Summary Table of Study Protocol

Title	Canadian Retrospective Observational Study of MVASI in Metastatic Colorectal Cancer
Protocol version identifier	20180360, Version 1.0
Date of last version of the protocol	N/A, Original Version
EU Post Authorization Study (PAS) Register No	TBD
Active Substance	N/A
Medicinal Product	N/A
Product Reference	MVASI (ABP 215)
Procedure Number	N/A
Joint PASS	No
Research Question and Objectives	To describe the safety of MVASI in first-line untreated mCRC patients in Canada.
Country of Study	Canada
Authors	PPD , Amgen Canada Inc. PPD , Amgen Canada Inc. PPD Amgen Inc.

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen
MAH Contact	PPD

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Canadian sites, 1-866-50-AMGEN.

Amgen's general number in the US (1-805-447-1000).

Investigator's Agreement

I have read the attached protocol entitled ***Canadian Retrospective Observational Study of MVASI in metastatic Colorectal Cancer***, dated 05 March 2020, and agree to abide by all provisions set forth therein.

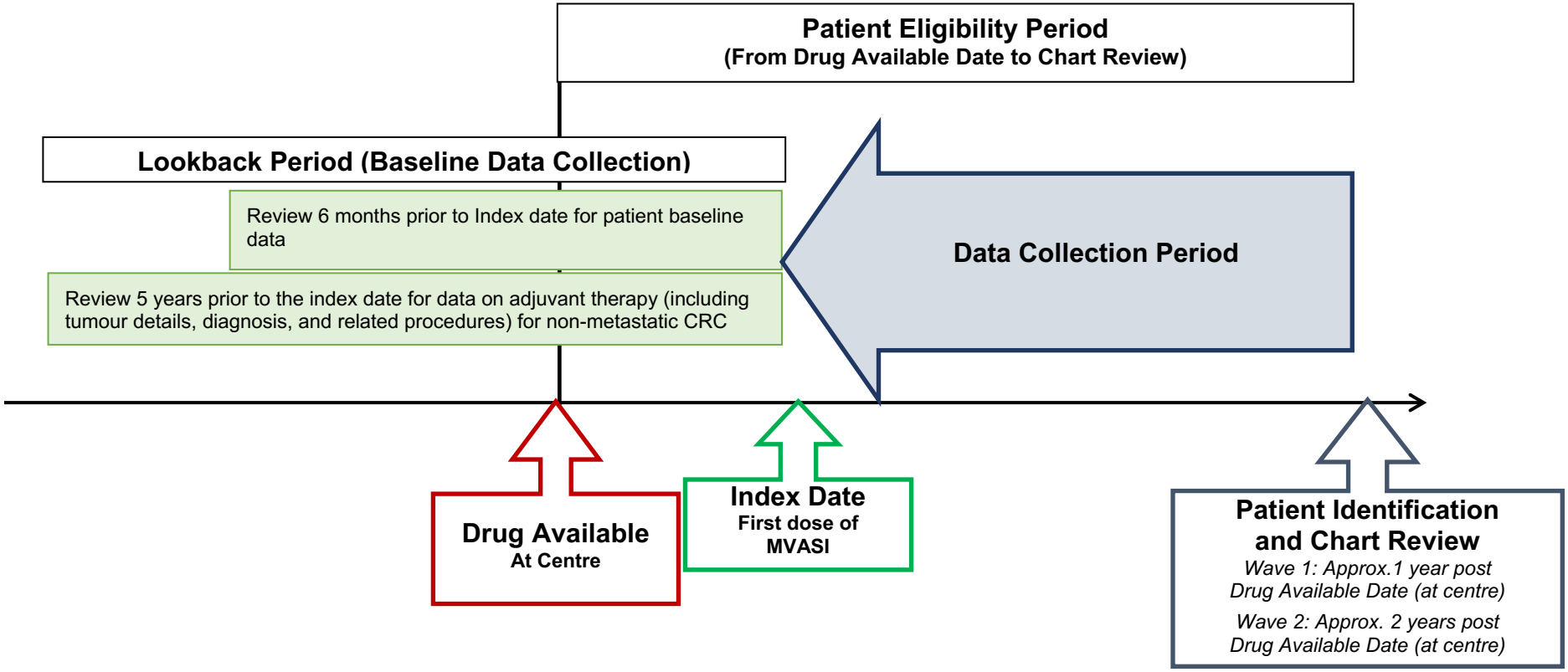
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Study Design Schema



* ***Note****: Drug Availability date will be centre-specific; it is defined as the date that the first patient receives the first dose of MVASI at the individual centre. Wave 1 data collection will begin at each Wave 1 centre approximately 1 year post-drug availability date at the specific centre. Wave 1 will continue until the total enrolment for Wave 1 is a minimum of 100 patient charts; additional centres will be activated as required.*

Wave 2 enrolment will occur approximately 2 years post-drug available date at each centre – Wave 2 centres will be different centres than Wave 1, and Wave 2 will continue until approximately 200 patient charts are enrolled, resulting in 300 patients combined between the 2 waves.

1. Table of Contents

List of Tables

List of Appendices

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CRC	Colorectal Cancer
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMR	Electronic Medical Records
EOIs	Events of Interest
FOLFIRI	Folinic acid, Fluorouracil, Irinotecan
FOLFOX	Folinic acid, Fluorouracil, Oxaliplatin
FU	Fluorouracil
GI	Gastrointestinal
ICH GCP	International Council for Harmonisation Good Clinical Practice
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFL	Irinotecan, Fluorouracil (leucovorin)
IgG1	Immunoglobulin G subclass 1
IRB	Institutional Review Board
KM	Kaplan-Meier
mAB	Monoclonal Antibody
mCRC	Metastatic Colorectal Cancer
NSCLC	Non Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
Q	Quartile (example Q1, Q3)
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumours
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event

SIV	Site Initiation Visit
TNM	Tumour, Nodes, Metastases – TNM Staging System
USPI	United States Package Insert
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
XELOX	Xeloda (capecitabine) and Eloxatin (oxaliplatin)

2. Responsible Parties

Study Sponsor:	Amgen Canada Inc. 6775 Financial Drive Mississauga, Ontario, CANADA Tel: 1-800-665-4273
Key Sponsor Contacts:	PPD Tel: PPD PPD PPD Tel: PPD PPD Amgen Canada Inc. 6775 Financial Drive Mississauga ON, CANADA PPD Tel: PPD PPD Amgen Inc. One Amgen Center Drive Thousand Oaks, CA, USA
Data Management:	Please refer to Section 7.6

3. Abstract

- **Study Title**: Canadian Retrospective Observational Study of MVASI in mCRC
- **Study Background and Rationale:**

MVASI is the first monoclonal antibody (mAb) biosimilar evaluated by Health Canada and compared with bevacizumab for the treatment of cancer. The clinical trial program to demonstrate biosimilarity between MVASI and reference bevacizumab consisted initially of a phase 1 pharmacokinetic study in healthy male patients and a phase 3 study evaluating efficacy and safety in patients with nonsquamous non-small cell lung cancer (NSCLC). These studies have demonstrated pharmacokinetic equivalence and comparative efficacy and safety vs bevacizumab (Avastin®).

