Summary Table of Study Protocol

Title	POWER: Real World Data of 1st line Panitumumab Treatment in Combination With Chemotherapy in non Resectable Wild Type (WT) *RAS* Metastatic Colorectal Cancer (mCRC) Subjects in Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania, Russia an Observational Ambidirectional Study
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Medicinal Product	Panitumumab (Vectibix®)
Product Reference	EMEA/H/C/000741
Joint PASS	No
Research Question and Objectives	To obtain characteristics of subjects with WT *RAS* non resectable mCRC receiving panitumumab in combination with chemotherapy as a 1st line treatment, and to describe the patterns of treatment, including 1st and 2nd line therapies.
Countries of Study	Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania, Russia
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Marketing Authorization Holder

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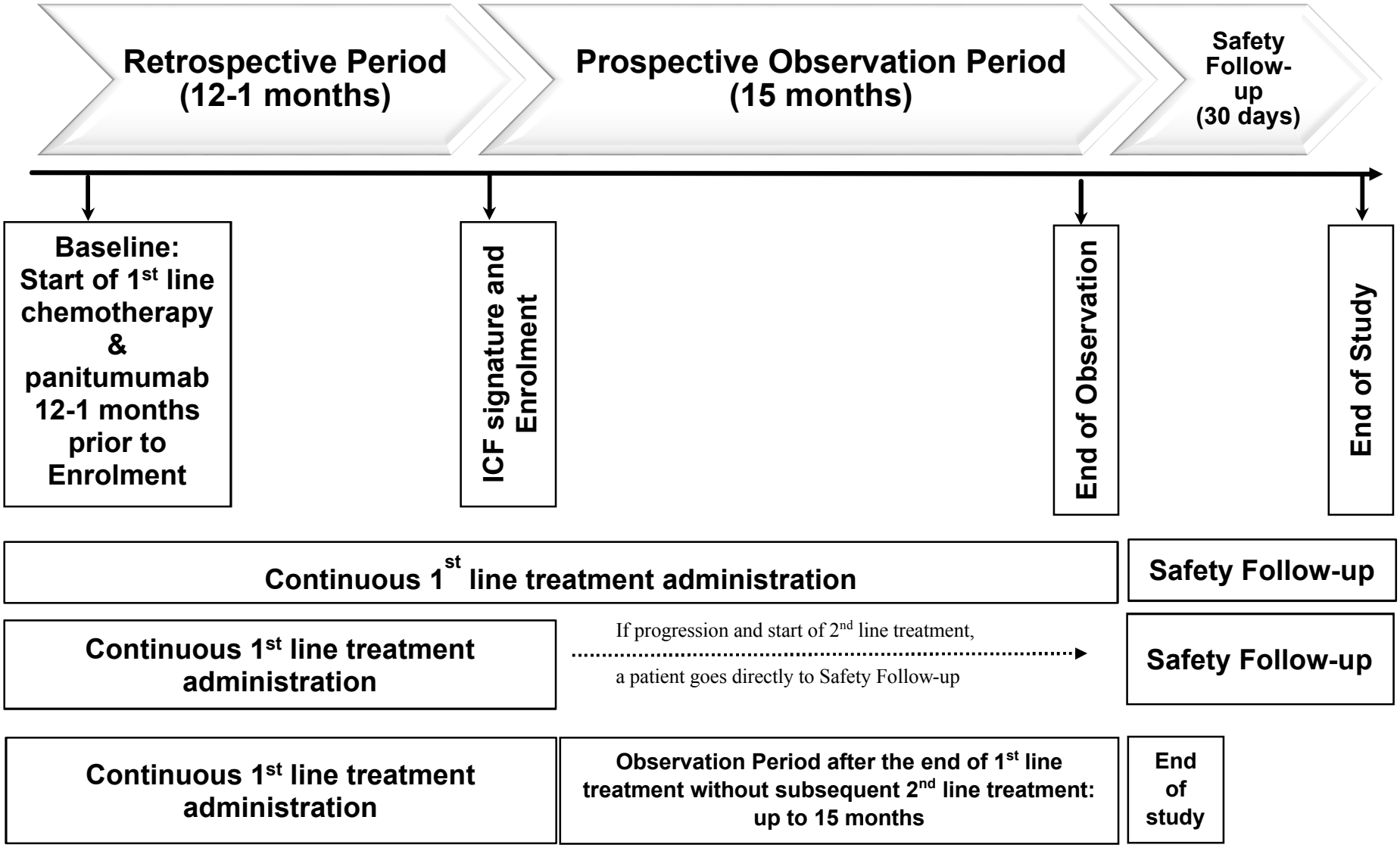
Name of Coordinating Investigator

Date (DD Month YYYY)

Figure 1. Study Design Schema



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2. List of Abbreviations and Terms

Abbreviation or Term	Definition/Explanation
ADR	adverse drug reaction
AE	adverse event
BRAF	B-Raf proto-oncogene serine/threonine kinase, gene of *RAF* Family
CA 19-9	cancer antigen 19-9
CapeOX	capecitabine/oxaliplatin
CEA	carcinoembryonic antigen
CEE	central and eastern Europe
CI	confidence Intervals
COPD	chronic obstructive pulmonary disease
CRC	colorectal cancer
CT	computer tomography
DpR	depth of response
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
EDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EGFRI	epidermal growth factor receptor inhibitor
EHR	electronic health records
ETS	early tumour shrinkage
FACT	functional assessment of cancer therapy
FOLFIRI	FOL (folinic acid, leucovorin,LV) F (fluorouracil,5FU) IRI (irinotecan)
FOLFOX	FOL (folinic acid) F (5FU) OX (oxaliplatin)
FOLFOXIRI	FOL (folinic acid) F (5FU) OX (oxaliplatin) IRI (irinotecan)
ICF	informed consent form
ICJME	international committee of medical journal editors
IEC	independent ethics committee
Ig	Immunoglobulin
IRB	institutional review board
IROX	IR (irinotecan) OX (oxaliplatin)
IVRS	interactive voice response system
KRAS	Kirsten rat sarkoma 2 viral oncogene homolog, gen of *RAS* family

Abbreviation or Term	Definition/Explanation
LV	Leucovorin, folinic acid
mCRC	metastatic colorectal cancer
MedDRA	Medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NRAS	neuroblastoma *RAS* viral oncogene homolog, gene of *RAS* family
ORR	objective response rate
OS	overall survival
OTC	over the counter
PET	positron emission tomography
PFS	progression-free survival
PP	percentage points
QoL	quality of life
RECIST	response evaluation criteria in solid tumours
RR	response rate
SAP	statistical analysis plan
SmPC	summary of product characteristics
TGFα	transforming growth factor-alpha
TNM	tumour node metastasis
WT	wild type
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
5-FU	fluorouracil
Baseline Visit	The date of start of 1st line chemotherapy and panitumumab
Enrolment Visit	The date of informed consent signature
End of Observation Visit	The visit at the end of Prospective Observation Period or the last visit before death or withdrawal of informed consent or lost to follow-up
End of Study Visit	The visit at the end of Safety Follow-up or at the end of Prospective Observation Period if panitumumab was not administered in the last 4 weeks of observation
Prospective Observation Period	Period between Enrolment and start of Safety Follow-up defined as 1) 15 months of continuous 1st line panitumumab plus chemotherapy treatment administration or 2) up to 15 months after stop of 1st line treatment without subsequent 2nd line treatment or 3) 1st line panitumumab plus chemotherapy until progression/start of 2nd line treatment or death or withdrawal of informed consent or loss-to follow-up, whichever occurs first

Abbreviation or Term	Definition/Explanation
Retrospective Period	Period between start of 1st line panitumumab plus chemotherapy and enrolment
Safety Follow-up (SFU)	30 days of follow-up after Prospective Observation Period for subjects who reached 15 months of 1st line panitumumab plus chemotherapy if panitumumab was administered in the last 4 weeks of observation or for subjects who started 2nd line treatment. Safety Follow-up period does not apply to subjects who completed 15 months of observation consisting of shortened 1st line treatment without subsequent 2nd line treatment (as described under #2 in the definition of Prospective Observation Period).

