6.2 Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Amgen, [redacted] agrees to keep all study-related records. The records should be retained by [redacted] according to local regulations or as specified in the Fully Executed Statement of Work, whichever is longer. [redacted] must ensure that the records continue to be stored securely for so long as they are retained.

If [redacted] becomes unable for any reason to continue to retain study records for the required period, Amgen should be prospectively notified. The study records must be transferred to a designee acceptable to Amgen.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless [redacted] and Amgen have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

[redacted] must obtain Amgen's written permission before disposing of any records, even if retention requirements have been met.

9.6.3 Obtaining Data Files

N/A

9.6.4 Linking Data Files

N/A

9.6.5 Review and Verification of Data Quality

N/A

9.7 Data Analysis

9.7.1 Analysis Populations

Data from all respondents who access the survey will be collected. Only data from those survey respondents who were eligible to participate in the survey and answered every question ("completers") will be the primary analysis population. The population included in the analysis will be defined as follows:

- All Respondents – The "All Respondents" population consists of respondents who accessed the survey using a unique code. This population will be used as the denominator for percentages in survey administration statistics and in the survey eligibility results analysis. This population includes any individual who accesses the survey, regardless of whether or not they meet the study's eligibility criteria.
- Eligible Respondents – The "Eligible Respondents" are those who completed all eligibility questions designated as eligible for the survey, regardless of whether or not they completed the entire survey.
- Non-Completed Surveys – The population will be considered "Non-Completers" if the respondent completed all eligibility questions and answered at least 1 question associated with 1 survey knowledge domain but did not complete the entire survey.
- Completed Surveys (Primary Population) – The population for a majority of the analyses includes only those respondents with completed surveys. "Completed" is defined as an eligible respondent who completed all eligibility questions, met all inclusion criteria and none of the exclusion criteria, and answered all questions associated with at least 1 key domain message. Any remaining questions not answered by this population will be identified in each analysis as either "missing data" if the respondent discontinued the survey before answering the question(s) or skipped the question, or "N/A" if the question(s) was not presented to the respondent due to skip logic in the survey. The "completed surveys" population will be a subset of the "eligible respondents" population.
- BKEMV REMS Data Population – The BKEMV REMS Data Population consists of patients who have been dispensed at least 1 dose of BKEMV.

9.7.2 Planned Analyses

Statistical analyses will be primarily descriptive in nature. Formal hypothesis testing will be conducted to evaluate whether pre-defined knowledge rate thresholds regarding survey knowledge domains have been met. rate thresholds regarding survey knowledge domains have been met. The primary criterion is the lower bound of the 95% confidence interval (CI) for each knowledge rate rather than point estimates. Hypergeometric two-sided 95% CIs (Berkopec 2007) will be calculated; meeting or exceeding the CI's lower

bound threshold will indicate that the prescriber knowledge objective has been achieved. This method ensures that knowledge rates are assessed with appropriate statistical rigor, accounting for uncertainty and providing a robust metric for threshold attainment.

9.7.3 Survey Administration Analyses

The survey administration data to be described in the Patient/Caregiver REMS Knowledge Assessment Survey Report includes. For details regarding alternating modalities during reminder letter outreach refer to Table 1:

- Number of Pre-Notification Letters distributed
- Number of Pre-Notification Letters returned as undeliverable
- Number of Invitation Letters distributed
- Number of Invitation Letters redistributed
- Number of Invitation Letters returned as undeliverable
- Number of Reminder Letters distributed
- Number of Reminder Letters returned as undeliverable
- Number of Reminder Letters redistributed
- Number of Outbound Calls to non-responders (ARs at Infusion Centers)
- Response rate after the Invitation Letter
- Response rate after each Reminder Letter
- Number of respondents screened for participation (All respondents)
- Number of respondents eligible for participation
- Number of respondents not eligible for participation
- Number of respondents eligible for participation who completed the survey
- Number of respondents who completed the survey via internet or telephone
- Time to complete survey (minutes)
- Description of survey participants includes:
    - Type of respondent (patient versus caregiver)
    - Patient age
    - Education Level
    - Length of time being treated with BKEMV
    - Past Completer versus Current Completer – if it is decided that prior survey completers are permitted to participate this analysis will be introduced. This decision will occur prior to Wave 2 and subsequent waves thereafter.
    - Geographic location

- Eligibility and reasons for ineligibility will be presented by counts and percentages.

9.7.3.1 Primary Analysis

The primary analysis will be executed upon data lock and data extraction of the Patient/Caregiver REMS Assessment Knowledge Survey.