Based on extensive in vitro product characterization and comparability exercise and these clinical data, in 2018, MVASI became the first mAb approved for the treatment of cancer through the Health Canada's biosimilar regulatory pathway. Because MVASI is highly similar to bevacizumab (Avastin®), with the totality of evidence supporting the similarity, Health Canada has approved MVASI for nonsquamous NSCLC and mCRC.

Although biosimilars may lead to significant cost savings, acceptance of biosimilar products would be enhanced with safety and effectiveness data in the real-world setting.

This retrospective chart review will provide MVASI safety and effectiveness data in the real-world setting for Canadian patients treated with MVASI for mCRC.

- **Research Question and Objectives:**

Objectives	Endpoints
Primary	
To describe the safety of MVASI treatment by assessing the frequency of Events of Interest (EOIs), in first-line mCRC patients in Canada.	The following Events of Interest will be collected: • Infusion reactions • Thromboembolic events • Gastrointestinal (GI) perforations • Hypertension • Hemorrhages • Wound-healing complications • Proteinuria • Ovarian Failure
Secondary	
To describe the effectiveness of MVASI treatment, including Objective Response Rate (ORR) and Progression Free Survival (PFS), in first-line mCRC patients in Canada.	• Objective Response (RECIST criteria) • Disease progression (if applicable)
Exploratory	
To describe the Overall Survival (OS) of patients receiving MVASI treatment as first-line treatment for mCRC in Canada.	• Death (if applicable)

  - **Hypothesis(es)/Estimation:** This is a descriptive safety study with no hypothesis testing. The estimates of frequency for Events of Interest will be reported as percentages with 95% confidence intervals (CI).

- **Study Design/Type:** Retrospective chart review.
- **Study Population or Data Resource:** Metastatic Colorectal Cancer (mCRC) patients treated with MVASI in Canada.
- **Summary of Patient Eligibility Criteria**
  - Adult patients ≥ 18 years of age at the index date (date of first dose of MVASI)
  - Metastatic CRC ie, confirmed histological or cytological adenocarcinoma of rectum or colon, stage 4
  - Previously untreated patients who receive MVASI as a part of their initial (first line) treatment for metastatic CRC
  - Patient has received at least 1 cycle of MVASI treatment as a part of their initial (first line) treatment for metastatic CRC
  - Index date (first dose of MVASI) is at least 1 month prior to chart review date
  - No prior treatment with bevacizumab for metastatic CRC, prior to first dose of MVASI

- **Follow-up:** N/A – retrospective chart review.
- **Variables**

Outcome Variables

Primary:

Events of Interest:

- Infusion reactions
- Thromboembolic events
- GI perforations
- Hypertension
- Hemorrhages
- Wound-healing complications
- Proteinuria
- Ovarian Failure

To be collected directly from patient charts; terms and grading using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Secondary:

- Objective Response (RECIST Version 1.1, eg, stable disease, partial response, etc.)
- Disease progression

To be collected from patient charts.

Exploratory:

- Death

To be collected from patient charts.

Exposure Variables

- Treatment regimen (components)
- Line(s) of therapy
- Dose(s) for component(s) of therapy
- Duration of therapy

Other Covariates

- Enrollment wave (1 or 2)
- Geographic region (province of study site)
- Type of centre (academic, community-based)
- Demographics
- Medical history

- Tumour characteristics (location, mutation status, resectability)
- ECOG performance status at baseline

- **Study Sample Size**

  The total sample size of combined Waves 1 and 2 will be approximately 300 subjects. The sample size is a convenience sample. For estimates of precision for a range of possible sample sizes and expected probabilities or frequencies, see Tables 1 and 2.

- **Data Analysis**

  Based on the literature, the Avastin® USPI and the Canadian Product Monograph, the incidence rates for the majority of the primary outcome EOIs are expected to be < 5%. Therefore, the probability of observing at least one event in our planned sample will be provided for each EOI. Point estimates and 95% CIs will be provided for primary, secondary and exploratory outcomes.

4. Amendments and Updates

N/A

5. Rationale and Background

5.1 Diseases and Therapeutic Area

Colorectal cancer (CRC) is the third most common type of cancer worldwide, and the second most common cause of cancer death in both men and women. With over 1.8 million cases of CRC reported in 2018, the incidence and mortality of colorectal cancer varies throughout different regions; CRC accounted for 880,792 deaths, with the highest mortality occurring in Eastern Asia, Central and Eastern Europe and North America (World Health Organization, 2018; International Agency for Research on Cancer, 2018). In Canada in 2017, 26,800 Canadians were diagnosed with colorectal cancer, representing an average of 73 Canadians being diagnosed with the disease each day (Canadian Cancer Society, 2018).

Approximately 20% of CRC patients will present with metastatic disease, and up to 50% will develop mCRC. Disease progression is driven by gene mutations that affect signaling pathways that regulate intestinal cells and their behaviour, giving cancer cells the ability to self-renew, grow and invade (Kindler, 2001). Metastases can occur in the liver, peritoneum, lungs, bone and brain, and can occur via the lymphatic system through hematogenous or peritoneal dissemination or contiguously (Kindler, 2001).

