Summary Table of Study Protocol

Title	A Survey of Experiences and Opinions Regarding Skin Toxicities Associated with Vectibix Among mCRC Patients
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Date of last version of the protocol	10 May 2019
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Medicinal Product	Panitumumab (Vectibix)
Product Reference	Not applicable
Procedure Number	Not applicable
Joint PASS	No
Research Question and Objectives	Among mCRC patients treated with Vectibix 1. Describe mCRC patient opinions regarding the risk of skin rash relative to the benefit of improved survival from Vectibix treatment 2. Characterize the timing and severity of rash among mCRC patients following Vectibix treatment 3. Describe mCRC patient opinions regarding the education they received to prevent and manage a Vectibix related skin rash 4. Describe how mCRC patients managed their skin rash before and after the rash emerged 5. Describe how a Vectibix rash affected the patient's quality of life Among mCRC patients not treated with Vectibix 6. Describe patient opinions regarding the risk of skin rash relative to the benefit of improved survival from Vectibix treatment
Country(-ies) of Study	United States
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Study Design Schema

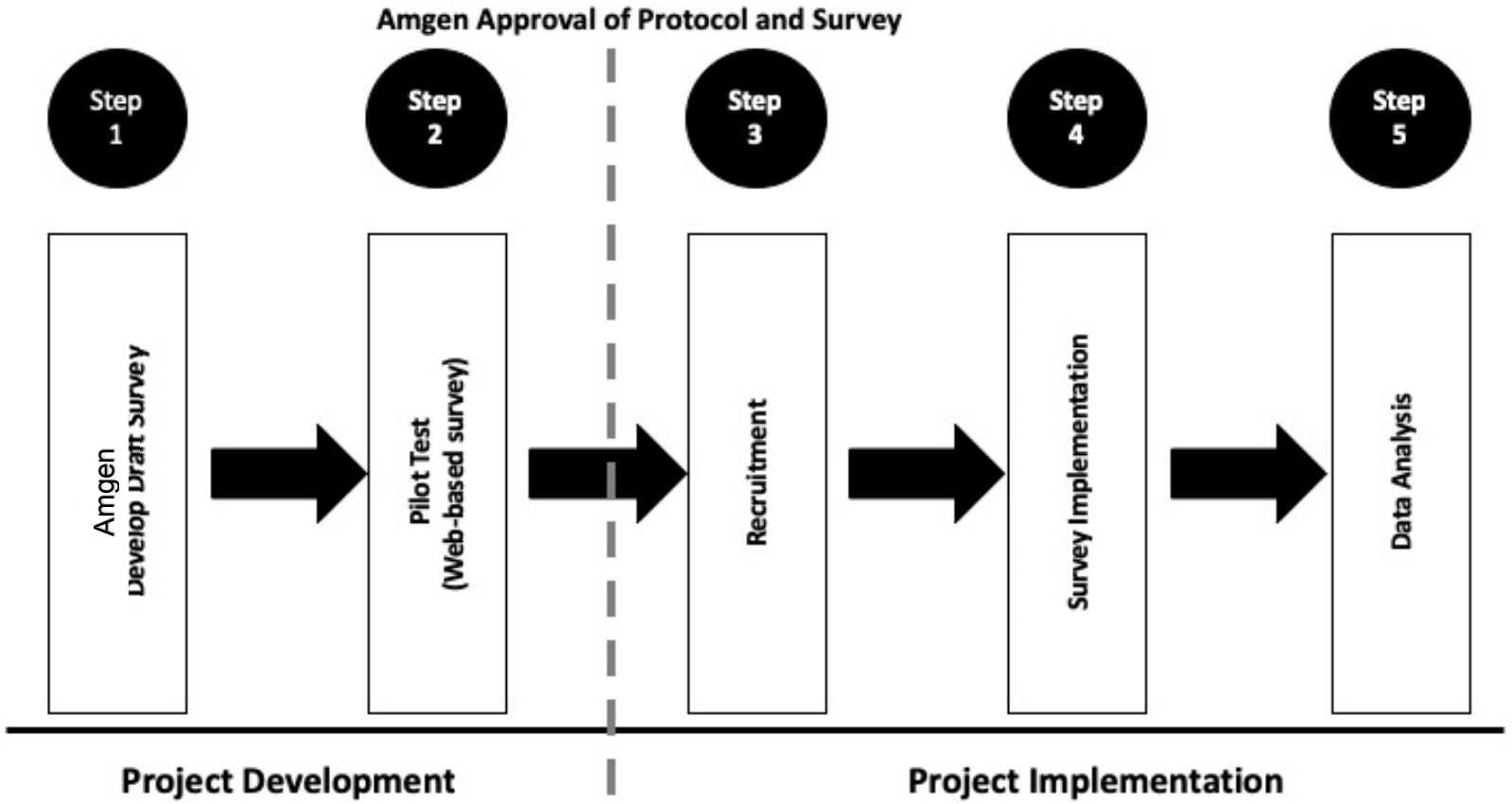

Figure 1. Study schema

1. Table of Contents

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2. List of Abbreviations

CRC – Colorectal Cancer

DLQI - Dermatology Life Quality Index

EGFR – Epidermal Growth Factor Receptor

ICF – Informed Consent Form

J-STEPP – Japan Skin Toxicity Evaluation Protocol with Panitumumab

mCRC – Metastatic Colorectal Cancer

QoL – Quality of Life

STEPP – Skin Toxicity Evaluation Protocol with Panitumumab

3. Responsible Parties

Co-Principal Investigator: PPD – Amgen, Inc.

Co-Principal Investigator: PPD – Amgen, Inc.

Co-Principal Investigator: PPD – Amgen, Inc.

Co-Principal Investigator: PPD - Amgen, Inc.

Co-Principal Investigator: PPD – Adelphi Research

4. Abstract

- **Study Title:** A Survey of Experiences and Opinions Regarding Dermatologic Toxicities Associated with Vectibix Among mCRC Patients
- **Study Background and Rationale**: There are currently no sanctioned standards for the management of dermatologic toxicities for mCRC patients who are treated with Vectibix, which occurs in approximately 75-85% of patients who are treated with an anti-EGFR. The typically-observed “acneiform rash” is associated with pruritus and pain, which can impair quality of life, and may result in dose reduction or treatment cessation in approximately one third of patients. However, associations between rash severity and positive survival outcomes have been reported. There is a current and urgent need to better understand the patient’s perspective regarding if they feel the risk of skin rash is worth the benefit of improved survival, how they were prepared for this skin toxicity, what they did to manage and treat their rash and how skin rash affects their quality of life. This information can be utilized by health care providers to better inform patients how to prepare for Vectibix treatment, which may ultimately improve the uptake of and adherence to Vectibix resulting in better survival probabilities among mCRC patients.
- **Primary Research Objectives**

Among mCRC patients treated with Vectibix:

1. Describe mCRC patient perceptions regarding the risk of skin rash relative to the benefit of improved survival from Vectibix treatment
2. Characterize the timing and severity of rash among mCRC patients following Vectibix treatment
3. Describe mCRC patient opinions regarding the education they received to prevent and manage a Vectibix related skin rash
4. Describe how mCRC patients managed their skin rash before and after the rash emerged
5. Describe how a Vectibix related skin rash affected the patients quality of life

Among mCRC patients not treated with Vectibix:

6. Describe patient opinions regarding the risk of skin rash relative to the benefit of improved survival from Vectibix treatment

- **Hypothesis(es)/Estimation**: This is a descriptive study and no formal hypotheses will be tested. This study is designed with the primary objective of assessing experiences and opinions regarding dermatologic toxicities that may develop among mCRC patients who are treated with and without Vectibix.
- **Study Design/Type**: We propose a cross-sectional study design which will utilize a patient survey to collect data.