3. Responsible Parties

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4. Abstract

Study Title

POWER: Real World Data of 1st line panitumumab treatment in combination with chemotherapy in non resectable wild type *RAS* metastatic colorectal cancer (mCRC) subjects in Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania, Russia an Observational Ambidirectional Study

Study Background and Rationale

Colorectal cancer (CRC) is the fourth most common cause of cancer mortality worldwide and the second most common cancer in Europe. Even up to 50% of all CRC subjects eventually develop metastatic disease. The predominant treatments for metastatic CRC (mCRC) are surgery and chemotherapy. In a number of cases, conventional agents alone are not adequate and targeted agents, including biologics, are necessary.

Panitumumab, an antibody against human epidermal growth factor receptor (EGFR), has been shown to be effective in mCRC and was first approved in the European Union in 2007 for the indication of adults with mCRC with non-mutated *RAS* gene. It was also approved as a 1st line agent in combination with FOLFOX (folinic acid/5-flourouracil/oxaliplatin) and launched in the selected European countries in 2015-2018.

Clinical studies with panitumumab revealed improvements of progression-free survival (PFS) and overall survival (OS) connected with early tumour shrinkage (ETS) in subjects with wild type (WT) *RAS* mCRC. However, these and other studies failed to collect enough information to assess the effect of right- and left-side colon cancer and their interactive responsiveness EGFR inhibition. In addition, more data is needed to assess the safety effects of injectable anti-EGFR agents, mainly skin toxicity that occurs in about 60—90% of subjects.

This study will address the question of the use of panitumumab as 1st line treatment in daily clinical practice in the selected European countries, especially with recent launch of the therapy. The study will also provide insight into the choice of 2nd line treatment regimen after disease progression from 1st line panitumumab plus chemotherapy. Further data will be collected to better understand the impact and management of skin toxicity. The real world data will be explored not just in terms of the long-term therapy optimization, but also in terms of the impact of chosen therapies on quality of life and health economic indicators.

Research Question and Objective(s)

- Primary Objective(s)

To obtain characteristics of subjects with WT *RAS* non resectable mCRC receiving panitumumab in combination with chemotherapy as a 1st line treatment, and to describe the patterns of treatment, including 1st and 2nd line therapies.

- Secondary Objective(s)
  - To assess the response to 1st line treatment.
  - To explore the relationship between Death and/or Disease Progression and subject / country characteristics.
  - To characterize the group of subjects with ETS outcome (if available).
  - To assess incidence of adverse drug reactions (ADR).
- Hypothesis(es)/Estimation

This study will be observational; no hypothesis will be carried out.

Study Design/Type

This is a multicentre, ambidirectional (retrospective-prospective), observational study in the selected European countries.

Study Population or Data Resource

The study population will consist of subjects (≥18 years old) with initially non resectable WT *RAS* mCRC receiving panitumumab in combination with chemotherapy as 1st line treatment. The observations will be conducted in the selected European countries, including but not limited to Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania and Russia. Study period will last 15 months of enrolment plus max.16 months of observation (min. 1 month of retrospective plus max. 15 months of prospective observation), plus 30 days of Safety Follow-up.

Summary of Subject Eligibility Criteria

Inclusion Criteria

- Subject who received first infusion of panitumumab in combination with chemotherapy as 1st line treatment between 1 and 12 months before enrolment and who continues treatment with panitumumab in combination with chemotherapy at the time of enrolment
- Subject with a record of WT RAS CRC diagnosis as per standard clinical practice
- Subject with metastatic carcinoma of the colon or rectum with at least one metastatic site recorded
- Subject with initially non resectable mCRC at the start of panitumumab plus chemotherapy treatment
- Subject who was diagnosed with a tumour, assessed by CT/MRI etc. prior to panitumumab plus chemotherapy initiation
- Histologically or cytologically confirmed carcinoma of the colon or rectum as the primary site
- Subject ≥ 18 years of age on the date of enrolment

- Subjects whose care will be managed primarily by the enrolling physician and/ or all records will be available from initiation of 1st line panitumumab plus chemotherapy treatment to end of safety follow up
- Subject or subject's legally acceptable representative has provided informed consent if applicable per local regulations

Exclusion Criteria

- Subject with proven brain metastasis
- Subject with mCRC as a secondary malignancy
- Ongoing or planned concurrent participation in any interventional clinical trial

Safety Follow-up

Safety Follow-up will last approximately 30 days after the start of 2nd line treatment, or after 15 months of observation if panitumumab was administered in the last 4 weeks of observation, whichever occurs first, except for death, withdrawal of consent or lost to follow-up. Relevant AE's will be reported during this time.

Variables

– *Outcome Variable(s)*

The primary outcome variables will contain demographics criteria, targeted medical history and the current status of disease, including dose, infusion schedule, and changes in 1st and 2nd line treatments.

Key secondary outcomes will include Death, Disease progression, response rate (RR), rate of conversion to resectable mCRC, tumour markers, ETS (if available) and ADR incidents. The relationship between Death, Disease Progression, ETS (if available), and subject characteristics with the particular interest in tumour location will be assessed.

CCI

– *Exposure Variable(s)*

The main exposure variables will be the country, location of tumour (left vs. right side), current disease status and treatment regimen.

– *Other Covariate(s)*

The potential influence of demographic covariates such as body weight, sex and age and covariates related to prior therapies will be explored.

Study Sample Size

Approximately a total of 600 subjects are planned to be enrolled at approximately 70 sites. The sample size will provide reasonable precision to statistical analysis. The size of subject population will fulfil the requirements of reimbursement agencies in the selected European countries.

The sample size of 600 would ensure that the half-width of the 95% confidence interval (CI) for the proportion of subjects reporting important outcome measures would be no larger than the 4 percentage points (p.p.) for the overall study population.

Data Analysis

The analysis of this study will be descriptive in nature. The categorical data obtained in the study will be examined with regards to precision rather than statistical power. Proportions and confidence intervals will be most useful if reported in subgroups rather than overall. The data will be summarized for the total study population and per country. Primary outcomes will be summarized using descriptive statistics. Secondary outcomes will be analysed using Kaplein Meier (death, disease progression) and will be summarized descriptively. CCI [redacted]

5. Amendments and Updates

Amendment No.	Date	Section of Protocol	Amendment	Reason
1	13 February 2019		See Summary of Changes	
2	29 April 2019		See Summary of Changes	

6. Milestones

Table 1. Planned Milestones for the POWER Study

Milestone	Planned date
Start of data collection (First Subject Enrolled)	Q4 2018
Last Subject Enrolled	Q1 2020
End of data collection (Last Subject Last Visit)	Q2 2021
Final report of study results	Q4 2021*

** Option to close the study when less than 5 subjects are in Safety Follow Up (SFU) phase*

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Epidemiology of colorectal cancer

Colorectal cancer (CRC) is the fourth most common cause of cancer mortality worldwide representing 8.5% of cancer deaths (Ervik, 2016). CRC is the second most commonly diagnosed cancer in men and the third in women worldwide with over 1.4 million new cases diagnosed in 2012 (Ervik, 2016) with an increasing tendency among adult populations under 50 years of age in recent years (Siegel, 2017). In Europe, CRC is the second most common cancer, and second most frequent cause of cancer death, after lung cancer (Ferlay, 2013). Approximately 20-25% of newly diagnosed cases have already developed metastasis and up to 50% of all CRC subjects eventually develop metastatic disease (Bolocan, 2012; Kurkjian, 2009). CRC has a 5-year survival of approximately 50% (Bolocan, 2012). However, the 5-year survival for subjects with metastatic colorectal cancer (mCRC) is between 5% and 8%, with metastasis to liver and lungs representing the main causes of death (Mitchell, 2013).