Treatment for mCRC can vary depending on primary tumour location, resectability and mutation status, as decided by the patient's healthcare team. Most patients present with unressectable metastatic disease. Optimal treatment for these patients is centered around prolongation of survival, improving tumour-related symptoms, stopping tumour progression and maintaining the patient's quality of life. Patients with potentially resectable mCRC may achieve success in using combination chemotherapy with targeted therapies to achieve conversion of the metastatic tumour from initially unresectable to resectable and chance to cure them of disease (Canadian Cancer Society, 2018; Van Cutsem 2014; Van Cutsem 2016).

Systemic therapies are the backbone of treatment for unresectable disease. Typical first-line chemotherapy includes a fluoropyrimidine (5-FU/leucovorin) used in various combinations and schedules with irinotecan and oxaliplatin. The chemotherapy combination of 5-fluorouracil with leucovorin and oxaliplatin (FOLFOX) or 5-fluorouracil with leucovorin and irinotecan (FOLFIRI) provide high response rates and progression free survival. Biological targeted medications, in the form of monoclonal antibodies or protein against vascular endothelial growth factor (VEGF) and against epidermal growth factor receptor (EGFR) in combination with chemotherapy should be considered in patients with mCRC, as they improve clinical outcomes in the first-line setting (Van Cutsem, 2016).

A current treatment option for first-line metastatic colorectal cancer (mCRC) is bevacizumab in combination with 5-fluorouracil (FU)-based chemotherapy (FOLFOX or irinotecan) and infusions FU (Avastin Product Monograph, 2018). In a randomized study, the addition of bevacizumab to irinotecan and bolus FU/leucovorin (IFL) compared to IFL alone, significantly improved survival (20.3 months versus 15.6 months, respectively; $p < 0.001$) (Hurwitz et al, 2004). The addition of bevacizumab to first-line oxaliplatin-based chemotherapy (FOLFOX4) demonstrated improved progression-free survival (PFS) (9.4 months for bevacizumab plus FOLFOX4 or capecitabine plus oxaliplatin [XELOX] versus 8.0 months for placebo plus FOLFOX4 or XELOX; $p = 0.0023$) (Saltz et al, 2008; DiValentin et al, 2012; Cunningham et al, 2013; Hurwitz et al, 2004).

Bevacizumab is a recombinant immunoglobulin G1 (IgG1) monoclonal antibody that binds to VEGF and inhibits the interaction of VEGF with its receptors, inhibiting establishment of new blood vessels necessary for the maintenance and growth of solid tumors (Avastin Product Monograph, 2018).

Avastin® (bevacizumab) is approved in Canada for use in metastatic Colorectal Cancer, locally advanced, metastatic or recurrent Non-Small Cell Lung Cancer, Ovarian, Fallopian Tube, and Primary Peritoneal Cancer, and Malignant Glioblastoma. Currently, there is data available on Avastin's® safety and efficacy in colorectal cancer in the Canadian, real world setting (Dranitsaris et al, 2010; Maroun et al, 2014; Otte et al, 2012; Bouganim et al, 2013; Beca et al, 2019; Renouf et al, 2011; Jang et al, 2012; Wasserman et al, 2011).

MVASI (ABP 215) is a recombinant IgG1 monoclonal antibody with an identical amino acid sequence to bevacizumab. MVASI (ABP 215) is developed for use by the same route of administration as Avastin® (bevacizumab) and has been approved in Canada for the treatment of patients with metastatic carcinoma of the colon or rectum as well as unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, malignant glioma (WHO Grade IV) – Glioblastoma; and has the same pharmaceutical form and dosage strength as bevacizumab. A comprehensive analytical characterization has shown that bevacizumab drug product and MVASI (ABP 215) drug product are comparable, notwithstanding minor differences that did not affect the safety, efficacy, and quality of the product (Seo et al, 2018; Markus et al, 2017). More recently, a Phase III study by Thatcher et al. compared the clinical efficacy and safety of MVASI with the bevacizumab reference product in patients with Non Small Cell Lung Cancer (NSCLC). The study demonstrated clinical equivalence in efficacy, safety, immunogenicity, and pharmacokinetics (Thatcher, 2019). The totality of evidence supports the approval of MVASI in non small cell lung cancer, as well as in glioblastoma and metastatic colorectal cancer.

5.2 Rationale

MVASI is the first monoclonal antibody biosimilar evaluated by the Health Canada and compared with bevacizumab for the treatment of cancer. The clinical trial program to demonstrate biosimilarity between MVASI and reference bevacizumab consisted initially of a phase 1 pharmacokinetic study in healthy male subjects and a phase 3 study evaluating efficacy and safety in patients with nonsquamous NSCLC. These studies have demonstrated pharmacokinetic equivalence and comparative efficacy and safety vs bevacizumab (Avastin®). Very few subjects developed anti-drug antibodies. No subject in either group developed neutralizing antibodies (Seo et al, 2018; Markus et al, 2017; Thatcher, 2019).

Based on extensive in vitro product characterization and comparability exercise and these clinical data, in 2018, MVASI became the first monoclonal antibody approved for the treatment of cancer through the Health Canada's biosimilar regulatory pathway. Because MVASI is highly similar to bevacizumab (Avastin®), with the totality of evidence supporting the similarity, Health Canada has approved MVASI for nonsquamous NSCLC, glioblastoma and mCRC.

Although biosimilars may lead to significant cost savings, acceptance of biosimilar products would be enhanced with safety and effectiveness data in the real-world setting. The current study will collect safety and effectiveness data for MVASI in the real-world setting in Canada..

5.3 Statistical Inference (Estimation or Hypothesis)

This is a descriptive safety study with no hypothesis testing. The estimates of frequency for Events of Interest will be reported as percentages with 95% confidence intervals (CI).

6. Research Question and Objectives

6.1 Primary

To describe the safety of MVASI treatment by assessing the frequency of Events of Interest (EOIs), in first-line mCRC patients in Canada.

6.2 Secondary

To describe the effectiveness of MVASI treatment, including Objective Response Rate (ORR) and Progression Free Survival (PFS), in first-line mCRC patients in Canada.

6.3 Exploratory

To describe the Overall Survival (OS) of patients receiving MVASI treatment as first-line treatment for mCRC in Canada.

7. Research Methods

7.1 Study Design

This retrospective observational chart review study will describe the safety and effectiveness of treatment with MVASI in patients with mCRC in Canada. Data collection will occur in 2 waves, approximately 1-year and 2-years after MVASI is commercially available at the individual centres. Note that the centres in wave 1 will be different from the centres in wave 2.