- **Study Population or Data Resource:** The study team will administer the electronic survey instrument to approximately 200 mCRC patients in the US, 100 of which will have been treated with Vectibix and 100 who were not treated with Vectibix. Patients will be recruited via a third party patient recruiter, Portable Insights. Patients who are interested in participating will be asked to provide informed consent at the start of the survey and answer screening questions to confirm their eligibility to participate.
- **Summary of Eligibility Criteria**:
  1. 18 years of age or older
  2. Have a self-reported physician diagnosis of mCRC
  3. Have consented to participate
- **Follow-up**

This is a cross-sectional study, as such there is no follow-up.

- **Variables**

  Outcome Variables (Refer to Appendix A for a complete list of survey questions.)

  1. Opinions and perceptions regarding risk/benefit profile of Vectibix

     The risk/benefit of Vectibix will be ascertained through a series of questions that ask the patient if they feel the risk of rash is worth the possibility of improved survival, and about information that may influence their decision to use or not use Vectibix

  2. Timing and severity of rash

     Among patients with a history of rash, questions will be asked to identify when the rash occurred, how severe it was and how long it took to resolve

  3. Opinions related to the education for preventing and managing rash

     Among patients who have used Vectibix, questions will be asked to identify the patients' experience of what information they received before and after the development of rash and if they felt that information was adequate

  4. Management strategies to prevent and/or treat rash

     Among patients who have used Vectibix, questions will be asked to identify the strategies they used before and after rash appeared, with a focus on the use of Sunscreen, Moisturizer, Oral antibiotics (prescription), Topical steroids (such as over the counter hydrocortisone cream}, and Topical steroids (prescription).

  5. Quality of life among Vectibix users who currently have a rash

     Among Vectibix patients who currently have a rash, and those who had a history of rash, questions will be asked to identify how the rash has affected their quality of life

- **Study Sample Size:** A convenience sample of at least 200 mCRC patients will participate in this study, 100 of whom are using or have used Vectibix and 100 who did not use Vectibix.
- **Data Analysis:**

  With the exception of a small number of open-ended questions, the majority of the survey questions include categorical responses. The proportion of patients who select each answer within a survey question will be summarized and confidence intervals will be estimated as the

estimated proportion ± 1.96 multiplied by the estimated standard error. We will stratify our analysis by the following variables:

- History of Vectibix use
- History of rash
- Use of pre-emptive strategies to prevent or reduce the severity of rash

5. Amendments and Updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1 None to date	*Date*	*Text*	*Text*	*Text*
2	*Date*	*Text*	*Text*	*Text*
...	*Date*	*Text*	*Text*	*Text*

6. Milestones

Milestone	Planned date
Amgen/Adelphi Research develop draft survey	*March 1*
Amgen Approval of Protocol and Survey	*March 28*
Pilot Test #1 – Electronic-based	*April 10*
Survey programming completed	*April 19*
Begin fieldwork/Implement survey	*April 29*
Fieldwork completed	*June 1*
Analysis completed	*June 15*
Draft report provided	*June 15*
Final report of study results	*July 1*

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States, in 2019, approximately 150,000 new cases are estimated to be diagnosed.[1] Approximately 20%-25% of new cases have metastatic disease at diagnosis and up to 50% of all patients eventually develop metastatic disease.[2,3] CRC is the third most common cause of cancer mortality in the United States, with an estimtated 51,000 new deaths in 2019.[1] CRC has a 5-year survival of approximately 50%.[4-6] However, the 5-year survival for patients with metastatic colorectal cancer (mCRC) is between 5% and 8% with metastasis to liver and lungs being the main causes of death.[3,7]

During the last decade, improvements in the treatment of mCRC patients have increased median survival time from 12 to 21 months.[8] Reasons for this improvement include, but are not limited to, the development of an antiangiogenic agent bevacizumab (Avastin) and therapies that target the epidermal growth factor receptor (EGFR) namely panitumumab (Vectibix) and cetuximab (Erbitux).[5]

7.2 Rationale

EGFR-inhibitors are associated with both acute (early) and chronic (later) skin toxicities. We are primarily interested in the patient's experience of acute dermatologic toxicity, which is commonly referred to as "acneiform rash". Although referred to as "acneiform," the rash associated with anti-EGFR use is distinct from a classical acne rash. This rash is typically abacterial and is driven by inflammatory processes rather than infection. The acneiform rash occurs to some degree in approximately 90% of patients who are treated with an anti-EGFR. Most rashes are usually grade 1-2, with only 15-20% of patients experiencing grade 3 or higher acute toxicity. The rash typically occurs early in the course of anti-EGFR therapy. It has been reported that up to 85% of patients develop the rash by the end of the second infusion cycle and all patients will develop some degree of the rash by the fourth treatment cycle. The rash is associated with pruritus and pain, which may impair quality of life (QOL), and may result in dose reduction or treatment cessation in approximately one third of patients.[9-11] However, rash severity has also been linked to positive survival benefits.[12]

The Skin Toxicity Evaluation Protocol with Panitumumab (STEPP)[13] and the Japan Skin Toxicity Evaluation Protocol with Panitumumab (J-STEPP)[14] were open-label, randomized trials designed and implemented to evaluate differences in pre-emptive versus reactive management of Vectibix-associated dermatologic toxicities among patients with mCRC. Both studies demonstrated reduced severity in Vectibix-associated dermatologic toxicities through the implementation of pre-emptive vs. reactive skin management; however, this management approach is not mandated for mCRC patients treated with Vectibix resulting in less than optimum provision of care.

A balance between the expected benefit with treatment and the possible risk of a detriment to a patient's QoL should be a mindful discussion between the doctor and the mCRC patient having to decide on challenging treatment options. This is especially important in the treatment of mCRC patients whose treatment aims are palliative rather than curative. These types of

conversations may be challenging for the health care provider given the limited data that currently exists on how skin rash may affect a patients QoL.[12] One study has prospectively demonstrated that skin toxicity resulting from treatment with cetuximab had no clinical impact on health-realted QoL or skin-related QoL.[12]

There is a current and urgent need to better understand the patient's perspective regarding if they feel the risk of skin rash is worth the benefit of improved survival, how they were prepared for this skin toxicity, what they did to manage and treat their rash and how skin rash affects their QoL. This information can be utilized by health care providers to better inform patients how to prepare for Vectibix treatment, which may ultimately improve the uptake of and adherence to Vectibix resulting in better survival probabilities among mCRC patients.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This is a descriptive study and no formal hypotheses will be tested. This study is designed with the primary objective of assessing patients' experiences and opinions regarding dermatologic toxicities that may develop among mCRC patients who are treated with Vectibix.

8. Research Question and Objectives

8.1 Primary

Among mCRC patients treated with Vectibix

- Describe mCRC patient opinions regarding the risk of skin rash relative to the benefit of improved survival from Vectibix treatment
- Characterize the timing and severity of rash among mCRC patients following Vectibix treatment
- Describe mCRC patient opinions regarding the education they received to prevent and manage a Vectibix related skin rash
- Describe how mCRC patients managed their skin rash before and after the rash emerged
- Describe how a Vectibix related skin rash affected the patients quality of life

Among mCRC patients not treated with Vectibix

- Describe patient opinions regarding the risk of skin rash relative to the benefit of improved survival from Vectibix treatment

9. Research Methods

9.1 Study Design

We propose a cross-sectional study design which will utilize a patient survey to collect data.