Treatment of mCRC

Surgery (for resectable tumours, liver resection and radical surgical removal of metastases) and chemotherapy are predominant treatment modalities for mCRC (Chiappa, 2009). However, subjects with smaller metastatic nodules, a non-bilobar site of disease, low tumour burden and advanced age, are usually not referred for surgery (Ksienski, 2010).

In subjects with non resectable tumour, the recommended 1st line conventional agents are fluorouracil (5-FU), leucovorin (LV), irinotecan, capecitabine, IRO (irinotecan/oxaliplatin), CapeOX (capecitabine/oxaliplatin), FOLFOX (Folinic acid/5-FU/oxaliplatin), FOLFIRI (5-FU/LV/irinotecan), or FOLFOXIRI (LV/5-FU/oxaliplatin/irinotecan) (Van Cutsem, 2010), which may be combined with one of 4 types of targeted agents:

- monoclonal antibody against vascular endothelial growth factor (VEGF): bevacizumab
- monoclonal antibody against the EGFR: cetuximab or panitumumab
- recombinant vascular endothelial growth factor receptor VEGFR-antibody: ziv-aflibercept
- multikinase inhibitor: regorafenib.

These combinations as well as monotherapies with irinotecan, cetuximab or panitumumab, were shown to alter the biology of progressive CRC disease (Van Cutsem, 2010).

EGFR inhibitor therapy

Panitumumab (Vectibix®) is a high-affinity (k_d 5 x 10^{-11}M), human immunoglobulin G2 (IgG2) monoclonal antibody directed against human EGFR (Davis, 1999; Yang, 1999). Panitumumab blocks the extracellular binding domain of EGFR that inhibits phosphorylation and activation of EGFR-associated kinases, such as epidermal growth factor (EGF), transforming growth factor-alpha (TGFα), and their ligands: amphiregulin, betacellulin, epiregulin, and heparin-binding EGF. The efficacy of panitumumab was similar to cetuximab (ASPECCT study; Price, 2014), but longer overall survival (OS) was observed in subjects treated with combination bevacizumab+panitumumab than bevacizumab+cetuximab (Price, 2016).

Therapeutic effect of panitumumab

The results of phase III study (PRIME) showed that panitumumab as 1st line treatment in combination with FOLFOX4 improved progression-free survival (PFS) of wild type (WT) *KRAS* subjects compared with FOLFOX4 alone (Douillard, 2010). Similarly, panitumumab+FOLFIRI vs. FOLFIRI monotherapy as 2nd line treatment resulted in improvements of PFS and OS (Peeters, 2015).

Panitumumab and bevacizumab were also compared in combination with FOLFOX as 1st line therapy PEAK - phase II study. Both treatments were associated with improved PFS, objective response rate (ORR), and resection rates, while OS was longer in the panitumumab+FOLFOX group (Schwartzberg, 2014).

Both PRIME and PEAK studies, highly evaluated on the Magnitude of Clinical Benefit Scale (MCBS) (Cherny, 2015), providing convincing evidence of the clinical validity of the high PFS and OS rates of panitumumab therapy.

RAS and BRAF gene analysis in CRC diagnostic

Mutations in *RAS* gene family: *KRAS* and *NRAS* predicted poor response to panitumumab+FOLFOX4 (Douillard, 2013) and to panitumumab+FOLFIRI (Peeters, 2015). Moreover, mutations in *BRAF* gene negatively predicted survival. Therefore, subjects with *BRAF* mutations are considered as high-risk regardless of other clinical parameters (Kohne, 2016).

The prevalence of *RAS* mutation was estimated at 43.6% (95% CI: 38.8-48.5%) based on 4,431 tumour samples (Kafatos, 2017).

RAS analysis is becoming routinely use based on the results of many studies, which support its predictive value (Rivera, 2017; Stintzing, 2016).

Early tumour shrinkage (ETS) as indicator of response to treatment

It was shown that early, rapid and deep tumour shrinkage predicted delay in tumour progression and prolonged survival for a certain population of subjects. In the PRIME study more subjects with WT *RAS* mCRC receiving panitumumab+FOLFOX4 showed ETS than FOLFOX alone which was associated with longer PFS and OS (Douillard, 2015) and with improvement in quality of life in subjects with tumour symptoms (Siena, 2016). In the PEAK study, ETS was observed in more subjects treated with panitumumab+FOLFOX than bevacizumab+FOLFOX. A meta-analysis of pooled data from 3 panitumumab studies (PRIME, PEAK and PLANET) showed that ETS (≥ 20% or ≥ 30% at week 8) was associated with improvement in OS, PFS and resection rates in subjects with WT *RAS* mCRC (Rivera, 2015; Rivera, 2016).

Based on these results, new response-related outcomes, such as ETS and depth of response (DpR) were proposed as alternative to OS (Stintzing, 2016). ETS shown after a short period of treatment may provide an early measure of sensitivity to therapy in subjects with mCRC. Multiple studies indicated that ETS predicts PFS and OS independently of chemotherapy or targeted therapy used (Heinemann, 2015; Heinemann, 2016).

Location of tumour (left/right side of colon)

Another prognostic factor is the primary tumour location, ie, right versus left side of colon. Recently more studies investigated subjects with right-sided colon cancer (Saltzstein, 2007) connected with different epidemiology, clinical presentation, pathology, and genetic mutations comparing to subjects with left-sided colon cancer (Hansen, 2012).

A recent study reported an association between tumour location and survival (Rivera, 2017), indicating shorter survival of subjects with right-sided primary tumours when compared with left-sided primary tumours (Matos, 2016). However, there also is conflicting evidence, as, better survival of 91,416 subjects with right-sided stage I-III colon cancer versus 39,474 left-sided subjects was shown (Warschkow, 2016). Moreover, the lack of activity of anti-EGFRs in right-sided tumours was demonstrated in 75 *RAS* and *BRAF* WT subjects (Moretto, 2016), raising a question of optimal treatment choices.

In the light of inconsistent data, no consensus has been reached; therefore additional research is needed to understand the differences between right- and left-side colon cancer and their interaction with EGFR inhibition.

Adverse drug reaction (ADR): skin reactions

Skin reactions are a pharmacological effect of EGFR inhibitors application. Injectable EGFR inhibitors rarely cause systemic toxicities generally associated with chemotherapy. However, these injectable anti-EGFR agents are associated with mild skin toxicities in more than 60—90% of subjects (Leporini, 2013; Melosky, 2009; Bonner, 2010: Velenik, 2010: Kim, 2016). These skin toxicities represent the most common adverse drug reactions caused by the injectable EGFR inhibitors (Kubo, 2016; Takahashi, 2015; Mittmann and Seung, 2011; Fabbrocini, 2015). In subjects treated with cetuximab and panitumumab, approximately 80% and 86%, respectively, experience a skin toxicity, the majority of which are mild (Velenik, 2010; Kim, 2016; Bonner, 2010). Severe grade skin toxicities, (grade 3 - 4), occur in only 5-18% of subjects treated with cetuximab and 14% in those treated with panitumumab (Abdullah, 2012). Safety analysis of PRIME study revealed skin toxicity in 38% of panitumumab+ FOLFOX4-treated and 2% of FOLFOX4-treated subjects.

According to the European SmPC (summary of product characteristics), the first symptom of a dermatological reaction is observed in median time of 10 days, and the median time to resolution of such a reaction after the last dose of panitumumab is 28 days.

Skin toxicities can have a profound impact on subject quality of life due to symptoms caused and potential aesthetic consequences. Furthermore, inappropriate management of skin toxicities can increase the risk of dose reduction, discontinuation or withholding of the cancer treatment (Boone, 2007). However, no significant differences in quality of life measured every 4 weeks between subjects with grade 0–2 skin toxicity and those with grade 3+ skin toxicity were reported in PRIME study (Siena, 2016).