Data collection will include all applicable data in the chart at the time of the chart review. Baseline data will be collected from 6-months prior to initiation of MVASI therapy in first line; data on prior adjuvant therapy for non-metastatic CRC will be extracted from a

5-year lookback period prior to the index date (first dose of MVASI). Following initiation of MVASI therapy, data collection from the chart review will focus on Events of Interest (EOIs), response to treatment, disease progression and survival.

7.2 Setting and Study Population

Data collection will begin at the first wave of centres approximately 1 year after MVASI is commercially available at the individual centres; note therefore that centres may begin data collection at different times.

The drug availability date will be defined for each centre as the date the first patient receives a dose of MVASI at the individual centre. Data collection will begin for Wave 1 at a specific centre approximately 1-year after the drug availability date; note that data collection cannot occur prior to 1-year post-drug availability date.

At this 1-year post-drug availability timepoint (by centre), wave 1 centres will identify all charts for patients treated with at least 1 dose of MVASI, to be screened for the study. If patient charts qualify for enrolment as per the Inclusion/Exclusion criteria, applicable data will be collected, including any applicable data available in the chart on the date of the chart review. The data collection period will continue for each Wave 1 centre until the centre has reviewed their charts to identify and enter data for eligible patient charts, up to a minimum total enrollment of 100 patient charts in Wave 1. Additional centres may be added to enroll a minimum of 100 patient charts.

The second wave of data collection will occur approximately 2 years after MVASI is commercially available at the individual centre. This 2nd wave of data collection will include different centres than the Wave 1 data collection.

At this 2-year post-drug availability timepoint, Wave 2 centres will identify all patient charts for patients treated with at least 1 dose of MVASI, for screening as per the Inclusion/Exclusion criteria. The data collection period will continue until each of the Wave 2 centres has reviewed their charts to identify and enter data for eligible patients, up to a total enrolment of approximately 200 patient charts in Wave 2 – for a combined total enrolment between the 2 waves of 300 patient charts. Additional centres may be added, if needed, in order to include a total of 300 patient charts in the study.

Patient charts will be screened for the study in order of increasing Index Date, ie. patients who received MVASI on the earliest date will be screened first. All patients who received 1 dose of MVASI who are screened for the study will be included in the safety analysis. Screening will continue at each individual centre until either all patients who

received one dose of MVASI are screened, or until the maximum number of patient charts per contract have been enrolled.

All screened patients will be assigned a study number in the format PPD . For example, the first patient chart screened at PPD will be assigned subject number PPD , and the 2nd patient chart would be assigned PPD .

If a centre has a high number of patients treated with MVASI, exceeding the number of patient charts in the study contract, the investigator should contact Amgen to discuss whether there is an option to increase the number of patient charts enrolled at their centre.

7.2.1 Study Period

The chart reviews will occur either 1-year or 2 years after MVASI is commercially available at the centres. Centres will review their charts for patients treated with MVASI; the study will include patients treated with MVASI as early as the date that MVASI is first commercially available at the individual centre ie, the centre-specific **Drug Availability Date** – this time period, from the date of the chart review to the date that MVASI is first available at the centre is the **Patient Eligibility Period.**

The date of the patient's first dose of MVASI is defined as the **Index Date.**

All patients will have a pre-index date **Look-back Period (Baseline Data Collection)** including a 6-month look-back for patient demographics and baseline data, and a 5-year look back for prior adjuvant treatment and diagnosis of CRC. The look-back period will be calculated from the index date.

The **Data Collection Period** will include data from the patient's first dose of MVASI (the index date) until the date of the chart review for the site (either 1 year or 2 years from **Drug Availability Date**). For patients enrolled in Wave 1, this data collection period could include data up to approximately 1-year after the patient's first dose of MVASI. For patients in Wave 2, the data collection period may be up to approximately 2 years in length.

All data will be collected in a retrospective fashion only ie, no prospective data will be collected. If a patient is visiting the clinic/hospital on the day of chart review, the data collection should be delayed until the chart is available following the patient's visit. After

the initial data collection is completed, individual patient charts will not be reviewed again for updated data, only to answer queries, if applicable.

7.2.2 Selection and Number of Sites

The study will be conducted at approximately 12 oncology centres/hospitals in Canada; it is anticipated that each wave will include approximately 6 centres. The total number of centres may vary according to the feasibility assessment, but it is anticipated that each Wave 1 centre will have approximately 15 to 20 patient charts meeting the protocol eligibility criteria, for a total of 100 patient charts in Wave 1. It is anticipated that each Wave 2 centre will have approximately 30 to 35 patient charts meeting the protocol eligibility criteria, for a total of 200 patient charts in Wave 2, and a total enrolment between the 2 waves of 300 patient charts. Note that the centres in wave 1 will be different from the centres in wave 2.

The team will attempt to balance the 2 waves in terms of geographic distribution and type of centre (academic vs. community, volume of patients).

Only sites/investigators already prescribing MVASI will be considered and assessed for participation during the feasibility phase. Sites/investigators will be selected based on patient population, resources, and their ability to provide data for patients meeting the protocol entry criteria. Although clinical research experience is preferred, this is not essential and could bias the selection of centres in the community setting.

The total number of centres/investigators may be updated after the completion of the initial feasibility assessment, depending upon the planned number of patient charts that each centre/investigator plans to contribute to this study.

Additional sites/investigators may be invited to participate to ensure study timelines are met. Sites that do not enroll any subjects within 1 month of activation may be closed.

7.2.3 Patient Eligibility

7.2.3.1 Inclusion Criteria

101 Adult patients ≥ 18 years of age at the **Index date** (first dose of MVASI)

102 Metastatic CRC ie, confirmed histological or cytological adenocarcinoma of rectum or colon, stage 4

103 Previously untreated patients who receive MVASI as a part of their initial (first line) treatment for metastatic CRC

104 Patient has received at least 1 cycle of MVASI treatment as a part of their initial (first line) treatment for metastatic CRC

105 Index date (first dose of MVASI) is at least 1 month prior to chart review date

7.2.3.2 Exclusion Criteria

201 Patient received an investigational product or participated in an investigational device or drug study at any time between 90 days pre-index date to 30 days post-last dose of MVASI

202 Patient previously treated with bevacizumab for metastatic CRC, prior to Index Date (first dose of MVASI)

203 Patient is pregnant at any time during treatment with MVASI

7.2.4 Matching

No matching on the study.