9.2 Setting and Study Population

The study population will consist of mCRC patients in the United States. A convenience sample of at least 200 mCRC patients will participate in this study, 100 of whom are using or have used Vectibix and 100 who did not use Vectibix. Patients will be recruited via a third party patient recruiter, Portable Insights. Portable Insights has an established panel of cancer patients that has signed up to participate in survey research. Patients from their panel will be invited to participate via email. If the total sample cannot be achieved from their panel, additional custom recruitment methods will be implemented. They will use social media to attract and contact potential patients, as well as outreach through patient advocacy groups with whom they have a long standing relationship. Patients will receive an email with a link to the online survey. If interested, the patient enters the link, provides informed consent, and then answers screening questions to confirm their eligibility for participation. If they qualify, they continue to complete the main survey.

9.2.1 Study Period

The study will begin in March, 2019 with pilot studies of the survey. The final survey is anticipated to be implemented between March 11th and April 29th, 2019. The survey will be open for 8 weeks. The analysis is expected to be completed by December 1, 2019.

9.2.2 Selection and Number of Sites

Not applicable

9.2.3 Subject/Patient Eligibility

9.2.3.1 Inclusion Criteria

1. 18 years of age or older
2. Have a self-reported physician diagnosis of mCRC
3. Have consented to participate

9.2.3.2 Exclusion Criteria

Patients not meeting inclusion criteria will be excluded. Additional exclusion criteria include treatment with cetuximab at any point.

9.2.4 Matching

Not applicable

9.2.5 Baseline Period

Not applicable

9.2.6 Study Follow-up

Not applicable, this is a cross-sectional study and therefore no follow-up will occur.

9.3 Variables

9.3.1 Exposure Assessment

- History of Vectibix use – patients will be asked if they have ever used Vectibix (See Appendix A)
- History of rash – Patients will be asked if they have ever had a Vectibix-related skin rash (See Appendix A)
- Use of pre-emptive strategies to prevent or reduce the severity of rash – patient responses will be categorized as pre-emptive if they indicated they utilized recommended strategies prior to the appearance of rash. (See Appendix A)

9.3.2 Outcome Assessment

- **Opinions and perceptions regarding the risk/benefit profile of Vectibix**

The survey will assess patient opinions regarding the risk/benefit of Vectibix through a series of questions that ask the patient about their tolerance of rash, and about information that may influence their decision to use or not use Vectibix. (See Appendix A)

- **Timing and severity of rash**

The survey will assess the history of rash with a focus on the timing, severity and resolution of symptoms. (See Appendix A)

- **Opinions related ot the education of preventing and managing rash**

The survey will assess patient experiences related to information they received from their health care providers before and after the development of rash and if they felt that information adequately prepared them to deal with the onset of rash. (See Appendix A)

- **Management strategies to prevent and/or treat rash**

The survey will identify the strategies patients used before and after the appearance of rash with a focus on (See Appendix A):

  - Sunscreen
  - Moisturizer

- Oral antibiotics (prescription)
- Topical steroids (such as over the counter hydrocortisone cream)
- Topical steroids (prescription)

- **Quality of life among Vectibix users who currently have a rash**

Among patients currently experiencing a rash, how the rash has affected a patient's quality of life will be assessed using the Dermatology Life Quality Index (DLQI), a validated 10-question survey used for a variety of skin conditions including anti-EGFR skin toxicities among mCRC patients.[15] (See Appendix A) Among patients with a history of rash, a series of questions will be asked to understand how the rash impacted their quality of life, these questions were adapted from Tischer et al.[16] (See Appendix A)

9.3.3 Covariate Assessment

- Age
- Age at mCRC diagnosis
- Gender
- State where cancer care was received
- Insurance type

9.3.4 Validity and Reliability

The Dermatology Life Quality Index (DLQI) is a validated 10-question survey used for a variety of skin conditions including anti-EGFR skin toxicities among mCRC patients.[15] This index will be incorporated into the patient survey to assess how a Vectibix skin rash affects the quality of life of mCRC patients.

Other exposure and outcome measures soliciated on the questionnaire seek to capture the patients experiences and opinions. Several questions were pulled from a recent patient survey on acceptance of skin toxicities from anti-EGFR therapies.[16] Remaining questions are novel questions not used in other surveys and are therefore not validated. We do however expect these questions to yield reliable data given the survey will go through two rounds of pilot testing that is accompanied with cognitive debriefing to maximize the questionnaire's readability and the patients comprehension of each question.

9.4 Data Sources

9.4.1 Testing and Implementation of the Survey Instrument

9.4.1.1 Pilot Study (Phase I)

Portable Insights is the recruitment vendor Adelphi will be using for this research; they will recruit respondents from a national database. By using a third-party vendor, Adelphi does not know any personal identifying information of the respondents who participate in this research.

During the development of the survey, 1 pilot interview will be conducted with mCRC patients with Vectibix experience who meet the eligibility criteria for the study (see sections 9.2.3.1 and 9.2.3.2). Patients will complete an online version of the survey and the moderator will observe their responses and be on the phone to ask questions and answer questions. During the interviews, patients will be asked to provide feedback with respect to anything they view as confusing, missing, or irrelevant in the survey. After completing the survey, respondents will be asked a series of debriefing questions to determine whether they understood the questions and response options, and were able to complete the questions in the survey appropriately, or if other response categories or skip patterns would be needed. As each interview is completed, suggested changes will be recorded based upon feedback received during the interview.

The objectives of this phase of the pilot study were as follows:

1. Identify anything the patients find to be confusing, irrelevant, or missing from the survey;
2. Confirm comprehension of the survey items;
3. Confirm the appropriateness of the response options and skip patterns;
4. Test that the survey can be completed within a 30-minute time frame.

Following the pilot test, the survey will undergo another round of revisions as needed. Following this review, the survey will be finalized.

9.4.1.2 Implementation of the Final Survey

Once the final draft of the survey has been approved by Amgen, Adelphi will implement the survey using an online tool via Confirmit Survey Software (version 19). The online survey is anticipated to take 30 minutes to complete. In an effort to minimize missing data, the online survey has been designed so that each question must be answered before the next question will appear in the online survey.

9.5 Study Size

A convenience sample of at least 200 US-based mCRC patients will participate in this study, 100 will have used Vectibix and 100 will not have used Vectibix. We anticipate this sample size will provide for a robust data set that can be analyzed by various sub-groups (history of Vectibix use, history of rash, and use of pre-emptive strategies to prevent or reduce the severity of rash).

9.6 Data Management

9.6.1 Obtaining Data Files

9.6.1.1 Data handling and electronic transfer of data

Data will be collected using Confirmit Survey Software (version 19). Raw data are exported from this application and are transferred to Amgen via secured cloud-based services for review and analysis.

9.6.1.2 Handling of missing and incomplete data

The survey is designed in a manner that will eliminate missing data. The patient must answer a question before moving to the next question. However, some patients may decide to stop the survey before they complete it resulting in missing data. We would expect this to occur infrequently considering participants will be compensated upon study completion. If drop outs are to occur more frequently than expected, we would compare the demographics of people who complete the survey to those who do not.