9.7.4 Planned Method of Analysis

9.7.5 General Considerations

Statistical analyses will be primarily descriptive in nature. Formal hypothesis testing will be conducted to evaluate whether pre-defined knowledge rate thresholds regarding survey knowledge domains have been met. All analyses will be performed at the respondent level; therefore, within respondent variation is not relevant. Furthermore, descriptive analyses will be performed by prescribing status. Counts and percentages will be calculated for each question/item in the questionnaire.

Two-sided 95% confidence intervals will be calculated using the hypergeometric model for this analysis. If the lower bound of the confidence interval for a specific knowledge rate meets or exceeds the established threshold, this will be considered evidence that the knowledge objective among patients/caregivers has been achieved.

The Clopper-Pearson (Clopper-Pearson, 1934) method will be utilized to estimate the CIs using procedure freq in SAS for all subgroup analyses. The following SAS code is provided below.

```
Proc freq data=<data>;

by <variable>;

tables <variable> / binomial (level = x) alpha = 0.05;

weight count /zero;
```

CIs for primary and secondary analyses will be calculated as inferential statistics to generalize the results to the entire targeted population. The *P* values for comparison of how representative the respective survey respondents are to the respective stakeholder population will be obtained from the Chi-Square test.

9.7.6 Primary Analysis

Primary analyses are performed for all survey knowledge domain questions and will be stratified by patient versus caregiver, if the number of caregivers exceeds 15. If the caregiver population is not exceeded, the analyses will be performed at the respondent

level. Responses from all questions/items from each survey knowledge domain will be summarized by counts and percentages. The primary analysis for a survey knowledge domain question evaluates the rate for each correct response to each individual question/item defined by the key domain message. "Select all that apply" questions will be counted as a single correct response if the respondent selects 80% or more of the correct responses and does not select any incorrect response. The specific correct response to each question/item is identified in the body of the Survey Knowledge Domain Table 2, Table 3, and Table 4. The hypergeometric method will be used to calculate the 95% CIs. The completed surveys (Primary Population) will be used for this analysis.

Example Table Output 2: Primary Analysis of Responses to Questions Linked to Survey Knowledge Domain 1 - Completed Surveys

Question	**Overall (N=XX)[a] n (%) [95% CI][b]**
Question 1:	
Number not missing (if applicable)	XX
Yes[c]	XX (XX.0) [XX.X - XX.X]
No	XX
I don't know	XX

[a] Total number of eligible respondents completing the survey.
[b] 95% exact 2-sided CIs are calculated using the hypergeometric distribution model.
[c] Correct response.

9.7.7 Additional Analysis

This analysis of the survey knowledge domains will be performed consisting of a frequency distribution of the number of correct responses to each survey knowledge domain question (ie, number and percentages will be shown by the number of correct responses). "Select all that apply" questions are handled as described in Section 9.7.6. Only those items that are presented to all respondents will be included in the secondary analysis. The hypergeometric method will be used to calculate the 95% CIs. The completed surveys (Primary Population) will be used for this analysis.

A prespecified threshold of at least 80% has been set. This prespecified threshold aligns with the FDA general guidance that 80% or higher should be the general standard for each REMS survey knowledge domain.

Example Table Output 1: Additional Analysis of Survey Knowledge Domain 1 - Completed Surveys

Correct Responses	Overall (N=XX)[a] n (%) [95% CI][b]
0 correct responses	XX (XX.0)
1 correct response	XX (XX.0)
2 correct responses	XX (XX.0)
3 correct responses	XX (XX.0)
4 correct responses	XX (XX.0)
Demonstrated understanding of Key Message Domain 1[c]	XX (XX.0) [XX.X - XX.X]

[a] Total number of eligible respondents completing the survey.
[b] 95% exact 2-sided CIs are calculated using the hypergeometric distribution model.
[c] To demonstrate understanding of Survey Knowledge Domain 1, the respondent must have answered all 4 questions correctly.