7.2.5 Baseline Period

The Baseline Period will include applicable data prior to the index date. The data collection for all patients will include a review of the patient's medical records for 6-months prior to the index date to collect demographics and baseline data, and a 5-year look back for details regarding prior adjuvant treatment and diagnosis of CRC. The lookback periods are calculated from the index date (first dose of MVASI).

The following data will be collected during the baseline period and look-back period:

- Patient demographics, including age, gender, race/ethnicity, geographic region (province), type of centre (academic, community)
- Relevant baseline and medical history, including:
    - Prior surgeries
    - Arterial Disease (previous thromboembolic events)
    - Cardiovascular Disease (MI, Stroke, CHF, PAD, etc.)
    - Renal disease
    - GI medical history (History of GI perforations, H. pylori infection, or other inflammatory bowel disease such as Ulcerative Colitis or Crohn's)
    - Other comorbidities – Type 2 Diabetes Mellitus (T2DM), Respiratory, Charlson comorbidity index
    - Smoking status at baseline (yes/no/previous smoker)
    - Select Concomitant Medications (anti-hypertensive, anticoagulant, antiplatelet, Cardiovascular drugs, other biologics)
    - Previous transfusions during the baseline period
    - Stool habit at baseline (for example, grade 1 or 2 diarrhea, or constipation)
- Adjuvant diagnosis details and treatment history, including:
    - Date of diagnosis
    - Tumour characteristics and disease stage at diagnosis of adjuvant disease (histology, TNM staging, grading)

- Location of primary tumour:
  - Right-sided: Cecum; Ascending colon; Hepatic flexure; Transverse colon; Splenic flexure (proximal to); Right-sided NOS.
  - Left-sided: Splenic-flexure (distal to); Descending colon; Sigmoid colon; rectum; Left-sided, NOS.
- Adjuvant treatments (chemotherapy agents, biologics, investigational agents)
- Response to treatment (RECIST Version 1.1 criteria: stable disease, partial response etc)
- Resections/surgeries (Primary tumour in place, Hepatectomy, lung resection, metastasectomy, Primary tumour, other procedures)

- Metastatic/baseline tumour characteristics, including:
  - Date of diagnosis
  - Tumour characteristics and disease stage at diagnosis of metastatic disease (histology, TNM staging, grade)
    - Pathology grade: Well, moderately or poorly differentiated
    - Lymphatic or vascular infiltration
    - Metastases: number and location of metastases
    - Metastatic presentation (at diagnosis vs. relapse)
    - Biomarkers (ie, RAS, BRAF)
- ECOG performance status at baseline

7.2.6 Study Follow-up

The study design is entirely retrospective; there is no follow-up period for the study.

7.3 Variables

7.3.1 Exposure Assessment

The following details will be collected related to each patient's MVASI treatment:

- MVASI dose, frequency, number of cycles, cycle length (planned regimen and actual dose delivered)
- Infusion time
- Concomitant Chemotherapy details: Chemotherapy agents and Dosing (planned and actual received)
- MVASI dose and timing of administration relative to surgery
- Co-therapies

7.3.2 Outcome Assessment

The outcomes will be assessed following the first dose of MVASI (Index Date), until the date of the chart review (up to approximately 1 year in wave 1, up to 2 years in wave 2). Events of Interest will be assessed until 30 days post last-dose of MVASI.

Events of Interest will be reported by cycle and overall for the full treatment period available for observation.

Primary Outcomes:

- The following Events of Interest will be collected, including the following:
  - Infusion reactions
  - Thromboembolic events, both arterial and venous
  - GI perforations
  - Hypertension (if change/grade increase from baseline)
  - Hemorrhages
  - Wound-healing complications
  - Proteinuria (if change/grade increase from baseline)
  - Ovarian Failure

All adverse events will be classified and graded using CTCAE (refer to **Appendix C**).

Secondary Outcomes:

- Objective Response using RECIST criteria (response criteria)
- Disease progression (if applicable)

In addition, any documented changes from baseline in ECOG performance status will be collected.

Exploratory Outcome:

- Death (if applicable)

If a patient receives Mvasi and is subsequently lost to follow-up, the potential reasons will be collected, for example: Patient switched centres, Patient relocation, Unknown.

7.3.3 Covariate Assessment

The following variables will be assessed during baseline (6-month lookback up to index date):

- Enrollment wave (1 or 2)
- Geographic location (province of study site)
- Type of centre (academic, community-based)
- Demographics
- Medical history
- Tumour characteristics (location, mutation status, resectability)
- ECOG performance status

7.3.4 Validity and Reliability

The standard against which the medical community will evaluate the validity and reliability of this study can be found in the published literature for bevacizumab. We expect the results of this study to be consistent with the safety and efficacy established by the historical record with respect to bevacizumab (Dranitsaris et al, 2010; Maroun et al, 2014; Otte et al, 2012; Bouganim et al, 2013; Beca et al, 2019; Renouf et al, 2011; Jang et al, 2012; Wasserman et al, 2011).

7.4 Data Sources

The data source is patient medical charts, either paper charts, or electronic records, or a combination of both. The standard limitations of chart review studies will apply to this study, such as missing or incomplete data.

7.5 Study Size

The total sample size of combined Waves 1 and 2 will be approximately 300 subjects. The sample size is a convenience sample based on timing of data collection and availability of patient data. Based on the literature and the Avastin USPI, the incidence rates for the majority of the primary outcome EOIs are expected to be < 5%. Therefore, the probability of observing at least one event in our planned sample is provided for a possible range of probabilities consistent with our expectation for the EOI (**Table 1**). Point estimates and 95% CIs (calculated using the method of Agresti and Coull, 1998) are provided for a range of possible observed frequencies (%) and sample sizes (**Table 2**).