9.6.1.3 Record Retention

All project information will be archived for a minimum of 10 years in addition to the five years in the production environment. No information can be deleted off the archive server without the approval of the Amgen senior management team.

9.6.2 Review and Verification of Data Quality

When answering the survey questions, the patient will have a list of predefined categorical answers to select from for most questions. For questions requiring an open numeric answer, an expected answer range will be programmed into the electronic survey and the survey will prompt the respondent to reconsider if the answer falls outside that range. We will also review the distribution of data at the end and remove any that are considered outliers. Skip patterns will be incorporated throughout the survey to direct patients to relevant questions, for example, patients who have not ever used Vectibix will not answer any questions about history of rash. Skip patterns reduce the burden on the participant as well as reduce the potential for erroneous responses.

In addition, data from any respondent who completes the survey in less than 10 minutes for Vectibix patients and less than 5 minutes for non-Vectibix patients will be identified and may not be included in the analysis, as this may signal poor-quality data or data with greater measurement errors. Computer and privacy settings may impact survey length records; survey length less than the times specificed above will not automatically result in removal. Length in addition to a thorough check of all data for logical responses will inform if removal from the survey is necessary. Edit, range, and logic checks will be performed on each variable of interest by the study programmer to ensure quality and completeness.

9.6.2.1 Quality Assurance

No patient-level, personal or confidential medical information will be collected during this study. Response data from all interviews will be assigned a unique study identification number. All electronic data files will be stored in password protected computers.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Analysis of Study Enrollment

The following descriptive statistics will be analyzed:

- Proportion of mCRC patients who agree to participate in the study
- Proportion of mCRC patients who meet the criteria for participation (i.e. eligibility rate)

The consent rate will be calculated as the proportion of eligible patients who consent to participate in the survey out of all eligible patients.

9.7.1.2 Stratified Analysis

Not applicable

9.7.2 Planned Method of Analysis

The proportion of patients who select each answer within a survey question will be summarized and confidence intervals will be estimated as the estimated proportion ± 1.96 multiplied by the estimated standard error.

9.7.2.1 General Considerations

This is a descriptive study and no formal hypothesis testing will be conducted.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Each question must be answered before the next question will appear in the online survey. However, some patients may decide to stop the survey before they complete it resulting in missing data. We would expect this to occur infrequently.

9.8 Quality Control

When answering the survey questions, the patient will have a list of predefined categorical answers to select from for most questions. For questions requiring an open numeric answer, an expected answer range will be programmed into the electronic survey and the survey will prompt the respondent to reconsider if the answer falls outside that range. We will also review the distribution of data at the end and remove any that are considered outliers. Skip patterns will be incorporated throughout the survey to direct patients to relevant questions, for example, patients who have not ever used Vectibix will not answer any questions about history of rash. Skip patterns reduce the burden on the participant as well as reduce the potential for erroneous responses.

In addition, data from any respondent who completes the survey in less than 10 minutes for Vectibix patients and less than 5 minutes for non-Vectibix patients will be identified and may not be included in the analysis, as this may signal poor-quality data or data with greater measurement errors. Computer and privacy settings may impact survey length records; survey length less than the times specificed above will not automatically result in removal. Length in addition to a thorough check of all data for logical responses will inform if removal from the survey is necessary

9.9 Limitations of the Research Methods

9.9.1.1 Measurement Error(s)/Misclassification(s)

We ask participants to recall their use of Vectibix and any history of rash. Paticipants who used Vectibix more recently may have better recall of events surrounding this medication. Participants with a history of rash that was painful or burdensome may have better recall of what they did to manage the rash before and after it appeared.

9.9.1.2 Selection Bias

mCRC patients eligible to participate in the study may decline to participate for various reasons and thus responses from the participating patients may not be generalizable to all eligible mCRC patients in the US. For instance, patients who are the sickest, or experiencing the most severe chemotherapy associated adverse reactions may be less likely to participate because of their poor health. The study will be unable to measure or control for this potential bias. However,

selection bias will be listed as a potential limitation of the study in the discussion of the study results.

9.9.2 External Validity of Study Design

Please refer to section 9.9.1.2 on selection bias.

9.9.3 Analysis Limitations

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Each question must be answered before the next question will appear in the online survey. However, some patients may decide to stop the survey before they complete it resulting in missing data. We would expect this to occur infrequently.

10. Protection of Human Subjects

10.1 Informed Consent

Prior to the conduct of the in-person pre-tests (described in sections 9.4.1.1 and 9.4.1.2), each patient will be given an Informed Consent Form (ICF) containing information about the study's goals and methods, as well as the rights and responsibilities of the patient as part of the study (Appendix B – Informed Consent). Patients will be asked to provide informed consent at the start of the survey.

During the pilot interviews and final survey administration, respondents will be provided electronic informed consent by clicking "I agree to participate." The informed consent text explains the aims, methods, data to be collected, anticipated benefits, and potential hazards of the study. Any respondent who does not provide consent will not continue in the study.

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

This study will undergo review through an external IRB at Sterling, https://sterlingirb.com/.

10.3 Subject/Patient Confidentiality

All patient interviews will be anonymized. Any identifying information revealed during phase I/II administered interviews will be removed from the interview transcript. No identifying information will be collected in our raw data file. All respondents will be assigned a unique ID number.

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

If any individual adverse event or other safety information regarding an Amgen product is made known during the study, standard operating procedures for the reporting of adverse events and

other safety information will be followed to ensure all adverse events are reported within one business day.

Adelphi Research will prepare an excel sheet called 'AE Reporting Rules' which outlines all closed-ended questions in the survey that will trigger an adverse event and all open-ended questions to review. This occurs prior to study launch. A copy of the sheets within the excel file is available in Appendix A following the patient survey. The Adelphi team will review the data together after soft-launch to confirm that the data file is formatted correctly. The Adelphi compliance specialist will review survey data daily on business days and will report adverse events to Amgen by EOD using the forms and contact information provided. (Appendix C)

Study recruitment will be done by Portable Insights through a nonreply email. In the event of technical difficulties patients may have accessing the survey, this email will contain a phone number to call and an alternate email that patients may contact with questions. Adelphi Research will train Portable Insights on Adverse Event Reporting to ensure Portable Insights completes the Amgen specific training, such that in the event safety information or an adverse event is reported to Portable Insights, they will know the appropriate procedures to report that event.

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient 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 product(s), whether or not 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)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

11.1.2 Serious Adverse Events

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

- is fatal
- is life threatening (places the <<*subject/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 significant medical hazard" 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 significant medical hazards" refer to important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the the 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

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

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- Pregnancy and lactation exposure,
- 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).

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 product or device after it is released for distribution to market or clinic by either

Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

11.2 Safety Reporting Requirements

This study is collecting information from mCRC patients at one point in time as part of a cross-sectional survey. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to Vectibix will be collected from signing of informed consent to find study contact. Adelphi Research is responsible for ensuring that all safety events they become aware of during study period, are recorded in the participants appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Adelphi Research's awareness. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendars days of Adelphi Research's awareness.

Safety events that are suspected to be related to any medicinal product where there is no exposure to Vectibix should be reported to the local authority in line with the local country requirements.

In addition, Adelphi Research will prepare an excel sheet called 'AE Reporting Rules' which outlines all closed-ended questions in the survey that will trigger an adverse event and all open-ended questions to review. This occurs prior to study launch. The Adelphi team will review the data together after soft-launch to confirm that the data file is formatted correctly. The Adelphi compliance specialist will review survey data daily on business days and will report adverse events to Amgen by EOD within one business day of receiving the report of the AE using the forms and contact information provided.