Another analysis is the demonstrated understanding of each key domain message, defined as answering 80% or more questions/items in a key domain message correctly. "Select all that apply" questions are handled as described in Section 9.7.6. The proportion of respondents who demonstrated understanding of the survey knowledge domain will be presented with 95% CIs. Additionally, the number and percentages of respondents who demonstrated understanding of all survey knowledge domains will be provided with 95% CIs. In this analysis, the proportion of respondents who demonstrated an understanding of the domain will be presented with 95% CIs. The REMS will be considered meeting its goals if the point estimates of Survey Knowledge Domain 1, Survey Knowledge Domain 2, and Survey Knowledge Domain 3 receive a demonstrated understanding of 80% or above. Additionally, the number and percentages of respondents who demonstrated understanding of all survey knowledge domains will be provided with 95% CIs. As stated in the FDA draft Guidance for "Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry" although there is no standard knowledge performance threshold that is generally accepted for all REMS Programs, in most cases it should be 80% or higher for each key domain message. The hypergeometric method will be used to calculate the 95% CIs. The completed surveys (Primary Population) will be used for this analysis.

9.7.8 Trend Over Time Analysis

A descriptive comparison in correct response rates to survey knowledge questions and the demonstrated understanding of each key domain message across the survey waves will be conducted to address possible trends in the knowledge rates of the survey completers. For the trend analysis, only those questions will be considered for the demonstrated understanding rates that are asked in all survey waves. Therefore, the

demonstrated understanding rates in the trend analysis may differ from the results of the previous waves. Additionally, the comparison will be completed to include no more than 2 previous waves and the current reporting period only. If any changes to the questions and/or the response options are made across the survey waves, those questions/responses will be identified as changed with an applicable footnote for identification.

This analysis will be performed following the completion of Wave 2.

9.7.9 Sub-Group Analysis

Subgroup analysis will be performed using the primary population (Completed Surveys) for each key domain message for both the primary and secondary analysis based on descriptive statistics. The sub-group analyses performed will be by type of respondent, respondent age, length of time being treated with BKEMV, awareness of the educational materials, responder versus non-responder, past completer versus new completer, and geographic location.

The denominator for the calculation of percentages is the number of available responses. All sub-group analyses will be programmed; however, only those with a meaningful sample size, ie, 10 or more respondents in at least 2 sub-groups, will be described in the Assessment Report. Sub-groups with low sample size may also be combined as appropriate. Should the patient/caregiver population change substantially (defined as an increase or decrease of 10% or more from the previous survey wave), the target sample size will be recalculated for clarity and to ensure the survey remains statistically appropriate; thus, updating the target number for sub-group analyses. The Clopper-Pearson method (Clopper-Pearson, 1934) will be used for these sub-group analyses.

All sub-groups will be derived from the survey data.

9.7.10 Analysis of Additional Survey Questions

All other questions, including those about demographics, inclusion/exclusion, behaviors, safety, requirements of the BKEMV REMS and awareness of the REMS educational materials, will be analyzed using descriptive statistics. The responses to each question will be summarized by frequency tables.

9.7.11 Categorization and Verbatim Responses

Free text and verbatim responses will be presented in data listings and, as appropriate, may be categorized for categorical data analysis.

9.7.11.1 Missing, Duplicate, or Incomplete Data and Lost to Follow-up

9.7.11.2 Missing Data

Regardless of survey method (internet/telephone) chosen to participate, there is a potential for missing data associated with demographic questions and non-related survey knowledge domain questions (the main survey content). Any remaining questions not answered by this population will be identified in each analysis as either "missing data" if the respondent discontinued the survey before answering the question(s) or skipped the question, or N/A if the question(s) was not presented to the respondent due to skip logic in the survey. The "completed surveys" population will be a subset of the "eligible respondents" population.

9.7.11.3 Duplicate Data

With any voluntary survey there is a possibility of duplicate surveys being received. If it is discovered that a respondent completed more than 1 survey (eg, during fulfillment reconciliation), only the results from the first completed survey (based on time completed) will be included in the analyses.

9.7.12 Descriptive Analysis

9.7.12.1.1 Description of Study Enrollment

The target sample size was derived based on the total population available and calculated based on an estimate of those who may have been dispensed at least 1 dose of BKEMV at time of survey execution. This number may be adjusted following enrollment and prior to survey launch so that it aligns with the FDA draft guidance identifying the estimated population including a margin of error of ±5% and 95% CIs.

Prior to each survey wave, a determination regarding the need for sampling will be made based on the most current data available about the patient/caregiver population. This assessment will consider whether the population size has changed substantially since the previous wave—defined as an increase or decrease of 10% or more from the previous survey period. If such a change is observed, the target sample size will be recalculated to ensure statistical appropriateness and alignment with FDA draft guidance as noted above.

The sampling method for this survey will utilize a simple random sampling design to ensure that the sample is representative of the eligible patient/caregiver population at the time of survey execution. The total population available will be used to estimate the

number of individuals to invite to participate in the survey, with adjustments made as necessary to reflect demographic shifts or changes in REMS enrollment.