In recent years, clinical guidelines recommend that prophylactic measures are the preferred option to managing acute skin reactions. Appropriate prophylactic measures can effectively reduce the severity (although perhaps not incidence) of skin reactions in subjects treated with injectable EGFR inhibitors and have therefore the potential to directly benefit subjects (Bonner, 2010; Melosky, 2009; Abdullah, 2012).

7.2 Rationale

The aim of the study is to gain an understanding of the country clinical landscape based on real-world evidence of the pattern of 1st line WT *RAS* mCRC treatment. Since panitumumab was not widely available in the most of target countries until its recent reimbursement (2017-2018), the physicians' experience is still limited and information on daily clinical practice relating to the use of panitumumab as 1st line treatment is lacking. More data using the combination of panitumumab with FOLFIRI as indicated in the label is needed, especially that the previous study (20120271) only allowed for combination with FOLFOX.

Furthermore, the details of 2nd line treatment regimen will also be collected. No local data has been acquired since the launch of 1st line panitumumab in Slovenia, Hungary, Romania Poland, and Russia. In these countries there are no local data or mCRC registries. Few countries have been included in the previous observational study of the use of panitumumab in combination with FOLFOX in routine clinical practice for subjects with mCRC in first line (Protocol number 20120271). However, the data on the use of panitumumab in combination with FOLFIRI has not been collected for Bulgaria, Czech Republic and Hungary.

The proposed study intends to close this data gap in the selected European countries. Countries with no mCRC registry would benefit in the first place. In countries where a national CRC registry is available and up-to-date, the data still does not cover all aspects of the subjects' characteristics, and therefore the study will not duplicate the existing registry. The data on sequential treatment with panitumumab as well as subject management after disease progression will be helpful in long-term therapy optimization and standardization across countries. It will allow for the appropriate adjustment of panitumumab therapy to specific subjects in accordance with the concept of personalized medicine.

The gathered data may also be used to indirectly support health technology assessments required by reimbursement agencies, and thus contribute to facilitating subject access to novel therapies.

The study will also seek to investigate safety outcomes including the prevention, incidence and management of skin toxicity associated with the use of panitumumab in clinical practice. So far, the results of 2 observational studies revealed that treatment pattern and clinical efficacy of panitumumab were comparable between randomized controlled studies and clinical practice. Nevertheless, the same studies showed that the prevalence of skin toxicity of 49% (all grades rash) was lower than expected based on randomized clinical studies data (Hebart, 2018). The aim in this study is to obtain further

data for the better understanding of impact and management of skin toxicity by the payer authorities, using the Functional Assessment Cancer Therapy (FACT)- EGFRI-18 quality of life (QoL) questionnaire (See Appendix F) if permitted in a country per local regulations and the collection of more information on different treatments strategies that may help to explain the differences found in the previous studies and the real world impact of this side effect on subjects and the health care system.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This study will be observational; no hypothesis will be carried out.

8. Research Question and Objectives

This study aims to describe the characteristics of subjects treated with panitumumab plus chemotherapy and the details of the therapy itself in the selected European countries.

8.1 Primary Objective

- To obtain characteristics of subjects with WT *RAS* non resectable mCRC receiving panitumumab in combination with chemotherapy as a 1st line treatment, and to describe the patterns of treatment, including 1st and 2nd line therapies.

8.2 Secondary Objectives

- To assess the response to 1st line treatment.
- To explore the relationship between death and/or disease progression and subject / country characteristics.
- To characterize the group of subjects with ETS outcome (if available).
- To assess incidence of adverse drug reactions (ADR).

8.3 Exploratory Objectives (if available)

CCI [redacted]

9. Research Methods

This is an observational study and thus real world data will be extracted from medical files and collected prospectively.

9.1 Study Design

This is a multicentre, ambidirectional (retrospective-prospective), observational study in the selected European countries, including but not limited to Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania and Russia.

The Study Design Schema is presented in Figure 1. In general, to gather the most comprehensive and recent data, the study consists of 3 phases: Retrospective Period, Prospective Observation and Safety Follow-up. Retrospective data will be collected from

1 to a maximum of 12 months preceding enrolment, Prospective Observation will be led by a maximum of 15 months and a Safety Follow-up of 30 days after the end of the observation, giving a total of a maximum 28 months of mCRC management data.

Subjects with initially non resectable WT *RAS* mCRC receiving panitumumab in combination with chemotherapy as first-line treatment will be eligible for the study. The decision on treatment with panitumumab should have been taken independently and prior to the decision to study enrolment.

Study participants must have received at least one dose of panitumumab in combination with chemotherapy between 1 and 12 months before enrolment (defined as the informed consent [ICF] signature date). Panitumumab as a 1st line treatment in combination with

chemotherapy should be ongoing at enrolment. Therefore, the Retrospective phase will last a maximum of 12 months for an individual subject. An Interactive voice response system (IVRS) system will be used for enrolment. Baseline data including demographics, characteristics and subjects' clinical information will be collected retrospectively from medical records up to the point of enrolment. From the enrolment point, prospective data will be recorded. The Prospective phase will consist of two periods: 1) observation during the 1st line treatment administration and 2) observation after the end of 1st line treatment. The maximum duration of the Prospective phase will be 15 months. In case of a change in therapy and 2nd line treatment implemented, subjects will enter into the Safety Follow-up phase.

Safety Follow-up will last approximately 30 days after the start of 2nd line treatment, or after 15 months of observation if panitumumab was administered in the last 4 weeks of observation, whichever occurs first, except for death, withdrawal of consent or lost to follow-up. If a subject receives panitumumab in combination with chemotherapy for 15 months, then 30 days of Safety Follow-up will be the 16th month of observation.

Table 2. Objectives and Outcomes

Objectives	Outcomes	Exposure variables
Primary		
To obtain **characteristics of subjects** with WT *RAS* non resectable mCRC receiving panitumumab in combination with chemotherapy as a 1st line treatment.	• Demographics • Disease history, including location of tumour (left vs. right side) • Current status of disease	• Country • Total
To describe the **patterns of treatment**, including 1st and 2nd line therapies.	• 1st line treatment • Any changes during 1st line treatment, including dose, infusion schedule, and reasons for changes • Type of progression leading to 2nd line choice • Type of 2nd line treatment (type of anticancer therapy)	• Country • Location of tumour (left vs. right side) • Oxaliplatin-based chemotherapy • Irinotecan-based chemotherapy • Total
	• Dose, schedule and reason for treatment selection • Subsequent treatment line/approach	

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Table 2. Objectives and Outcomes

Objectives	Outcomes	Exposure variables
Secondary		
To assess the **response to 1st line** treatment described by: the relationship between death, disease progression, ETS (if available), and subject characteristics with the particular interest in tumour location	• Death • Disease Progression • Response rate • Rate of conversion to resectable mCRC • Tumour markers: CEA and CA 19.9 • Early tumour shrinkage (if available)	• Country • Location of tumour (left vs. right side) • Current disease status • Oxaliplatin-based chemotherapy • Irinotecan-based chemotherapy • Total
To assess incidence of **adverse drug reactions** (ADR) events (general)	• ADR reports: type and duration of ADR incident	• Country • Total
Exploratory (if available)		
CCI [redacted]		

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9.2 Setting and Study Population

It is planned to include approximately 600 subjects with initially non resectable WT *RAS* mCRC receiving panitumumab in combination with chemotherapy as 1st line treatment. The observations will be conducted in the selected European countries. Study period will last 15 months of enrolment plus max.16 months of observation and Safety Follow-up.