See Appendix C. Safety Reporting Form(s), Appendix D. Additional Safety Reporting Information regarding the adverse event grading scale used in this study.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study Case Report Forms (CRFs) where safety data may also be recorded (eg, Event CRF).

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations.

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.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

The results of this study will be submitted for presentation at a scientific conference and will be submitted for publication in a peer-reviewed journal.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

Patients will be compensated for time required for his or her participation in the interviews (i.e., payment will be commensurate with research purposes). Patients will be compensated for more time in the pilot phase of the study (online pilot test and interview).

Compensation will be as follows for each stage:

[redacted]

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16. Appendices

Appendix A. Survey

Patient perceptions related to potential skin toxicity following Vectibix treatment

Thank you for agreeing to be part of this survey. This study will allow us to learn more about the experiences mCRC patients are having related to skin reactions that can occur following treatment with panitumumab, brand name Vectibix. We are interested to know the types of information and education cancer you may have received around this potential adverse event. We hope to identify how the education surrounding the management of skin reactions could be improved for cancer participants like you.

We know your time is valuable and we appreciate all of the information you'll be sharing with us today during this brief survey. We've designed the survey to take approximately 30 minutes to complete.

Screening questions

Are you 18 years or older?
[] Yes
[] No

Has a physician ever told you that you have metastatic colorectal cancer?
[] Yes
[] No

Have you ever been treated with cetuximab (brand name Erbitux)?
[] Yes
[] No

I. Basic demographics for all survey participants

1. Age
____yrs

2. Gender
[] Male
[] Female

3. Age at diagnosis of metastatic colorectal cancer
_____ yrs

4. In what State did you primarily receive treatment for metastatic colorectal cancer?
Drop down menu of all US states

Which insurance did you use when you initiated treatment for metatstatic colorectal cancer? Please select all that apply
[] Private insurance
[] Medicare
[] Other _____
[] Unknown

5. Which of the following options best describes your treatment for metastatic colorectal cancer? (Please select one response)
[] I am currently being treated by my doctor for metastatic colorectal cancer
[] I am not currently being treated, but had treatment in the past for metastatic colorectal cancer
[] I have not had treatment for metastatic colorectal cancer

6. What is your RAS biomarker status, if known?
[] RAS wild type
[] RAS mutant
[] I am not sure

7. Have you ever been treated with panitumab (brand name Vectibix)? Please note the remainder of the survey will utilze the brand name Vectibix.
[] Yes
[] No **If No, skip to Q60**

II. History of Vectibix use

If ever treated with Vectibix (Q7)= Yes

8. For how many months were you treated with Vectibix?

_____ months (FILL IN)

If ever treated with Vectibix (Q7)= Yes

9. In which line of treatment have you received Vectibix? (Select all that apply):

[] 1st line (*the first therapy you received as a mCRC patient*)
[] 3rd line (*treatment that is given when both initial treatment (first-line therapy) and subsequent treatment (second-line therapy) don't work, or stop working*)
[] Beyond 3rd line
[] Other _____
[] Unsure, I have received Vectibix but I do not know the line of treatment it was in
[] I don't know if I ever used Vectibix

III. History of rash

Vectibix is commonly associated with a skin rash. By rash, we mean a painful or itchy skin rash (that can sometimes look like acne) and can cover more than 30% of the body surface including the face; this rash can last for several weeks.

If ever treated with Vectibix (Q7) = Yes:

10. Have you ever had a skin rash associated with Vectibix treatment?

[] Yes
[] No **If No, skip to Q23**

If ever had a Vectibix rash (Q10)=Yes

When did you first experience a skin rash associated with Vectibix treatment?

[] My rash first appeared within the last month
[] My rash first appeared 1-3 months ago
[] My rash first appeared 4-6 months ago
[] My rash first appeared 7-9 months ago
[] My rash first appeared 10-12 months ago
[] My rash first appeared more than 1 year ago
[] I don't recall when my rash first appeared

If ever had a Vectibix rash (Q10)=Yes

11. After which line of Vectibix treatment did you experience a rash? (check all that apply):

[] 1st line
[] 3rd line
[] Beyond 3rd line
[] Other _____
[] I am unsure of which line of treatment the rash followed

The following questions are focused on your experience with skin rash associated with Vectibix treatment.

If ever had a Vectibix rash (Q10)=Yes

12. After starting treatment with Vectibix, at what point do you recall first noticing the rash?

[] Within a week of my first dose of Vectibix
[] Between 2 and 4 weeks following my first dose of Vectibix
[] More than 4 weeks following my first dose of Vectibix
[] I experienced a rash from Vectibix, but I don't recall when it started

13. How would you describe the severity of the rash you experienced?

[] Mild, defined as having minimal symptoms with no impact on daily activities
[] Moderate, defined as itchy or painful pimples or skin bumps covering less than one third of your skin, including your face. This can limit your ability to prepare meals, shop, use the telephone, and manage money.

[] Severe, defined as having itchy or painful pimples or skin bumps that cover more than one third of your skin including the face. This can limit your ability to bathe, shower, dressing or undressing, feeding yourself, using the toilet, or taking your medications.

14. Which areas of your body were affected by the rash? Select all that apply

[] Face
[] Scalp
[] Neck
[] Ears
[] Arm(s)
[] Fingers
[] Leg(s)
[] Toes
[] Back
[] Stomach
[] Chest
[] Buttocks
[] Other _____please specify
[] I do not recall

15. How would you describe your rash over time?
[] My rash improved while on Vectibix treatment
[] My rash didn't change while on Vectibix treatment
[] My rash continued to get worse while on Vectibix treatment

If rash improved (Q15)=Yes

16. While on Vectibix treatment, after how many weeks did you notice your rash begin to improve?
[] My rash started to improve 4 weeks after starting Vectibix
[] My rash started to improve 6 weeks after starting Vectibix
[] My rash started to improve 8 weeks after starting Vectibix
[] My rash started to improve more than 8 weeks after starting Vectibix

17. Are you still currently on Vectibix treatment?
[] Yes **If Yes, skip to Q21**
[] No

If currently on Vectibix (Q17)=No

18. After stopping the treatment with Vectibix, did your rash resolve?
[] Yes
[] No

If Vectibix rash resolved after stopping (Q18)=Yes

19. How would you describe the resolution of your rash once you stopped Vectibix treatment? (Please select one)
[] Once I stopped the first line of Vectibix, my rash resolved within 4 weeks
[] Once I stopped the first line of Vectibix, my rash resolved between 4 and 6 weeks later
[] Once I stopped the first line of Vectibix, my rash resolved after 6 weeks
[] Once I stopped the first line of Vectibix my rash resolved, but I don't recall how long it took to resolve

If Vectibix rash resolved after stopping (Q18)=No

20. How would you describe the persistence of your rash after stopping Vectibix treatment? (Please select one)
[] I stopped Vectibix treatment less than one month ago and my rash has not yet completely resolved
[] I stopped Vectibix treatment between 4 and 6 weeks ago and my rash has not yet completely resolved
[] I stopped Vectibix treatment more than 6 weeks ago and my rash has not yet completely resolved
[] I don't recall when I stopped Vectibix treatment and my rash has not yet completely resolved