In simple random sampling, every individual in the eligible population has an equal chance of being selected, which minimizes selection bias and enhances the representativeness of the sample.

All sampling procedures and calculations will be documented prior to survey launch. Any modifications to the sampling approach will be transparently reported in the study documentation to ensure compliance with regulatory guidance and best practices. This methodology supports the integrity of the survey results and enables meaningful categorical data analysis while maintaining alignment with simple random sampling principles. SAS® software (Version 9.4 or later) will be used for this randomization process.

Table 5 shows the precision of the estimated level of understanding for the survey knowledge questions identified for respondents using the lower bound of exact hypergeometric CI for a sample size of 25 completed surveys. Hypergeometric is narrower than the exact binomial CI, which assumes infinite population size. The lower bound of the CI will be used to determine whether the target knowledge rate threshold has been met. Using hypergeometric (Berkopec 2007) CIs with an assumed population of 49 will make it easier for the lower bound of the CI to meet the target threshold.

Table 5: Exact Hypergeometric Distribution for a Population of 49

	Sample Size				
	0.85	**0.87**	**0.9**	**0.93**	**0.95**
16	0.571	0.653	0.653	0.735	0.735
21	0.673	0.673	0.735	0.735	0.796
25	0.694	0.735	0.735	0.776	0.837
16	0.571	0.653	0.653	0.735	0.735
17	0.592	0.673	0.673	0.735	0.735
18	0.612	0.694	0.694	0.755	0.755
19	0.633	0.633	0.694	0.776	0.776
20	0.653	0.653	0.714	0.714	0.776
21	0.673	0.673	0.735	0.735	0.796
22	0.694	0.694	0.755	0.755	0.796

9.7.12.1.2 Description of Patient/Caregiver Characteristics

Patients who are 18 years of age who have been dispensed at least 1 dose of BKEMV will be invited to participate in this survey.

Caregivers of patients of all ages who have been dispensed at least 1 dose of BKEMV will be invited to participate in this survey.

9.7.12.1.3 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Exact two-sided 95% confidence intervals are determined using the hypergeometric distribution model.

9.7.12.1.4 Stratified Analysis

Primary analyses will be conducted for all survey knowledge questions and stratified by patient, caregiver, and overall if each group (ie, patient/caregiver) includes at least 15 in each category; otherwise, the analyses will be combined and presented as Overall Respondents.

9.7.12.1.5 Sensitivity Analysis for Residual Confounding and Bias

N/A

9.7.12.1.6 Other Sensitivity Analysis

N/A

9.7.13 Analysis of Safety Endpoint(s)/Outcome(s)

Safety data will not be collected or analyzed in this study.

9.8 Quality Control

The [redacted] Knowledge Survey System programming will be reviewed by [redacted] Quality Control (QC) and simulated users [User Acceptance Testing (UAT)] prior to implementation. At the completion of data collection, the Knowledge Survey System data will be mapped to SAS datasets (SAS v9.4 or higher) by a SAS programmer/designee. These original SAS datasets will be validated by double programming and QC. The validated original SAS datasets will then be used by a SAS programmer to create a set of summary tables and listings according to the analysis text and mock-up tables. If derived analysis datasets are required to produce these summary tables, the derived analysis datasets will be created and independently validated according Standard Operating Procedures (SOPs). All TL (Tables and Listings) output will be independently validated and documented according to the

established SOPs. Summary tables will be reviewed by the appropriate team members and included in the assessment report that is sent to Amgen along with the final document to be submitted to the FDA. No respondent contact information is included in the tables or in the assessment report.

9.9 Limitations of the Research Methods

The Patient/Caregiver REMS Assessment Knowledge Survey recruitment strategies are intended to recruit those meeting the inclusion criteria as stated earlier in this document. Patients/Caregivers will be self-selected because they will voluntarily respond to the invitation to participate, so the potential exists that those who choose to respond to the survey may differ in their understanding of the REMS Program requirements from those who elect not to participate. This is a common limitation of all studies that rely on voluntary participation.

The second limitation is that the survey can assess respondents' understanding of the REMS requirements, but it cannot clearly determine which channel the respondents gained the information from. While the survey asks respondents where the information was gained, recall of information may not be reliable. Inherent in survey research is the reliance on the respondent's recall of whether the REMS educational materials were received and read. It is possible, however, that respondents may simply not recall receiving and/or reading any one or more of the REMS educational materials that were, in fact, received and/or read. It is also possible that the respondents have acceptable understanding of the important product information associated with the use of BKEMV despite not receiving or recalling that s/he received and/or read the REMS educational materials prior to completing the survey.