9.2.1 Study Period

Study period will be divided to 3 observation phases:

I. Retrospective data collection from the period of 1 to a maximum of 12 months prior to enrolment
II. Prospective Observation Period, lasting a max. of 15 months
III. Safety Follow-up, lasting 30 days after the end of the Observational Period

9.2.2 Selection and Number of Sites

In the participating countries, approximately 70 in-patient and out-patient investigative centers that routinely treat subjects with mCRC will have designated involvement in the study. Centers will include academic, public and private settings and will be distributed in diverse geographical regions within each country. Subject enrolment will last from the day of site opening until end of the study, with a total of 15 months for all participating countries. Sites will be eligible to participate in the study if they are listed among the sites to receive and administer panitumumab according to the formulary and will receive a target to recruit into the study based on the country level. Country Level enrolment will allow sufficient numbers to facilitate the representativeness of each country and to ensure appropriate level of data collection to support any applicable regulatory submissions. Each site will provide account of the number of patients receiving panitumumab in combination with chemotherapy as 1st line treatment during the last 12 months prior to site initiation.

9.2.3 Subject/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

I. Subject who received first infusion of panitumumab in combination with chemotherapy as 1st line treatment between 1 and 12 months before enrolment and who is continuing on treatment with panitumumab in combination with chemotherapy at the time of enrolment
II. Subject with a record of WT RAS CRC diagnosis as per standard clinical practice
III. Subject with metastatic carcinoma of the colon or rectum with at least one metastatic site recorded

IV. Subject with initially non resectable mCRC at the start of panitumumab plus chemotherapy treatment

V. Subject who was diagnosed with a tumour, assessed by CT/MRI etc. prior to panitumumab plus chemotherapy initiation

VI. Histologically or cytologically confirmed carcinoma of the colon or rectum as the primary site

VII. Subject ≥ 18 years of age on the date of enrolment/ICF signature

VIII. Subjects whose care will be managed primarily by the enrolling physician and/ or all records will be available from initiation of 1st line panitumumab plus chemotherapy treatment

IX. Subject or subject's legally acceptable representative has provided informed consent

9.2.3.2 Exclusion Criteria

I. Subject with proven brain metastasis

II. Subject with mCRC as a secondary malignancy

III. Ongoing or planned concurrent participation in any interventional clinical trial

9.2.4 Matching

Not applicable

9.2.5 Baseline, Retrospective Data Collection and Enrolment Visit

The detailed schedule of procedures to be performed during the study is provided in Appendix E.

Baseline is defined as the date of the start of panitumumab in combination with chemotherapy. The decision on treatment with panitumumab should have been taken independently from the decision to study enrolment and prior to it.

The data will be abstracted from subject's medical records and entered into the electronic case report form (eCRF) by the Investigator or designee during the enrolment Visit (after the subject signed informed consent).

The required data should be collected where available and recorded as standard clinical practice, including but not limited to the following information:

- Demographics: age, sex
- Targeted medical history / comorbidities: chronic obstructive pulmonary disease (COPD), diabetes, other neoplasia, anaemia, hypertension, coronary disease/incident, obesity
- Physical measurement, including height and body weight

- Vital signs
- 1st line treatment data:
  - 1st line treatment choice and treatment goal
  - chemotherapy: selection of chemotherapeutic agents, dosage and interval
  - start date of therapy and total number of cycles
  - changes in dosing and reasons for changing (for example AEs) (dose changes related to the changes of body weight are not considered dose changes)
  - treatment interruption if longer than 30 days in one single interval and reasons for interruption
  - changes in biologic treatment (both chemotherapy and targeted therapy) for any reason
- Panitumumab administration:
  - dose and schedule
- Substance use
- Laboratory tests: haematology and chemistry prior to or at Baseline
- Reproductive status
- Eastern Cooperative Oncology Group (ECOG) performance status
- Disease history:
  - type of primary tumour diagnosed using all or any of the following methods: computer tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and the date of diagnosis
  - site of primary tumour: rectum vs colon, right vs left colon
  - surgical procedures
  - lymph nodes: number and involvement
  - tumour node metastasis (TNM) stage
  - adjuvant chemotherapy, including regimen if applicable
  - sites of metastatic disease: liver, lung, other diagnosed by chest X rays, bone X rays, ultrasound assessments (any performed) or radio nuclear examinations
- Tumour evaluations:
  - evaluation and re – evaluation / assessment (methods, criteria, timing Q2M), RECIST criteria (if available)
  - ETS at week 8 (if available, as per clinical practice) measured using all or any of the following methods: CT, MRI, PET
- Site characteristics.

Safety data will not be collected retrospectively, however side effects related to panitumumab treatment, and details of skin toxicity management will be collected as part of medical history.

The following key data will also be collected at Baseline where available. These data must originate from the time prior to the subjects' first dose of panitumumab in combination with chemotherapy:

- Method (incl. Brand name, if available) and date of RAS testing (test requested and result available), if available. Data on other biomarkers, if conducted, will also be collected.

9.2.6 Prospective Observation Period

The Prospective Observation Period will start at the enrolment Visit and subject visits should be registered on a monthly basis. Data will be collected on a monthly basis for 15 months during 1st line treatment administration. In case of earlier discontinuation of 1st line treatment, the data from maintenance treatment (other than 2nd line treatment) will be collected for the Observation Period of 15 months.

Data obtained during the 15-month Observation Period will be reported into the eCRF.

The following data will be collected on a monthly basis:

- Physical measurement
- Vital signs
- ADR events: type and duration of ADR incident; prophylaxis for skin toxicity, occurrence of skin toxicity and details of skin toxicity management using FACT - EGFRI-18 QoL questionnaire (See Appendix F) if permitted in a country per local regulations.
- Concomitant medications
- 1st line treatment pattern including:
  - chemotherapy: drug, dosage and interval
  - changes in dosing and reasons for the change
  - treatment interruption if it is longer than 30 days in one single interval and reason of interruption
  - changes in biologic treatment (both chemotherapy and targeted therapy) for any reason
  - stop date and reason for treatment discontinuation.
- 2nd line treatment pattern including:
  - biological agents: drug name/s, dose and schedule
  - chemotherapy: drug name/s, dosage and interval
- Panitumumab administration:
  - dose and schedule
- Laboratory values: haematology and chemistry

- ECOG performance status
- Tumour evaluations:
  - evaluation and re – evaluation / assessment (methods, criteria, timing Q2M), RECIST criteria (if available)
  - ETS at week 8 (if available, as per clinical practice) measured using all or any of the following methods: CT, MRI, PET
  - disease evaluation as routinely monitored (if different than RECIST criteria), including chest X rays, bone X rays, ultrasound assessments (any performed) or radio nuclear examinations
  - information about biomarker status (if available).

9.2.7 End of Observation Visit

The End of Observation Visit is defined as a visit at completion of the 15-month observation period, or at the end of 1st line treatment; whichever occurs first. The End of Observation Visit is also defined as a last visit before death, withdrawal of consent, or lost to follow-up; whichever occurs first.

The following data will be collected at the End of Observation Visit:

- Adverse events: type and duration of AE; prophylaxis treatment for skin toxicity, occurrence of skin toxicity and details of skin toxicity management using FACT - EGFRI-18 QoL questionnaire (See Appendix F) if permitted in a country per local regulations.
- All other safety events with the exception of the protocol exempted events.
- Date and reason for ending study:
  - 15-month observation period reached (measured from the enrolment visit)
  - start of 2nd line treatment
  - death – date and primary cause of death to be recorded
  - lost to follow-up
  - withdrawal of informed consent
- Tumour evaluations using all or any of the following methods: CT, MRI, PET, chest X rays, bone X rays, ultrasound assessments (any performed) or radio nuclear examinations
- Resection status as applicable.

9.2.8 Safety Follow-up

Safety follow-up will last approximately 30 days after the start of 2nd line treatment, or after 15 months of observation if panitumumab was administered in the last 4 weeks of observation, whichever occurs first, except for death, withdrawal of consent or lost to follow-up.