IV. Patient education on rash

If ever had a Vectibix rash (Q10) =Yes

21. Do you feel that your health care providers informed you adequately/appropriately of what to expect regarding rash?
[] Yes
[] No

If ever treated with Vectibix (Q7) = Yes

22. Which of the following information/education did you receive regarding background information on a Vectibix-related rash from your health care provider? Mark all that apply

[] Information on how commonly patients may experience a rash
[] Information on levels of rash severity
[] Information on how the presence of rash might be associated with better treatment outcomes

If ever treated with Vectibix (Q7) = Yes

23. Which of the following information/education did you receive regarding how to minimize or manage a Vectibix-related rash from your health care provider? Mark all that apply

[] Education on the importance of wearing skin protective garments to prevent sun exposure (including hats and UV barrier clothing)
[] Education on the increased sensitivity to the sun while on treatment
[] Education/instruction on wearing sunscreen
[] Education/instruction on use of moisturizers
[] Education/instruction on skin care products or ingredients to avoid
[] Recommendations for the use of oral antibiotics
[] Education/instruction on when to seek treatment for rash
[] Recommendations for seeing a dermatologist
[] I did not receive any information or education on how to minimize or manage my rash

If ever had a Vectibix rash (Q10) = Yes

24. Did you receive this information before or after your rash appeared?

[] Before only
[] After only
[] I received information both prior to and following the appearance of rash
[] I don't recall if the information was given before and/or after the rash appeared

V. Patient management of rash before and after treatment

The following questions are focused on how you managed your skin rash during Vectibix treatment.

If ever had a Vectibix rash (Q10)=Yes

25. Did you use any of the following treatments or strategies to prevent rash ***before*** the rash occurred? Choose all that apply

[] Sunscreen
[] Moisturizer
[] Oral antibiotics (prescription)
[] Topical steroids (such as over the counter hydrocortisone cream}
[] Topical steroids (prescription)
[] Other _____
[] I did not do anything to prevent the rash

26. Did you use any of the following treatments or strategies to treat the rash ***after*** the rash appeared? Choose all that apply

[] Sunscreen
[] Moisturizer
[] Oral antibiotics (prescription)
[] Topical steroids (such as over the counter hydrocortisone cream}
[] Topical steroids (prescription)
[] Other _____
[] I did not use any treatment for the rash

VI. Patients tolerability of potential Vectibix side-effects

Skin rash is a known potential side effect of Vectibix treatment, with some people experiencing rash that may cover parts of their face, neck and/or body that can be painful and burdensome. Data from a clinical trial has shown that the use of Vectibix in combination with chemotherapy in first line treatment results in improved survival compared to chemotherapy alone. Additional data further suggests that patients who experience a rash have better treatment outcomes, although further studies are underway to confirm this association.

27. THIS QUESTION WILL BE DELETED

~~How would you describe your opinions/feelings about Vectibix treatment (Please select one response):~~

~~[] I feel the possibility of improved survival is worth the risk of developing a rash, even if it's severe~~
~~[] I feel the possibility of improved survival is worth the risk of developing a rash, even if it's moderate~~
~~[] I feel the possibility of improved survival is worth the risk of developing a rash, only if it is a mild rash~~
~~[] I do not feel the possibility of improved survival is worth the risk of developing a rash~~

[Q28 - Q30] When thinking about the potential side effect of a moderate to severe rash resulting from Vectibix treatment, how much influence do the following pieces of information have on your decision to ***use*** Vectibix?

28. Knowing there are preventive strategies proven to reduce the severity of rash	[] A lot	[] Some	[] A little	[] None
29. Knowing that in the majority of patients, rash does resolve and causes no permanent damage to the skin	[] A lot	[] Some	[] A little	[] None
30. Knowing that patients who use Vectibix may have better survival outcomes	[] A lot	[] Some	[] A little	[] None

[Q31-Q34] When thinking about the side effect of a moderate to severe rash resulting from Vectibix treatment, how much influence do the following pieces of information have on your decision to ***not use*** Vectibix?

31. The risk of a rash that affects my appearance	[] A lot	[] Some	[] A little	[] None
32. The risk of a rash that affects my quality of life	[] A lot	[] Some	[] A little	[] None
33. The risk of a rash that is painful	[] A lot	[] Some	[] A little	[] None
34. The risk of a rash that lasts more than 2-weeks	[] A lot	[] Some	[] A little	[] None

VII. Health-related Quality of life section

If ever had a Vectibix rash (Q10)=Yes

35. During the past week, have you been experiencing a new or existing skin rash related to Vectibix treatment?

[] Yes
[] No

If current skin rash (Q35) = Yes, answer DLQI [Q36 to Q46], if (Q35) =No skip to Q74

Dermatology Life Quality Index (DLQI)
The aim of this questionnaire is to measure how much your skin problem has affected your life **OVER THE LAST WEEK**. Please select one response for each question

36. Over the last week, how **itchy, sore, painful or stinging** has your skin been?	□Very Much	□A lot	□ A Little	□Not at all
37. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	□Very Much	□A lot	□ A Little	□Not at all
38. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	□Very Much	□A lot	□ A Little	□Not at all

39. Over the last week, how much has your skin influenced the **clothes** you wear?	☐Very Much	☐A lot	☐ A Little	☐Not at all
40. Over the last week, how much has your skin affected any **social** or **leisure** activities?	☐Very Much	☐A lot	☐ A Little	☐Not at all
41. Over the last week, how much has your skin made it difficult for you to do any **sport**?	☐Very Much	☐A lot	☐ A Little	☐Not at all
42. Over the last week, has your skin prevented you from **working** or **studying**?	☐Yes	☐No		
43. If "No", over the last week how much has your skin been a problem at **work** or **studying**?		☐A lot	☐ A Little	☐Not at all
44. Over the last week, how much has your skin created problems with your partner or any of your **close friends** or **relatives**?	☐Very Much	☐A lot	☐ A Little	☐Not at all
45. Over the last week, how much has your skin caused any **sexual difficulties**?	☐Very Much	☐A lot	☐ A Little	☐Not at all
46. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	☐Very Much	☐A lot	☐ A Little	☐Not at all

If ever had a Vectibix rash (Q10)=Yes

[Q47-Q59] Tischer et al

Please think of the time when the symptoms of your skin rash were most severe: Please indicate whether each of the following conditions applied *not at all*, *a little bit*, *somewhat*, *quite a bit*, or *very much*.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Statement	1	2	3	4	5
47. My skin or scalp felt irritated?	[]	[]	[]	[]	[]
48. My skin or scalp was dry or flaky?	[]	[]	[]	[]	[]
49. My skin or scalp itched	[]	[]	[]	[]	[]
50. My skin bled easily	[]	[]	[]	[]	[]
51. I was bothered by a change in my skin's sensitivity to the sun	[]	[]	[]	[]	[]
52. My skin condition interfered with my ability to sleep	[]	[]	[]	[]	[]
53. My skin condition affected my mood	[]	[]	[]	[]	[]
54. My skin condition interfered with my social life	[]	[]	[]	[]	[]
55. I was embarrassed by my skin condition	[]	[]	[]	[]	[]
56. I avoided going out in public because of how my skin looked	[]	[]	[]	[]	[]
57. I felt unattractive because of how my skin looked	[]	[]	[]	[]	[]
58. My skin condition made my life difficult	[]	[]	[]	[]	[]
59. The skin rash interfered with household tasks	[]	[]	[]	[]	[]

VIII. Participants' opinions on their tolerability of potential rash following Vectibix treatment among participants who have NOT used Vectibix

If ever treated with Vectibix (Q7)= No, Answer Q60 through Q67

Vectibix is commonly associated with a skin rash. By rash, we mean a painful or itchy skin rash (that can sometimes look like acne) and can cover more than 30% of the body surface including the face, this rash can last for several weeks. Data from a clinical trial has shown that the use of Vectibix in combination with chemotherapy in first line treatment results in improved survival compared to chemotherapy alone. Additional data further suggests that patients who experience a rash have better treatment outcomes, although further studies are underway to confirm this association.