Table 1. Probability of Observing an Event

	Probability of Observing ≥1 Event for varying sample sizes					
Event Probability	**N = 50**	**N = 100**	**N = 150**	**N = 200**	**N = 250**	**N = 300**
0.01	0.39	0.63	0.78	0.87	0.92	0.95
0.02	0.64	0.87	0.95	0.98	0.99	1.00
0.03	0.78	0.95	0.99	1.00	1.00	1.00
0.04	0.87	0.98	1.00	1.00	1.00	1.00
0.05	0.92	0.99	1.00	1.00	1.00	1.00

Table 2. 95% Confidence Intervals by Frequency and Sample Size

Frequency (%)	N = 50	N = 100	N = 200
1%	(0.1%, 8.9%)	(0.2%, 5.4%)	(0.3%, 3.6%)
2%	(0.4%, 10.5%)	(0.6%, 7.0%)	(0.8%, 5.0%)
3%	(1.6%, 14.9%)	(2.2%, 11.2%)	(2.7%, 9.0%)

7.6 Data Management

The sponsor has delegated the data management of this study to a third party vendor, which includes CRF development, EDC, data analysis and quality checking of the data, and the final report.

Prior to the commencement of the study, study site staff will be provided with training to review all pertinent study details, such as the study objectives, completion of case report form (CRF), the data query process, and other key data elements. Training must occur prior to the first patient being identified and/or beginning of data capture and will be conducted during site initiation visits (SIVs). Study site staff will be provided with a copy of the eCRF Completion Guideline.

The collection/abstraction of relevant data from eligible patient medical records will be performed by trained study site staff.

7.6.1 Review and Verification of Data Quality

All subject data relating to the study will be recorded in the electronic CRF. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

Throughout the study, and prior to any analysis, data quality, completeness and accuracy will be verified through pre-specified database integrity checks. These database integrity checks will be programmed and run during the study. Data queries will be generated and sent to the study site for resolution. Database quality acceptance sampling procedures will be performed to assess the database quality throughout the study, and prior to database lock. All data processing and management activities will be performed following the data management vendor's Standard Operating Procedures,

which are in line with good clinical data management practices and compliant with ICH guidelines.

7.7 Data Analysis

The frequency of EOIs will be calculated as the number of patients who experience at least one event during the observation period divided by the total number of patients under observation in the interval. The estimate will also be provided adjusted for time of observation. Frequency of EOIs will also be reported by cycle. Standard time to event analysis using the Kaplan-Meier method will be used for estimates of ORR, PFS, and OS. Baseline demographics and exposure data will be presented with standard summary statistics: frequency and percentages for categorical data; mean, standard deviation, standard error, quantiles (Q1, median, Q3), minimum and maximum for continuous variables.

7.7.1 Planned Analyses

7.7.1.1 Analysis by Waves

Wave 1 analysis will be conducted independently of Wave 2 analysis. There will be no overlap in patients between the two analyses.

7.7.1.2 Primary Analysis

The Primary analysis of Wave 1 data will be conducted approximately 4 months following the conclusion of data extraction for the Wave 1 sample.

Similarly, analysis of Wave 2 data will be conducted following the completion of the data extraction for the Wave 2 sample.

7.7.2 Planned Method of Analysis

7.7.2.1 General Considerations

The analysis is entirely descriptive in nature with no hypothesis testing. The analysis of Wave 1 after only 1 year of MVASI availability at the respective centres will provide an initial look at the safety and effectiveness of the product in the mCRC population in Canada.

Baseline demographics and clinical characteristics will be evaluated for the wave 1 cohort, and assessed for potential channeling bias in physician selection of patient treatment, to determine whether the study population is generalizable to the mCRC population.

If significant differences are noted from the expected mCRC population based on patient demographics and clinical characteristics, modifications to the planned analyses would be reflected in an amendment to the protocol.

The Wave 2 analysis will extend the opportunity for evaluation to 2 years or more of treatment availability.

7.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The completeness of the data record will be entirely dependent upon the data provided within the medical records. It will be assumed that events not found in the record did not occur. No imputation for missing data will be employed.

7.7.2.3 Descriptive Analysis

7.7.2.3.1 Description of Study Enrollment

Study enrollment will be tabulated by Wave (1 or 2) overall and by province and type of centre (academic vs. community-based centres) within each wave.

7.7.2.3.2 Description of Subject/Patient Characteristics

Patient demographics, relevant medical history, tumour characteristics will be tabulated by Wave overall, and by province and type of centre (academic, community-based centres) within each wave.

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

Primary Analysis: estimation of frequency for EOIs

- Frequency estimation for each of the EOIs will be based on the number of patients who experience the events (at least one event per patient) divided by the total number of patients under observation. A frequency estimate for each EOI will also be provided by treatment cycle. Confidence intervals, 2-sided 95% (Agresti and Coull, 1998) will be provided.
- An additional frequency estimate of patients experiencing at least one instance of each EOI adjusted for duration of observation will also be provided.

Secondary Analysis: ORR, PFS

- Descriptive methods will be used to characterize the proportion of patients demonstrating best overall response for the qualifying MVASI regimen specified in the secondary objectives. Responses will be classified as Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD); Not Evaluable (NE); or Undocumented. Some patients will have documented RECIST categories; however, others will be classified based on other indication of response in the record. The following levels of evidence will be used in order of priority: provider statement of response using standard RECIST categories, provider statement of response not using standard RECIST categories, quantitative or qualitative change in tumor status, change in overall patient status.
- Standard Kaplan-Meier (KM) estimation of time to event analysis of progression free survival will be provided for each Wave separately. Confidence Intervals for the KM quartiles will be provided (Brookmeyer and Crowley, 1982). Confidence intervals, 2-sided 95%, (Agresti and Coull, 1998) will be generated for the ORR estimates.

Exploratory Analysis: OS

- Overall survival will be estimated by Kaplan-Meier methodology separately for Waves 1 and 2. Confidence intervals will be generated as described for PFS. It is expected that estimation within Wave 1 may be limited by the short time of observation and small sample size and may not provide reliable estimates.

7.7.2.5 Sensitivity Analysis

In order to optimize the use of the full sample and to increase precision of the point estimates, a sensitivity analysis of primary, secondary and exploratory analyses will be conducted with a pooled sample of wave 1 and wave 2 data. However, in order to eliminate bias due to the difference in the administrative censoring times in waves 1 and 2, the potential observation time for wave 2 will be divided into 2 1-year segments; ie wave 2 part A data will be those patients identified during the first year of observation with an administrative censoring date at 1 year from the **Drug Availability Date** for each site; wave 2 part B will be those patients identified during the second year of observation jn wave 2 with an administrative censoring date at the end of the wave 2 observation period (2 years from the **Drug Availability Date** for each site). There will be no overlap between patients in wave 2 part A and wave 2 part B. The sensitivity analysis dataset will be the pooled data from wave 1, wave 2 part A, and wave 2 part B.