A third limitation is that of social desirability where respondents are more likely to answer "yes" when they are asked "did you read this?" or "did you do this?" because they assume this is the expected answer. Social desirability bias tends to result in higher scores, particularly for questions with a true/false response.

BKEMV is a rare disease drug, therefore, the population of patients may be limited.

9.9.1 Measurement Error(s)/Misclassification(s)

N/A

9.9.2 Information Bias

Controls will be in place to ensure the survey is conducted in a professional manner and to minimize biases, including the following:

- A standardized script will be used for telephone interviews, and all telephone interviewers will be carefully trained in interview techniques to minimize interviewer bias.
- The survey will be programmed to ensure:
  - Questions are asked in the appropriate sequence and all questions will be presented in a standard order to reduce exposure bias.
  - Respondents cannot skip ahead and will only allow for missing data when caused by skip patterns.
  - The list of response options within a multi-item question are randomized to minimize the potential for positional bias.

Regardless of modality, internet or telephone respondents will be instructed that they cannot go back to a question once they have progressed to the next question and cannot. Both the telephone and the internet questionnaire will be programmed with a standardized approach.

Respondents will be provided with a unique code during the recruitment process and will then be asked to provide the unique code to gain access to the internet-based system or when calling the SCC. The code will be inactivated after use to minimize exposure bias and fraud.

9.9.2.1 Selection Bias

Potential patients/caregivers will be self-selected since they will voluntarily respond to the invitation to participate. Reminder letters will be sent to non-responders to reduce non-response bias.

Additionally, the following measures are in place to assist in minimizing potential biases in the survey sample:

The population of potential patients/caregivers are those as defined in Section 9.2.3. No random sampling will be performed until the population is <1,000.

- To reduce exposure bias, the following will be excluded:
  - Respondents who do not agree to participate in the survey.
  - Respondents who are currently working for and/or whose immediate family members are currently working for or are consultants to Amgen, [redacted], or the FDA.
  - Respondents who report having a conflict of interest.
  - Respondents who have participated in QR.
  - Respondents who have previously participated may be eligible to participate in future surveys. This eligibility criteria will be dependent upon

the number of patients receiving treatment with BKEMV, prior to launch of subsequent survey waves.

- Two methods are available for survey completion: internet and telephone. Providing more than 1 method for survey data collection allows for wide survey access to a heterogeneous population and minimizes intervention bias.
- The list of respondent names will be checked for duplicates so that an individual's responses will not be included in the survey assessment more than once.

9.9.2.2 Confounding

N/A

9.9.3 External Validity of Study Design

N/A

9.9.4 Analysis Limitations

N/A

9.9.5 Limitations Due to Missing Data and/or Incomplete Data

N/A

9.10 Other Aspects

If any protocol deviations occur during survey processing that may have an impact on the survey data and analysis, they will be reported in the final assessment report.

10. Protection of Human Participants

10.1 Informed Consent

The survey will begin with an introduction to the survey providing the respondents with general information about the research sponsor and the survey expectations followed by letting them know how their information will be used, how their privacy will be protected, how they can learn more about the survey, and instructions on taking the survey. Once this information is reviewed and the respondents proceed to the first survey question, they will be presented with one final statement which is: "Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and compensation to be rendered in connection with those services", concluding with their first question asking if they agree to participate in the survey about BKEMV. If respondents select "Yes" they will proceed through the screening module to confirm respondents' eligibility and should they select "No", the survey will immediately terminate, and their session will end. If deemed ineligible, respondents participating via the internet-based survey are immediately notified with a "thank you" message that

survey participation has ended. For those respondents participating in the survey via the telephone with the SCC, the SCC Associate will communicate the "thank you" message that, based on the respondent's answer, they are not eligible to participate.

10.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

It is the responsibility of [redacted] to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (eg, statement regarding agreement to participate), and other relevant documents, (eg, recruitment advertisements), if applicable, from the Institutional Review Board (IRB). All correspondence with the IRB should be retained by [redacted]. Copies of IRB approvals should be forwarded to Amgen.

Please note that IRB approval is required for this study.

10.3 Participant Confidentiality

[redacted] must ensure that the participant's confidentiality is maintained for documents submitted to Amgen.