Nearly all patients will experience skin toxicity to some degree. A mild form of skin reaction means it is a local reaction showing minimal symptoms and has no impact on daily activities.

In addition, there is a certain probability that some patients develop a **severe form of skin rash**. This means that you would have itching or painful pimples or skin bumps that cover more than one third of your skin including the face. This can limit your ability to bathe, shower, dressing or undressing, feeding yourself, using the toilet, or taking your medications. The skin rash occurs in the first weeks after starting the treatment and may last up to 6 to 8 weeks.

Although nearly all patients develop a mild form of skin reactions, your doctor is not able to predict for which patient the therapy causes **severe skin rash** and for which patients not.

60. THIS QUESTION WILL BE DELETED
~~How would you describe your opinions/feelings about Vectibix treatment (Please select one response):~~
~~[] I feel the possibility of improved survival is worth the risk of developing a rash, even if it's severe~~
~~[] I feel the possibility of improved survival is worth the risk of developing a rash, only if it is a moderate rash~~
~~[] I feel the possibility of improved survival is worth the risk of developing a rash, only if it is a mild rash~~
~~[] I do not feel the possibility of improved survival is worth the risk of developing a rash~~

When thinking about the potential side effect of a moderate to severe rash resulting from Vectibix treatment, how much influence would the following pieces of information have on your decision to ***use*** Vectibix?

61. Knowing there are preventive strategies proven to reduce the severity of rash	[] A lot	[] Some	[] Little	[] None
62. Knowing that in the majority of patients, rash does resolve and	[] A lot	[] Some	[] Little	[] None

causes no permanent damage to the skin				
63. Knowing that the patients who use Vectibix may have better survival outcomes	[] A lot	[] Some	[] Little	[] None

When thinking about the side effect of a potential moderate to severe rash resulting from Vectibix treatment, how much influence would the following pieces of information have on your decision to ***not use*** Vectibix?

64. The risk of a rash that affects my appearance	[] A lot	[] Some	[] Little	[] None
65. The risk of a rash that affects my quality of life	[] A lot	[] Some	[] Little	[] None
66. The risk of a rash that is painful	[] A lot	[] Some	[] Little	[] None
67. The risk of a rash that lasts more than 2-weeks	[] A lot	[] Some	[] Little	[] None

The following statements are related to skin reactions as possible side effect of Vectibix treatment. Using a 10-point scale, please indicate to what extent you agree with the statements. "1 = completely disagree" and "10 = completely agree

	Completely disagree								Completely agree	
Statement	1	2	3	4	5	6	7	8	9	10
68. If Vectibix may improve survival, I would accept skin rash as a possible side effect	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]
69. A severe skin rash caused by Vectibix would negatively impact my quality of life	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]
70. If I had a choice between a more effective cancer therapy causing more severe skin reactions and a less effective therapy causing less severe skin reactions, I would choose the more effective therapy	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]
71. If there was a drug or product(s) to prevent or lessen the severity of skin reactions during Vectibix treatment, I would ask the doctor for it	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]

72. If I were to be treated with Vectibix, I would feel comfortable talking to my oncologist about things I can do to lessen the severity of the rash?
[] Yes
[] No

73. If I were to be treated with Vectibix, I would be willing to do the following things if it would lessen the severity of the rash (check all that apply)?

[] Stay out of the sun
[] Wear sun protective clothing
[] Wear sunscreen daily
[] Use skin moisturizer daily
[] Use over-the-counter hydrocortisone cream
[] Use prescription-level hydrocortisone cream (if prescribed)
[] Use prescription-level antibiotic cream (if prescribed)
[] Use prescription-level oral antibiotics (if prescribed

IX. mCRC treatment history

This section is to be asked of every participant

74. What 1st line treatment(s) have you received for metastatic colorectal cancer?
The first line of treatment refers to the first therapy you received as a mCRC patient.

[] Chemotherapy alone
[] Chemotherapy plus Vectibix
[] Chemotherapy plus Erbitux
[] Chemotherapy plus Avastin
[] Other _____
[] I do not recall my 1st line treatment
[] Does not apply, I have not yet had 1st line treatment

75. Did the possibility of skin rash influence your choice of 1st line treatment for metastatic colorectal cancer? (Please select one)

[] Yes
[] No
[] I was not aware of the possibility of skin rash during my first line of treatment
[] My doctor choose my treatment

76. What 3rd line treatment(s) have you received for metastatic colorectal cancer?
The third line of treatment refers to treatment that is given when both initial treatment (first-line therapy) and subsequent treatment (second-line therapy) don't work, or stop working.

[] Chemotherapy alone
[] Vectibix
[] Erbitux with or without chemotherapy
[] Avastin with or without chemotherapy
[] Other _____
[] I do not recall my 3rd line treatment
[] Does not apply, I have not had 3rd line treatment

77. Did the possibility of skin rash influence your choice of 3rd line treatment for metastatic colorectal cancer? (Please select one)

[] Yes
[] No
[] I was not aware of the possibility of skin rash during my third line of treatment
[] My doctor choose my treatment

END

Thank you for your time. Your opinions and experiences provide valuable information that will be used to identify the gaps in patient education surrounding Vectibix related skin rash. Your responses can be used to improve education strategies among health care providers to better inform mCRC patients how to prepare for Vectibix treatment

AE Reporting Rules, excel sheet provided by Adelphi

Summary Sheet

Data services to complete	
Name Data Services Exec	
Date Received by Data Services	
Date programmed	
No. of Adverse Events passed to researcher	
Researcher to complete	
Closed questions	
Download intervals required (daily, weekly etc.)	
Process options (delete as appropriate)	
Excel sheet to be passed to research team to raise the Adverse Event and send to drug safety	
Data Services to produce Adverse Event form and pass to team to send to drug safety	
Open questions	
Download required (daily weekly etc.)	

Closed Sheet

Name of rule *: The number of the question from which an adverse event might arise*
AE definition *: The response codes corresponding to adverse events*
Adelphi notes *: Any additional information which the DP exec should be aware of prior to building the AE processor*
AE definition for form *: The text to be included in the definition section of the AE reporting form when this particular AE occurs*
Client comments *: Any additional comments from the client which are relevant to the reporting procedure*

Name of Rule	AE Definition (Response Combinations)	AE Definition for Form	Other relevant details to complete AE report		Repondent ID	Country	Consent to contact drug safety

Open-ended Sheet

Name of open ended question *: The number of the question. Remember to include others.*
Adelphi notes *: Any additional information which the coder/research team might need to identify the Adverse Event*
Responsibility for reviewing and raising Adverse Event *: This can be coder, research team etc.*
Probability of receiving AE: *All open-ended must be reviewed but this gives an indication of the probability of receiving an AE*
Client comments *: Any additional comments from the client which are relevant to the reporting procedure*

Name of Open-Ended	Adelphi Notes	Probability of receiving AE Minimum Risk, Low Risk, High Risk	Responsibility for reviewing and raising Adverse Event	Client Comments

Appendix B. Informed Consent

Study Title: A Survey of Experiences and Opinions Regarding Skin Toxicities Associated with Vectibix Among mCRC Patients

Study #: 20190025

Sponsor: Amgen

Study Investigator: PPD

Adelphi Research

2005 South Easton Road, Suite 300, Doylestown, PA 18901

Telephone Number: PPD

Before you begin, please review the following information about this study and how the information will be used.