The following data, at the End of Observation Visit will be collected where available and recorded as standard clinical practice:

- Adverse Events: type and duration of AE incident; occurrence of skin toxicity and details of skin toxicity management using FACT- EGFRI-18 QoL questionnaire (See Appendix F) if permitted in a country per local regulations.
- All other safety events with the exception of the protocol exempted events.
- Concomitant medications
- Laboratory values: haematology and chemistry
- Tumour evaluations:
  - evaluation and re – evaluation / assessment (methods, criteria, timing Q2M), RECIST criteria (if available)
  - ETS at week 8 (if available) measured using all or any of the following methods: CT, MRI, PET
  - disease evaluation as routinely monitored (if different than RECIST criteria), including chest X rays, bone X rays, ultrasound assessments (any performed) or radionuclear examinations
  - information about biomarker status (if available).

9.2.9 End of Study Visit

At the end of the Safety Follow-up Period or after reaching the end of 15-month observation period if panitumumab was not administered in the last 4 weeks of observation, the End of Study Visit should be performed.

The following data will be collected:

- safety events per protocol
- concomitant medications.

9.3 Variables

The list of variables for each objective is summarized in Table 2. described in the section 9.3.2 below.

9.3.1 Exposure Assessment

Exposure will be calculated taking into account both Retrospective and Prospective phases of the study and in line with the study design, will cover all subjects who received at least one infusion of panitumumab in combination with chemotherapy as a 1st line treatment prior to enrolment. The time of exposure will be counted from the date of the first dose of 1st line chemotherapy and panitumumab (Baseline) to the date of discontinuation of 1st line treatment. The number of doses of panitumumab in combination with chemotherapy received during exposure will be collected. The exact dates of receiving doses will not be collected.

9.3.2 Outcome Assessment

Primary outcomes

As primary outcomes the following data will be collected:

- characteristics of subjects with WT RAS non resectable mCRC receiving panitumumab in combination with chemotherapy as a 1st line treatment, including:
  - demographics: age, sex
  - targeted medical history: type of primary tumour and the date of diagnosis; site of primary tumour: rectum vs colon, right vs left colon; surgical procedures; lymph nodes: number and involvement; TNM stage; adjuvant chemotherapy, including regimen if applicable; sites of metastatic disease: liver, lung, other;
  - current status of mCRC: ECOG performance status, RECIST criteria (if available), ETS at week 8 (if available)
- pattern of treatment composed of:
  - 1st line treatment: agents and doses at baseline, any changes during 1st line treatment, including dose, infusion schedule, and reasons for changes
  - 2nd line treatment: type of progression leading to 2nd line choice, type of 2nd line anti-cancer therapy, dose, schedule and reason for treatment selection

Secondary outcomes

In the secondary outcomes the following data will be gathered:

- Response to 1st line treatment measured as:
  - Death
  - Disease Progression
  - response rate (RR)
  - rate of conversion to resectable mCRC
  - tumour markers: CEA and CA 19.9
  - ETS (if available as per clinical practice) at week 8 measured by all or any of the following methods: CT, MRI, PET in comparison to the baseline.
- Safety assessments:
  - ADR reports related to panitumumab treatment
  - type and duration of ADR incident

Exploratory outcome

CCI

[redacted]

CCI

In study sites routinely performing biomarkers assessment in liquid biopsies, disease biomarkers information will be collected as per local regulations.

Since this is an observational study, all tests will be performed in line with routine clinical practice and no additional procedures are posed by the protocol.

9.3.3 Covariate Assessment

Certain pre-treatment factors (covariates) may be found to affect the pattern of treatment with panitumumab in combination with chemotherapy, therefore covariates will be investigated to evaluate their influence. However, subgroup analysis will be performed based on availability of data.

The following covariates may be analysed:

- Demographic: body weight, age, sex
- Location of primary tumour: colon (right or left) vs. rectum
- oxaliplatin-based chemotherapy for mCRC: yes vs. no
- irinotecan-based chemotherapy for mCRC: yes vs. no
- country
- total

9.3.4 Validity and Reliability

To ensure that observations will be consistent across time and sites, the eCRF will be developed to only abstract data as documented in the medical record. During data abstraction the emphasis will be put on objectivity and lack of data interpretation. To determine the reliability of data, measures of quality will be frequently performed on data transfers during the study period.

The observation instruments used in the study, like RECIST and ECOG are validated, acceptable and have been shown in cancer trials to be sensitive to change.

The Investigator and/or designee will be involved in validation of the data recording activities.

Amgen will define critical data and will control the data lifecycle to assure data integrity. Data lifecycle validation will include data creation and capture, data processing, review,

reporting (incl. handling of invalid and atypical data), data retention and retrieval. Amgen will prepare adequate training and procedures (SOPs) that will provide users the ability to review the existing data source, such as electronic health records and process the data in an effective and efficient process.

9.4 Data Sources

Retrospective data will be retrieved from medical files and will include subject's medical records from Baseline (the date of the start of panitumumab in combination with chemotherapy) to enrolment (the date of signing ICF).

During the study, data will be collected by the treating physician during subject's routine clinic visits. Data will be coded using the latest version of the medical dictionary for regulatory activities (MedDRA). Data will be validated using the electronic CRF.

In countries where the use of the FACT-EGFR1-18 (See Appendix F) questionnaire is allowed per local regulations and local language is available, additional data will be collected from subjects by means of a paper questionnaire.

9.5 Study Size

This study will enrol approximately 600 subjects in total with initially non resectable wild type *RAS* mCRC receiving panitumumab in combination with chemotherapy as 1st line treatment.

The sample size will provide reasonable precision to enable statistical analysis as described in Section 9.6 The size of the subject population will fulfil the requirements of reimbursement agencies in the selected European countries.

9.6 Data Management

Data are abstracted by site staff from subject medical files into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all site staff delegated to abstract subject data. An eCRF Completion Guideline will be provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor or designee is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The Clinical Monitor, or designee is to have access to subject

medical records and other study-related records needed to verify the entries on the eCRFs in accordance with the local laws and regulations.

The Investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic and via a paper questionnaire (in countries where FACT- EGFRI-18 QoL questionnaire (See Appendix F) use is permitted):

- All source documentation supporting entries into the electronic eCRFs must be maintained and available upon request.
- Updates to electronic eCRFs will be automatically documented through the software's "audit trail". The data from the paper questionnaire (See Appendix F) will be entered by site staff into the electronic data capture (EDC) system database
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and ICH GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by an Amgen reviewer.
- The Investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the Investigator inspected or reviewed the data on the CRF, the data queries, and site notifications, and agrees with the content.

9.6.1 Obtaining Data Files

Not applicable

9.6.2 Linking Data Files

Not applicable

9.6.3 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

9.7 Data Analysis

The analysis of this study will be descriptive in nature. Data will be summarised by appropriate descriptive statistics. Two-sided 95 confidence intervals will be presented where appropriate.

9.7.1 Planned Analyses

The baseline data will be summarized using descriptive statistics for subjects with mCRC who received panitumumab in combination with chemotherapy as 1st line treatment according to the type of chemotherapy received.

The data will be summarized for the total study population (all subjects with mCRC who received panitumumab in combination with chemotherapy as 1st line treatment) divided by the type of chemotherapy received: FOLFOX, FOLFIRI and others.

The data will be summarized for the total study population and per country. Further details will be provided in Statistical Analysis Plan (SAP).

9.7.1.1 Interim Analysis/Analyses

Not Applicable

9.7.1.2 Primary Analysis

Not Applicable

9.7.1.3 Final Analysis

The final analysis will occur when all enrolled subjects have completed the study.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The analysis of this study will be descriptive in nature. Counts and percentages will be provided for categorical outcomes. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum and maximum values. Time to event data will be analysed using Kaplan Meier estimator.