7.7.2.5.1 Subgroup Analysis

Tabulations will be provided by Wave (1 or 2). Categories for demographic considerations (ie, province, type of centre (academic, community-based)) will be provided but there is no expectation that differences in outcomes will be observed and no comparisons will be made.

7.7.2.5.2 Stratified Analysis

No stratified analysis is planned.

7.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

No analysis is planned to explore confounding and bias.

7.7.2.5.4 Other Sensitivity Analysis

None planned.

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

Safety analysis for EOIs will be conducted on the full analysis set of all enrolled subjects, where exposure to study drug and 1 round of therapy are eligibility requirements. The analysis will be a standard safety event analysis where any patient with at least one

instance of the observed event will be counted as an event. The frequency will be estimated as:

Total number of patients experiencing the event divided by the total number of patients under observation. Estimates will also be provided by treatment cycle. An additional estimate adjusted for duration of observation will also be provided (overall observation time, not by cycle).

Coding of events will be based on CTCAE (Refer to **Appendix C**).

7.8 Quality Control

The study monitoring activities will be completed according to the Monitoring Plan. The Clinical Monitor will spot-check eCRF data entry completeness remotely to assess whether data is being entered in completeness ie, no blank/missing fields, and in accordance to the protocol, by the site. Any issues observed during the remote review should be queried in the eCRF system by the Clinical Monitor.

7.9 Limitations of the Research Methods

Small sample size and duration of observation are limitations of the study. The primary analysis of safety EOIs is limited by the expected (based on historical data) low event rate, thus reducing the precision of the estimates.

The generic limitations of retrospective studies based on medical chart records apply to this study.

Consistency of data abstraction conducted by the trained abstractors may vary across sites. To mitigate this risk the team will ensure that an eCRF Completion Guideline is provided to each trained data abstractor and that training and clarification of issues that arise are communicated through a single channel (eg, study manager or designee).

7.9.1 Internal Validity of Study Design

The study is a retrospective chart review at primary care sites across Canada. All patients at a site who received MVASI during the Patient Eligibility Period are expected to be identified by the chart review and should be included in the study. It is possible that some patients are overlooked in this process.

7.9.1.1 Confounding

No prediction or comparison is included in the study design, so confounding is not relevant.

7.9.2 External Validity of Study Design

While sites from across Canada will be sought, due to the small sample size it is possible that the enrollment from the larger provinces will dominate. This factor may limit the generalizability of the results.

7.9.3 Analysis Limitations

The small sample size (approximately 100 and 200 in each of 2 waves, respectively) combined with the expected low frequencies for the primary endpoints limits the precision of the estimates.

7.9.4 Limitations Due to Missing Data and/or Incomplete Data

The data is entirely dependent upon the completeness of the patient charts. There is no means to estimate the amount of missing or incomplete data.

A potential limitation is incompleteness of the baseline data and patient history, since all patients may not have 5 years of prior data in their medical records.

In addition, the response outcomes for patients may not be clearly documented in the patients' charts using RECIST criteria. This limitation is minimized by using the documentation process (levels of priority) as described in Section 7.7.2.4.

8. Protection of Human Subjects

8.1 Informed Consent

Informed consent will not be collected for this retrospective observational (chart review) study. No direct subject contact or collection of additional subject data will occur, and subject data will be deidentified. Amgen CRA/Monitors (or designee) will not review patient medical charts; Source Document Verification (SDV) is not applicable in this study.

Study results will be in tabular form and aggregate analyses that omit patient identification. Any publications and reports will not include patient identifiers.

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

A copy of the protocol must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol must be received by Amgen before study can be executed.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments. The Investigator is to notify the IRB/IEC or other relevant ethical review board of deviations

from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

8.3 Patient Confidentiality

This study will comply with applicable laws regarding patient privacy. Investigators must ensure the patient's confidentiality is maintained for documents submitted to Amgen.

In compliance with Local country regulations and ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the patient's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

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

9.1 Definition of Safety Events

9.1.1 Adverse Events (AEs)

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.

9.1.2 Adverse Drug Reactions (ADRs)

AEs that are considered related to the Amgen product(s) are classified as adverse drug reactions (ADRs).

In the context of this study, AEs that are explicitly stated in the medical record to be related to an Amgen product are classified as ADRs.

9.1.3 Serious Adverse Events (SAEs)

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

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

"Other medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the 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.

9.1.4 Serious Adverse Drug Reactions (SADRs)

SAEs that are considered related to the Amgen product(s) are classified as serious adverse drug reactions (SADRs).

In the context of this study, SAEs that are explicitly stated in the medical record to be related to an Amgen product are classified as SADRs.

9.1.5 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) 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).

9.1.6 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), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

9.2 Safety Collection, Recording and Submission to Amgen Requirements

The Investigator is responsible for ensuring that all SADRs, product complaints and other safety findings for any Amgen product(s) are submitted to Amgen via the applicable Amgen Safety Reporting Form.

All clearly documented SADRs, product complaints and other safety findings, including pregnancy and/or lactation are to be reported to Amgen within 1 business day of the Investigator's date of awareness using the protocol specific form provided.

Amgen Canada Global Patient Safety: 1-888-264-3655

This study is analyzing secondary data from medical charts. In addition to the reporting described above, the safety outcomes that are listed in section Outcome Assessment 7.3.2 (Outcome Assessment) will be documented in the eCRF and analyzed in this study. These will be reported in aggregate in the final study report as proportions and rates. See section Outcome Assessment 7.3.2 (Outcome Assessment) for safety outcomes and definitions. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

This study is collecting information from patient charts, retrospectively. All safety events (adverse events and other safety findings) considered to have occurred following subject exposure to MVASI will be collected from start of data extraction/chart review date. The Investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the patient's appropriate study documentation.

9.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities.

Submission within 15 days of awareness

- Serious adverse drug reactions
- Unusual reports of lack of efficacy

10. Administrative and Legal Obligations

10.1 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. The Research Ethics Board (REB) must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the REB to Amgen.

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

11. Plans for Disseminating and Communicating Study Results

The results of the study will be submitted for publication.