What is the purpose of this form?

The purpose of this form is to help you decide if you want to be in this research study. Participation is voluntary and you should take part in this study only if you want to.

Before you decide if you want to take part in this research study, it is important that you read the information below.

If you complete this form, it means that you agree to take part in this study. This form describes what the study is about and what will happen. You can change your mind about taking part in this study at any time. You may leave the study at any time, even if you have completed this form. You do not have to give a reason. There will be no penalty to you, and you won't lose any benefits. Please ask the study investigator or study staff any questions you have.

The sponsor of this study is a pharmaceutical company. The pharmaceutical company is paying the consulting firms Adelphi Research and the related research sites for conducting this research study. Adelphi Research is totally independent as a company

and would like you to be Adelphi Research complies with all national laws protecting your personal data and all industry codes.

Why is this study being done?

The purpose of this study is to understand patients experiences and opinions regarding dermatologic toxicities associated with specific colorectal cancer therapies. Data resulting from this study will be used primarily for scientific and research and development purposes. No information will be collected that may identify you to the sponsor, and all responses will be treated as confidential information. The survey being used in this study is for research purposes only and is not intended to be promotional. Approximately 200 patients from varying geographic regions are expected to participate in completing the online survey.

What are the study procedures?

If you agree to take part in this study, you will first complete this Informed Consent Form. Once you have completed the Informed Consent form, you will (depending upon the invitation you received) participate in:

You may be asked to participate in a 60 minute online pilot test and interview. If you participate in a 60 minute online pilot test and interview, you will receive $150 after completion; or

You may participate by completing a web-based survey on your own regarding your experiences and opinions of colorectal cancer therapies. The survey takes approximately 20 minutes to complete. If you complete the survey, you will receive $85

Your responses to the online survey will automatically save as you proceed, therefore you may close and rejoin the questionnaire at any point. Upon completion of the questionnaire, you will receive compensation as described above.

You have the right to withdraw from the survey at any time and to withhold information as you see fit. If you withdraw from the study, you will not lose any benefits to which you are entitled, although data already collected will be retained by the system and may be used in analysis.

The study investigator or study staff or the sponsor company has the right to stop your participation in the study at any time, with or without your consent. This could happen if:

The study investigator or study staff believes it is best for you to stop being in the study

You do not follow directions about the study

The sponsor stops the study for any reason.

If the study investigator or study staff learns any new information that might change your mind about continuing in the study, they will tell you about it.

Your participation will end after the survey completion is finished, unless you or a member of the research team decides to conclude your participation in this study without completing the interview and/or survey. After your participation ends, the results of the survey will be aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to you as an individual.

The sponsoring pharmaceutical company may publish the findings of this research in publically available scientific journals or forums. All information provided will only be reported as group data with no identifying information.

What are the alternatives?

Your alternative is to not be in the study.

What are the risks and benefits?

There is the potential risk of loss of confidentiality of your information; however, all efforts will be made to keep your information confidential.

Although all data will be anonymized (directly identifying information removed), it is possible that, if you are participating in an interview, your voice may be recognized on the recording. Please ask the study investigator or study staff if you would like to know more about how your information will be protected while you are in this study.

Your participation in the study may contribute to information about physicians' discussions with patients about skin toxicities associated with colorectal cancer therapies. You will not benefit from this study, but it may benefit other people in the future.

How will my information be protected?

Your identity will be kept confidential and none of your details will be passed on to the pharmaceutical company or any 3rd party, unless required by law. The information collected about you will not directly identify you (for example, by name, address, or social security number). Instead, a code number will be used for your information. Be aware that your study records (which include your consent form, audio recordings [if applicable], survey responses, and other information) will be shared as needed for the study. For example, the sponsor may look at your study records.

Physician Payments Sunshine Act

Federal and certain State laws, along with comparable company policies, may require that the pharmaceutical sponsor report any payment received by you for your participation in the study, if the pharmaceutical sponsor is aware of your identity. If the pharmaceutical sponsor recognizes you by name, you can either allow your name and the amount of any payments made to you for participation in the research to be released and reported as per the Sunshine Act requirements or you can agree to forfeit any potential payments for your participation in this study.

By signing this consent form you agree to participate in the research/interview under these conditions.

Adverse Event Reporting

Adelphi Research is required by the pharmaceutical company to pass on details of adverse events/product complaints for any of the pharmaceutical company's products, mentioned during the course of the research interviews.

Although this is a research interview and what you say will be treated in confidence, should you raise during the discussion an adverse event in a patient or patients, Adelphi Research will need to report this even if it has already been reported by you directly to the company or the regulatory authorities.

In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in

relation to that adverse event/product complaint. Everything else you say during the course of the interview will continue to remain confidential.

Who do I call if I have questions?

If you have any questions, please contact Adelphi at 617-720-0001 during business hours or at 877-202-4215 after business hours, and reference study code 20190025.

You can find out more about Adelphi Research at www.adelphigroup.com/marketresearch.

You can ask questions about the study at any time. You can call the study investigator or study staff at any time if you have any concerns or complaints. You should call the study investigator or study staff at the phone number listed on page 1 of this form if you have questions about the study procedures, study costs (if any), or study payment (if any).

Do you agree to participate in this study?

I have read this form, and I have been able to ask questions about this study. By consenting to be in this study, I confirm that I have read, understood and accept the information above and I agree to participate in this study. I do not give up any of my legal rights if I agree to be in the study.

☐ Yes, I agree

☐ No, I do not agree

Appendix C. Safety Reporting Form(s)

Observational Research Safety Reporting Form Instructions

This form is for use for observational studies that are using paper report form

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 (e.g., 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 (e.g., 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: 20190025	AMGEN	Observational Research Safety Reporting Form	Date of Reporter Awareness: / Date Reported to Amgen:
		Fax reports to: Amgen Local Office **1-888-814-8653 (US)**	

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	*Height*	*Race*	*Is patient also reporter?*
☐ lbs ☐ kg	☐ in ☐ cm		☐ 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** **01** Fatal **02** Immediately life-threatening **03** Required/Prolonged hospitalization **04** Persistent or significant disability /incapacity **05** Congenital anomaly/birth defect **06** Other significant medical hazard **07** Non serious	**Action Taken** 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=drug rechallenge (state outcome)	**Outcome** **01** Recovered/ Resolved **02** Recovering/ Resolving **03** Not recovered/not resolved **04** Recovered/ resolved with sequelae **05** Fatal **06** 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

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	 Yes	Continuing No	 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 D. Additional Safety Reporting Information (Pregnancy and Lactation Notification Forms)

Amgen Proprietary - Confidential

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: 20190025

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:** _____

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: 20190025

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:** _____

[redacted]

Appendix E. ENCePP Checklist for Study Protocols

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☒	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	
Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	
10.2 Are descriptive analyses included?	☒	☐	☐	
10.3 Are stratified analyses included?	☒	☐	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	
10.6 Is sample size and/or statistical power estimated?	☐	☒	☐	

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☐	☒	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	