For each outcome parameter, the covariates listed in Section 9.3.3 may be assessed in a logistic or general linear model overall for the selected European countries where data is appropriate. If available, non-significant factors will be eliminated stepwise until only covariates significant at the 5% level remain, thereby indicating which covariates have an important influence on treatment pattern. Summary statistics will then be reported for each level of the significant covariates and will be subject to local data availability.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

All available data collected during the retrospective and prospective observation periods, the safety follow-up period, and the end of study visit will be used in the analysis. The eCRFs will be designed to minimise missing data and to optimise the integrity of collected data. Subjects' records will not be excluded because of missing data and missing data will not be inputted. For categorical variables, missing responses will be shown as a separate category in the analysis. For numeric variables, the number of non-missing observations will be presented.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrolment

All eligible subjects' enrolled into the study will be included in the full analysis set and will be included in all summaries and analyses. To assess whether sites are representative cross country, summary statistics of site characteristics and the number of subjects enrolled in the study by site will be provided.

9.7.2.3.2 Description of Subject Demographics/Subject Characteristics

Baseline (retrospective) data will be summarized for subjects with mCRC who received panitumumab in combination with chemotherapy as 1st line treatment according to the type of chemotherapy received and overall. The baseline data will also be summarized overall for the selected countries and by treatment (Oxaliplatin/Irinotecan based).

Baseline demographics/characteristics will be summarized using descriptive statistics. Demographic and clinical characteristics of subjects in the study outlined in Section 9.3.3 will be summarized. Measurements such as age will be calculated based on the subject status at the start of the Observation Period (Baseline), and clinical characteristics as morphological tumour changes, surgeries, hospitalization, new metastatic sites, etc. will be captured throughout the Observation Period.

9.7.2.4 Analysis of the Primary, Secondary and Exploratory Outcomes

Primary Outcomes

Characteristics of subjects:

Descriptive statistics will be used to summarize subject demographic and baseline characteristics including age, sex, height, body weight, reproductive status, disease history, and current status of disease. The duration of Safety Follow-up will also be summarized.

Patterns of treatment:

Description of 1st line treatment, including type of chemotherapy combined with panitumumab, start and stop dates, dose, unit, route, frequency and reason for cessation of chemotherapy and/or Panitumumab will be summarized across the entire observation period using descriptive statistics.

Type of progression leading to 2nd line choice, type of 2nd line anti-cancer therapy including infusion schedule will be summarized using descriptive statistics.

Treatment patterns in relation to tumour location (left vs. right): frequency and percentage of subjects with left or right location of tumour will be provided.

Secondary Outcomes

Response to 1st line treatment:

Death and Disease Progression per Investigator assessment will be analysed using Kaplan Meier estimator.

Response rate (RR) and conversion to resectability will be summarized using descriptive statistics.

Tumour markers (CEA and CA 19.9) will be summarized descriptively for total population.

ETS (if available, per clinical practice) at week 8 will be provided.

Response rate, tumour markers, type of progression leading to 2nd line choice, type of 2nd line anti-cancer therapy and subsequent treatment line will be summarized descriptively according to the location of the tumour and current disease status.

Exploratory Outcomes

CCI

[redacted]

9.7.2.5 Sensitivity Analysis

Selected sensitivity analyses may be performed to assess the impact of using other analysis sets if appropriate.

9.7.2.5.1 Subgroup Analysis

Subgroup analysis may be used to investigate the covariates listed in section 9.3.3. If there is insufficient number of subjects in each level of a subgroup (eg, < 10 subjects), then the subgroup analysis will not be performed.

9.7.3 Analysis of Safety Outcomes

Number of subjects with serious and non-serious ADRs leading to discontinuation of panitumumab and serious ADRs associated with fatal outcomes will be tabulated by system organ class and preferred term.

Measures of skin toxicity management (FACT- EGFRI-18 QoL questionnaire (See Appendix F) if allowed per local regulations), type of measures, duration, severity of skin toxicity, and type of treatment will be summarized.

9.8 Quality Control

The overall procedures for quality assurance of clinical study data are described in the Amgen Standard Operational Procedures. In short, data quality and integrity will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor. The data in the eCRF will be verified electronically. Discrepancy reports will be generated and transferred to the site for resolution of the Investigator.

9.9 Limitations of the Research Methods

Potential limitations of the study design relate to the ability to include a sufficient sample of subjects meeting the eligibility criteria, namely having non resectable wild type *RAS* mCRC and receiving panitumumab in combination with chemotherapy as 1st line treatment. To minimize the risk, the study will include a sufficient number of centres to be able to capture an adequate study population that represents subjects treated with panitumumab. The results gathered in central and eastern European (CEE) countries may be generalized, especially for countries having similar health care systems.

Data sources limitation is expected to be low due to the mainly prospective design of the study. In case of unexpected or incorrect data, clarifications will be sought based on medical records. Any inconsistencies will be reviewed and resolved during frequent data extractions.

9.9.1 Internal Validity of Study Design

9.9.1.1 Selection Bias

There are 3 major areas of potential selection bias for the study. Firstly, recruited subjects should have metastatic stage of the disease and should receive at least one infusion of panitumumab in combination with chemotherapy prior to enrolment. There might be a small group of subjects who cease treatment after first dose, usually because of death or disease progression. The survival bias may be slightly inflated and impact other collected data. However, due to the prospective design of the study, subjects will

be alive at enrolment. For deceased subjects, the Safety Follow-up data will be impossible to obtain. The nature of an observational study involves some difficulties in obtaining data, therefore the bias of missing data is anticipated.

Lastly, subject selection may depend to a certain extend on the reimbursement which differs per country. Because of financial burden of treatment a more wealthy subject population may be enrolled that does not represent the selected countries population of subjects with mCRC. Different reimbursement policies may result in differences in subject characteristics in each country.

9.9.1.2 Confounding

Any confounding factors, such as demographic (eg, age, gender, country) or clinical characteristics (eg, primary tumour location, oxaliplatin-based chemotherapy for mCRC, irinotecan-based chemotherapy for mCRC) have been considered and the effort will be made to complement them during the study. For data analysis, the confounding factors will be controlled.

9.9.2 External Validity of Study Design

The planned selection of the study population assumes the inclusion of subjects who are currently treated with panitumumab in combination with chemotherapy.

Study population may depend on the type of recruitment centre. To avoid centre selection bias, two approaches are planned: to include a wide range of hospital types covering the entire area of the country and to review the data extractions frequently.

9.9.3 Analysis Limitations

The analysis could be limited by the availability of genetic data, like *RAS* status and other important biomarkers that are tested in centres with routine practice of liquid biopsy only.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

As the study design is mainly prospective, this will minimize missing data. There is a risk that there will be some incomplete data and it will not be possible to go back to the medical records to complete it adequately so incomplete data may need to be excluded from the analysis. We will be performing frequent data extractions to review any inconsistencies within the data.

10. Protection of Human Subjects

The study will comply with all the local applicable laws, regulations, and guidance regarding human subject protection. For more details, see Appendix A.4.

10.1 Informed Consent

An Informed Consent Form must be signed by the subject before enrolling in the study as per local regulations.

Before the subject medical chart may be used, the participating physician is responsible for obtaining written ICF from the subject, in order to have permission to use the necessary data, if applicable.

The acquisition of ICF should be documented in the subject's medical records, and the ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent and assent form should be provided to the subject.

10.2 Independent Ethics Committee (IEC)

The study will be conducted in accordance with country specific legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

All data will be handled in the strictest confidence in conformity with national and European data protection regulations (such as Directive 95/46/EC).

A copy of the protocol, and all other documents as per local regulation, must be submitted to the Ethics Committee and Regulatory Agency for written approval. A copy of the written approval of the protocol must be received by Amgen before the study can be executed.

The Sponsor must submit and obtain approval from the Ethics Committee and Regulatory Agency for all subsequent protocol amendments.

10.3 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained:

- On the CRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with age and/or year of birth on the demographics CRF.
- For ADRs, SADRs, product complaints and other reportable safety events reported to Amgen, subjects should be identified by their, age and/or year of birth and a subject identification number.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with local regulations, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC direct access to review the subject's original medical records for verification of study-related data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records, including personal information, without violating the confidentiality of the subject.