Participants will be assigned a unique identifier by [redacted]. All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Participant personal data will be stored at [redacted] in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. [redacted] will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, [redacted] shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons regarding the processing of personal data, when study data are compiled for transfer to Amgen and other authorized parties, any participants names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Amgen or other authorized parties will be identified by this single, participant-specific code. [redacted] will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In the case of data transfer,

Amgen will maintain high standards of confidentiality and protection of participants' personal data consistent with the vendor contract and applicable privacy laws.

For serious adverse events reported to Amgen, participants are to be identified by their unique participant identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by [redacted], except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that [redacted] permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review study related data. [redacted] is obligated to inform and obtain the consent of the participant to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Participants Decision to Withdraw

Participants have the right to withdraw from the study at any time and for any reason.

Withdrawal of consent for a study means that the participant does not wish to or is unable to continue further study participation. Participant data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. As per local regulations, upon withdrawal of consent, the participant has the right to request removal of their data that was collected and not have it further processed. [redacted] is to discuss with the participant appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

11.1 Definition of Reportable Events

An Adverse Event (AE), Other Safety Finding (OSF) and Product Complaint (PC) are collectively referred to as REs.

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated

with the use of a medicinal product, combination product, or medical device, whether considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event/adverse device effect as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the participant/patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other medically important serious event” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

“Other medically important serious events” refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant/patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings/Special Situations

Other Safety Findings (OSF) (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents through a contaminated Amgen product,
- Reports of uses outside the terms for authorized use of the product including -off label use,
- Accidental exposure or Occupational exposure,

- Any lack or loss of intended effect of the product(s), unexpected therapeutic benefit.

11.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients and/or caregivers prospectively at one point in time through the completion of an online-based survey or telephone-based survey. All reportable events (adverse events, product complaints, and other safety findings) considered to have occurred following exposure to BKEMV will be collected following patient and/or caregiver enrollment within the study through to the final study contact. The Vendor is responsible for ensuring that all reportable events they become aware of during the study period are recorded in the appropriate study documentation. It is the Vendor's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen. If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the Vendor/participants. All reportable events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in Table 6.

Table 6: Types of Safety Data to be Collected and Reported in Primary Data Collection Studies Collecting all Reportable Events

Reportable Events/Event Type	Reporting Timeframe	Vendor Managed studies: Primary Reporting Method
• SAEs (related and non-related)	Within 1 business day from when Vendor first becomes aware of the event	Enter into vendor managed EDC system and also report/submit to Amgen on the paper-based Observational Research Safety Reporting Form

• Product Complaints	Within 1 business day from when Vendor first becomes aware of the event	Enter into vendor managed EDC system and also report/submit to Amgen on the paper-based Observational Research Safety Reporting Form
• Other Safety Findings/Special Situations (serious and non-serious, and regardless of association with an AE)	Within 1 business day from when Vendor first becomes aware of the event	Enter into vendor managed EDC system and also report/submit to Amgen on the paper-based Observational Research Safety Reporting Form
• Pregnancy and/or Lactation Exposure	Within 1 business day from when Vendor first becomes aware of the event	Report/submit to Amgen using the paper-based Pregnancy Notification Form and/or the Lactation Notification Form.
• Non-serious AE (related and non-related)	Within 15 calendar days from when Vendor first becomes aware of the event	Enter into vendor managed EDC system and also report/submit to Amgen on the paper-based Observational Research Safety Reporting Form

*** More stringent reporting timelines may apply per local requirements**
Note: Date of Awareness is the earliest date that the Investigator or Vendor receives information that constitutes a RE (ie, the earliest date any verbal communication (eg, face to face, telephone call or voicemail), non-verbal communication (eg, fax, email, text, mail), date of extraction, etc.).\

Reportable events that are suspected to be related to any Amgen medicinal product, combination product or device where there is no exposure to BKEMV should be spontaneously reported to Amgen within 1 business day of vendor's awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting

Reportable events suspected to be related to any non-Amgen medicinal product should be reported to the local authority in line with the local country requirements.

See Appendix CB for sample Safety Report Form(s) and Appendix DC for sample Pregnancy and Lactation Notification Forms. The Investigator may be asked to provide additional information for any event submitted. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

11.2.1 Collection of Pregnancy and Lactation Information

Female Patients Who Become Pregnant

Vendor will collect pregnancy information on any female patient who becomes pregnant following exposure to BKEMV if reported by the patient and/or caregiver during completion of the online-based survey or telephone-based survey.