11.1 Publication Policy

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:

1. 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.

12. References

1. Agresti A and Coull B. Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions, *The American Statistician* 1998:52:119-126.
2. AVASTIN Product Monograph, *Hoffmann-La Roche Limited* 2018: https://www.rochecanada.com/PMs/Avastin/Avastin_PM_E.pdf
3. Beca J, Pataky R, Tran D et al. Real-world safety of bevacizumab with first-line combination chemotherapy in patients with metastatic colorectal cancer: Population-based retrospective cohort studies in three provinces. *Canadian Centre for Applied Research Control in Cancer (ARCC)* 2019: www.cc-arcc.ca
4. Bouganim N, Mamo A, Wasserman DW et al. Bevacizumab-based therapy for colorectal cancer: experience from a large Canadian cohort at the Jewish General Hospital between 2004 and 2009. *Curr Oncol* 2013;20(5):247-251.
5. Brookmeyer R and Crowley J A Confidence Interval for the Median Survival Time, *Biometrics* 1982;38:29-41.
6. Canadian Cancer Society, 2018: http://www.cancer.ca/en/cancer-information/cancer-type/colorectal/statistics/?region=on http://www.cancer.ca/en/cancer-information/cancer-type/colorectal/treatment/?region=on
7. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *The Lancet Oncology* 2013:14(11):1077-1085.
8. Di Valentin T, Alam Y,Alsharm AA et al. Eastern Canadian Colorectal Cancer Consensus Conference: application of new modalities of staging and treatment of gastrointestinal cancers. *Current Oncology* 2012;19(3):169-174.
9. Dranitsaris G, Edwards S, Edwards J, Leblanc M, Abbott R. Bevacizumab in combination with folfiri chemotherapy in patients with metastatic colorectal cancer: an assessment of safety and efficacy in the province of Newfoundland and Labrador. *Current Oncology* 2010:17(5):12-16.
10. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. *N Engl J Med* 2004; 350:2335-2342.
11. International Agency for Research on Cancer, 2018: http://gco.iarc.fr/today/index_ie.php
12. Jang RWJ, Enright K, Booth CM, et al. Serious adverse events among a population-based cohort of patients receiving first-line chemotherapy for metastatic colorectal cancer (mCRC). *ASCO Meeting Library* 2012: https://meetinglibrary.asco.org/record/74250/abstract
13. Kindler HL, Shulman KL. Metastatic colorectal cancer Opinion Statement. *Current Treatment Options in Oncology* 2001;2(6):459-471.
14. Markus R, Chow V, Pan Z, Hanes V. A phase I, randomized, single‐dose study evaluating the pharmacokinetic equivalence of biosimilar ABP 215 and bevacizumab in healthy adult men. *Cancer Chemother Pharmacol* 2017;80:755–763

15. Maroun JA, Marginean H. Retrospective review of FOLFIRI with or without bevacizumab (bev) for patients with metastatic colorectal cancer (mCRC): Reviewing a single-center standard clinical practice. *ASCO* 2014: https://meetinglibrary.asco.org/record/89754/abstract; Poster A53.

16. Otte FX, Aubin F, Tehfé M, et al. Assessment of safety of bevacizumab use for metastatic colorectal cancer in elderly patients treated at the Centre Hospitalier de l'Université de Montréal (CHUM): A retrospective study. *Gastro Canc Sympos* 2012: Poster.

17. Pataky R, Beca J, Tran D et al. Real-world cost-effectiveness of bevacizumab with first-line irinotecan-based chemotherapy in patients with metastatic colorectal cancer: Population-based retrospective cohort studies in three provinces. *Canadian Centre for Applied Research Control in Cancer (ARCC)* 2019: www.cc-arcc.ca

18. Renouf DJ, Lim HJ, Speers C et al. Survival for Metastatic Colorectal Cancer in the Bevacizumab Era: A Population-based Analysis. *Clinical Colorectal Cancer* 2011;10(2):97-101.

19. Saltz LB, Clarke S, Diaz-Rubio E. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. *J of Clin Oncology* 2008:26(12):2013-2019.

20. Seo N, Polozova A, Zhang M, Yates Z, Cao S, Li H, Kuhns S, Maher G, McBride HJ, Liu J. Analytical and functional similarity of Amgen biosimilar ABP 215 to bevacizumab. *mAbs* 2018; DOI: 10.1080/19420862.2018.1452580.

21. Thatcher N, Goldschmidt JH, Thomas M et al. Efficacy and Safety of the Biosimilar ABP 215 Compared with Bevacizumab in Patients with Advanced Nonsquamous Non–small Cell Lung Cancer (MAPLE): A Randomized, Double-blind, Phase III Study. *Clinical Cancer Research* 2019: doi: 10.1158/1078-0432.CCR-18-2702.

22. Tran D, Beca J, Pataky R et al. Real-world effectiveness of bevacizumab with first-line combination chemotherapy in patients with metastatic colorectal cancer: Population-based retrospective cohort studies in three provinces. *Canadian Centre for Applied Research Control in Cancer (ARCC)* 2019: www.cc-arcc.ca.

23. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Annals of Oncology* 2016;27(8):1386-1422.

24. Van Cutsem E, Cervantes A, Nordlinger B et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2014;25(suppl_3): iii1–iii9.

25. Wasserman DW, Bouganim N, Batist G, et al. Bevacizumab (Bev)-based therapy for patients (pts) with colorectal cancer (CRC): McGill University and Segal Cancer Centre experience. *ASCO* 2011: https://meetinglibrary.asco.org/record/58919/abstract.

26. World Health Organization, 2018: https://www.who.int/news-room/fact-sheets/detail/cancer http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf

13. Appendices

Appendix A. ENCePP Checklist for Study Protocols

Appendix B. Sample Safety Reporting Forms

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

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

4. Contact Details (Vendor/Investigator)

Name	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

5. Reporter ID

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

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	State/Province	Postal Code
Phone	Fax	

7. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No
Weight	**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

Reporter Signature: _____ Page 3 of ____

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

FORM-067758 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

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

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

Date Day Month Year	Test / Unit										
	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).

Reporter Signature: _____ Page 4 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes
FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE) will be used for grading Adverse Events.

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING consequences; urgent intervention indicated.
5	DEATH related to AE

The CTCAE is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.