Information will be recorded on the Pregnancy Notification Form (see Appendix D). The form must be submitted to Amgen Safety within 1 business day of when Vendor first becomes aware of the patient's pregnancy (Note: Vendor is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety or designee will provide the reporter with a consent form and questionnaire to collect additional information. After obtaining the reporter's signed consent for release of pregnancy and infant health information, Amgen Safety or designee will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female patient who becomes pregnant following exposure to BKEMV through 6 months after the last dose of BKEMV. This information will be forwarded to Amgen Safety per applicable processes. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety per applicable processes, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female patient experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Vendor will report the event as a serious adverse event.

Male Patients with Partners who Become Pregnant or Were Pregnant at the Time of Enrollment

In the event the respondent notifies the vendor of a male patient who fathers a child following exposure to BKEMV the information will be recorded on the Pregnancy Notification Form. The form (see Appendix D) must be submitted to Amgen Safety within 1 business day of when the Vendor first becomes aware of the pregnancy. (Note: Vendor is not required to provide any information on the Pregnancy Notification Form that violates the country or region's local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety or designee will provide the respondent with a consent form and questionnaire to collect additional information. Amgen Safety or designee will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, Amgen Safety or designee will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety per applicable processes.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety per applicable processes regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Vendor will collect lactation information on any female patient who breastfeeds while taking BKEMV through 6 months after last dose if reported by the healthcare professional during completion of the online-based survey or telephone-based survey.

Information will be recorded on the Lactation Notification Form (see Appendix D) and submitted to Amgen Safety within 1 business day of when the Vendor's first becomes aware of the lactation exposure.

With the female patient's signed consent for release of mother and infant health information, Amgen Safety or designee will collect mother and infant health information and complete the lactation questionnaire on any female patient who breastfeeds while taking BKEMV through 6 months after last dose after discontinuing BKEMV.

11.2.2 Safety Reporting Requirement to Regulatory Bodies

AE is related to an Amgen product prior to reporting the AE to Amgen, in addition, causality is to be recorded in the appropriate study documentation.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. When Amgen amends the protocol and distributes the protocol amendment to the sites, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval for all protocol amendments that Amgen provides to the site. The Investigator **must** send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

Once the survey results are finalized, if applicable, a discussion will be included to address the extent to which the REMS goals related to knowledge are met, how that determination is made, and if the demonstrated understanding is below the pre-specified threshold, outline steps to achieve the desired knowledge rates (eg, enhancing REMS

educational materials or outreach activities as outlined the BKEMV REMS Supporting Document).

During the reporting phase, all data analyses tables and listings will be generated in Excel and provided to Amgen for inclusion for submission to FDA.

The REMS Survey methodology protocol and instrument will be submitted to FDA in both a Portable Document Format and word format.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of an Amgen product, Amgen should be informed immediately.

In addition, the investigator will inform Amgen immediately of any urgent safety measures taken by the party responsible for collecting data from the participant to protect the study participants against any immediate hazard, and of any serious breaches of this non-interventional study protocol that party becomes aware of.

13.1 Publication Policy

The results of this study will not be submitted for publication.

14. Compensation

All respondents, regardless of modality of survey completion, who complete the survey and who provide their contact information will receive a mailing to begin distribution at survey close and will be sent directly to the respondent based on the address provided during survey completion. This mailing will include:

- Thank you letter for completing the Patient/Caregiver REMS Knowledge Assessment Survey
- Compensation meeting a fair market value amount will be provided for their time in completing the survey
- Correct answers to important survey questions about the safe use of BKEMV

15. References

1. Berkopec, Aleš (2007). HyperQuick algorithm for discrete hypergeometric distribution. Journal of Discrete Algorithms. 5 (2): 341–347.

2. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934; 26 (4):404–413.

3. Nair I., Patel B. (2014). Attain 100% Confidence Limits in Your Confidence Interval. Proceedings for PharmaSUG Conference 2014. Available at https://www.pharmasug.org/proceedings/2014/IB/PharmaSUG-2014-IB05.pdf.

4. Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry. Draft Guidance. https://www.fda.gov/media/119789/download. Issued January 24, 2019.

5. US Food & Drug Administration. REMS Assessment: Planning and Reporting. Draft guidance. January 2019. Accessed September 29, 2023. https://www.fda.gov/media/119790/download.

16. Appendices

Appendix A. List of Stand-alone Documents

None

LIST OF TABLES

LIST OF FIGURES

Not applicable.

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2: PARTICIPANT QUALITATIVE RESEARCH PLAN AND SCREENER

Qualitative Research to Assess Comprehension and Clarity of Key Message Survey Questions Associated with the BKEMV Knowledge, Attitudes, and Behavior (KAB) Survey of Patients

Amgen Inc.

Removed to allow unbiased data

Appendix B. Sample Safety Reporting Form(s)

General Instructions

The protocol will provide instruction on what types of events to report for the study.
***Indicates a mandatory field.**

What to report on this form:

- **All adverse events (AEs) are associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol.**
- **The following safety findings are to be reported on this form as events regardless of association with an AE:**
  - **medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **transmission of infectious agents**
  - **reports of uses outside the terms for authorized use of the product including off label use**
  - **occupational exposure**
  - **any lack or loss of intended effect of the product(s)**
  - **product complaint (PC)**
  - **adverse device effect (ADE)**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **pregnancy and lactation reports**

1. **Initial or Follow-up*** – Please tick the appropriate box
2. **Site Number* –** Enter your assigned site number for this study. **Subject Number* –** Enter the entire number assigned to the subject.
3. **Indicate event type* –** Tick the relevant box which applies to the event(s) you are reporting. Please note, more than one box can be ticked.
4. **Contact Details* –** Provide your name, phone, address, etc. (These contact details should be for the Vendor or Investigator)
5. **Reporter ID* –** Provide name or ID of reporter, phone, address, etc. (This could be the Investigator details if vendor details are added in section 4.
6. **HCP Contact Details (if other than reporter)* –** Provide name or ID of reporter, country, phone, address, etc.
7. **Patient* –** Enter the subjects demographic information.
8. **Medical History (include primary diagnosis)* –** Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event, allergies and any relevant prior therapy, such as radiation. Include dates if available.
9. **Suspect Product Information (include dosing details)* –** Provide Product/Device information, Indication, start date, stop date, dose, route, frequency, Lot#, Serial#. It is important that all efforts are taken to provide the Lot number, were possible.
10. **AE, Other Safety Finding, PC/ADE Information*:**

    AE Diagnosis or Syndrome*:
    - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
    - If a diagnosis is not known, the relevant signs/symptoms should be entered.
    - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Onset Date* – Enter date the AE first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Resolved Date* – Enter date the AE ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Hospitalization* – If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an AE. Protocol specified hospitalizations are exempt.

Serious Criteria Code* – This is a mandatory field for serious events. Select the appropriate code for the event(s) being reported

Action Taken* – State what action has been taken with suspect drug/device.

Outcome* – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Severity* – State the severity of the safety event being reported.

Relationship to Product/Device*:

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported.

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (eg, prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (eg, heating pads, infusion pumps)**

11. Concomitant Medications* – Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event.

Continuing – Indicate if the subject is still taking the medication.

Event Treatment – Indicate if the medication was used to treat the event.

12. Relevant Laboratory Tests* – Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

13. Other Relevant Tests* – Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results, and units (if applicable).

14. Description* – Describe Event.

Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of each page and fax the form to Amgen.

Project ID: 20240214	A	**Observational Research Safety Reporting Form**	Date of Reporter Awareness: / Date Reported to Amgen:
	Fax reports to: Amgen Local Office	<<*populate LAO fax here or delete language*>>	

1. Initial: ☐ Follow-up: ☐
2. Site Number: Subject Number:
3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator)

Name	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

5. Reporter ID

Name or ID	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	State/Province	Postal Code
Phone	Fax	

7. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No
Weight: ☐ lbs ☐ kg	Height: ☐ in ☐ cm	Race	Is patient also reporter? ☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) **Cause of Death:** (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx; Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: U1 Fatal; U2 Immediately life-threatening; U3 Required/Prolonged hospitalization; U4 Persistent or significant disability /incapacity; U5 Congenital anomaly/birth defect; U6 Other significant medical hazard; U7 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: U1 Recovered/ Resolved; U2 Recovering/ Resolving; U3 Not recovered/not resolved; U4 Recovered/ resolved with sequelae; U5 Fatal; U6 Unknown	Severity: 1=mild 2=moderate 3=severe	Relationship to Product/Device: Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N

Reporter Signature: Internal Use Only General and Administrative Page # of

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix C. Additional Safety Reporting Information

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/ Study Number: _20240214_____

Study Design: ☐ Interventional ☒ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Internal Use Only General and Administrative

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _20240216_____

Study Design: ☐ Interventional ☒ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐Yes ☐No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

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Appendix C. Correct Answer Document

Removed to allow unbiased data