10.4 Subjects Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The Investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

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

11.1 Definition of Safety Events

11.1.1 Adverse Events

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

An adverse event can therefore be any unfavourable 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.

There is no requirement to monitor study subjects for adverse events after end of study. However, if adverse events are reported, the investigator is to report

them to Amgen or to the local health authorities.

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 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 events" 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 subject 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, out-patient surgery, or other events that require other urgent intervention.

11.1.3 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).

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

11.1.5 Safety Collection, Recording and Submission to Amgen Requirements

This study is analysing secondary data from sources including, but not limited to, administrative claims, electronic health records (EHR) and medical charts. The safety outcomes that are listed in section 9.3.2 will be documented on medical chart review forms and analysed in this study.

These will be reported in aggregate in the final OR study report as Tables, Figures and Listings.

See section 9.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

11.1.5.1 Prospective Observational Period

This study is collecting information from subjects ambidirectionally (retrospectively-prospectively). All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to

panitumumab will be collected from signing of informed consent form with the exception of the protocol exempted events listed in appendix G to final study contact. The Investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the subject's 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 Investigator awareness. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendars days of Investigator awareness.

If the electronic data capture (EDC) system is unavailable to the site staff, the adverse event which is considered serious must still be reported to Amgen within 1 business day of Investigator's awareness using the paper Adverse Event Contingency Report Form. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available. Non-serious Adverse Events (AEs) must be

reported in an expeditious manner, not to exceed 15 calendars days of Investigator awareness.

See Appendix B and Appendix D Additional Safety Reporting Information. 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 in the study documentation where safety data may also be recorded.

Protocol Exempted Events

Non-serious adverse events that are anticipated to occur in this study population because they are known adverse reactions to chemotherapy or are known to occur in the context of the underlying disease are not planned to be collected in this study. Exempted events are those adverse events that are listed as adverse reactions for panitumumab treatment in the European Medicinal agency's summary of product characteristics and not relevant for any of the study objectives.

Safety data on panitumumab are routine clinical care setting worldwide, panitumumab has been marketed for more than 11 years worldwide. In this single arm observational study, where only approximately 600 exposed patients will be enrolled, it is very unlikely that this will create any such substantial new pharmacovigilance data when adverse events not considered by the Investigator to have a causal relationship with panitumumab are collected. A list of all events and corresponding MedDRA preferred terms that are not to be collected in the study is provided in Appendix G.

Other safety findings and product complaints (see definitions in Section 11.1.3 for Other Safety Findings and 11.1.4 for Product complaints) are required to be collected and reported to Amgen in this study.

If any of the exempted events are serious or have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of Investigator awareness.

All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.

Protocol exempted events and safety events that are suspected to be related to any medicinal product other than panitumumab should be reported to the local authority in line with the local country requirements.

See Appendix B. Sample Safety Reporting Form(s) and Appendix C. Pregnancy and Lactation Notification Worksheets. 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 in the study documentation where safety data may also be recorded.

11.1.6 Collection of Pregnancy Information

11.1.6.1 Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant while taking Panitumumab through the study and 2 months after the last Panitumumab dose. Information will be recorded on the Pregnancy Notification Worksheet (see Appendix C). The worksheet must be submitted to Amgen Safety within 1 business day of learning of a subject's pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws). After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information.

After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking Panitumumab through the study and 2 months after discontinuation of Panitumumab. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

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

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

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a foetal or neonatal congenital anomaly) the Investigator will report the event as a serious adverse event.

Any adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to Amgen Safety within 1 business day.
Any female subject who becomes pregnant while participating will discontinue Panitumumab

11.1.6.2 Male Subjects With Partners Who Become Pregnant

In the event a male subject fathers a child during treatment, and for an additional 2 months after discontinuing Panitumumab, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Appendix C) must be submitted to Amgen Safety within 1 business day of the Investigator awareness of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.
Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of foetal status (presence or absence of anomalies) or indication for procedure.

11.1.7 Collection of Lactation Information

Investigator will collect lactation information on any female subject who breastfeeds while taking Panitumumab through the study and 2 months after the last Panitumumab dose. Information will be recorded on the Lactation Notification Worksheet (see Appendix C) and submitted to Amgen Safety within 1 business day

of the Investigator's awareness. Study treatment will be discontinued if female subject breastfeeds during the study.

After receipt of the Lactation Notification Worksheet, Amgen Safety will provide Investigator with an authorisation form and questionnaire to collect additional information. With the female subjects signed authorization for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking Panitumumab through the study and 2 months after discontinuing Panitumumab.

11.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, Institutional Review Boards (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. The IEC must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IEC 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 IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several Principal Investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other Investigators and to collaborate with authors and Amgen staff as defined in the Publication Charter. Membership on the committee (both for Investigators and Amgen

staff) does not guarantee authorship—the criteria described below should be met for every publication.

13.1 Publication Policy

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) 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, multicentre 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.

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15. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number.	Date	Title
1	B	01 Feb 2016	Sample Safety Reporting Form
2	C	27 Mar 2011 & 03 Apr 2012	Pregnancy and Lactation Notification Worksheets
3	D	27JuL 2018	Additional Safety Reporting Information
4	E	12 Jul 2018	Schedule of Assessments
5	F	12 Jul 2018	Functional Assessment of Cancer Therapy-EGFRI-18
6	G	26 Nov 2018	Protocol Exempted Events

A.1. Contact details of responsible party

Clinical Study Sponsor:	Amgen Ltd. 240 Cambridge Science Park, Milton Road, Cambridge, UK Phone: Fax:
Key Sponsor contacts:	PPD Therapeutic Area Head Oncology/Haematology, Europe North East - Medical Amgen (Europe) GmbH Dammstrasse 23 CH-6301 Zug Switzerland

Appendix B. Sample Safety Reporting Form(s)

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for Observational Research Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

What to report on this form:

- **All adverse events 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 adverse event**
  - **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 ONLY IF ASSOCIATED WITH AN ADVERSE EVENT**

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**
- **Product complaints without association with an AE**

1. **Site Information**
   Site Number* – Enter your assigned site number for this study
   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested
2. **Subject Information**
   Subject ID Number* – Enter the entire number assigned to the subject
   Age at event onset, Sex, and Race – Enter the subject's demographic information
   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. **Adverse Event**
   Provide the date the Investigator became aware of this Information
   Adverse Event 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.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalizion. 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.**
   Date Ended – Enter date the adverse event 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.
   Is event serious?* – Indicate Yes or No. This is a mandatory field.
   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   Immediately life-threatening: Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

4. **IP Administration including Lot # and Serial # when known / available.**
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg. Rave) when it becomes available.

criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

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. **This is a mandatory field.**

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)**

Outcome of Event – Enter the code for the outcome of the event at the time the form is completed if outcome is known.
Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

5. **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 adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

6. **Amgen drug Under Study Administration including Lot # and Serial # when known / available.**
Initial Start Date – Enter date the product was first administered, regardless of dose.
Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
Action Taken with Product – Enter the status of the product administration.

7. **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

8. **Relevant Medical History**
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. **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.

10. **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).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

11. **Case 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 page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

A Study 20170734 Vectibix	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the **EDC system (eg, Rave)**, provide the adverse event term: _____
and start date: Day ____ Month ____ Year _____

3. ADVERSE EVENT

Provide the date the investigator became aware of this information: Day ____ Month ____ Year ____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study?								Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						<drug/device>		<drug/device>		<drug/device>		<drug/device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 08 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

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Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<< Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg. chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Test / Unit / Date Day Month Year												

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

A Study 20170734 Vectibix	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

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-ees-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20170734

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115129 Version 1.0 Effective Date: 24-Sept-2015

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8658, Non-US fax: +44 (0)207-136-1046 or email (worldwide): sr-eep-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20170734

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 withdrew from the study? ☐ Yes ☐ No

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

Appendix D. Additional Safety Reporting Information

For oncology studies, the CTCAE is to be used. The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

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

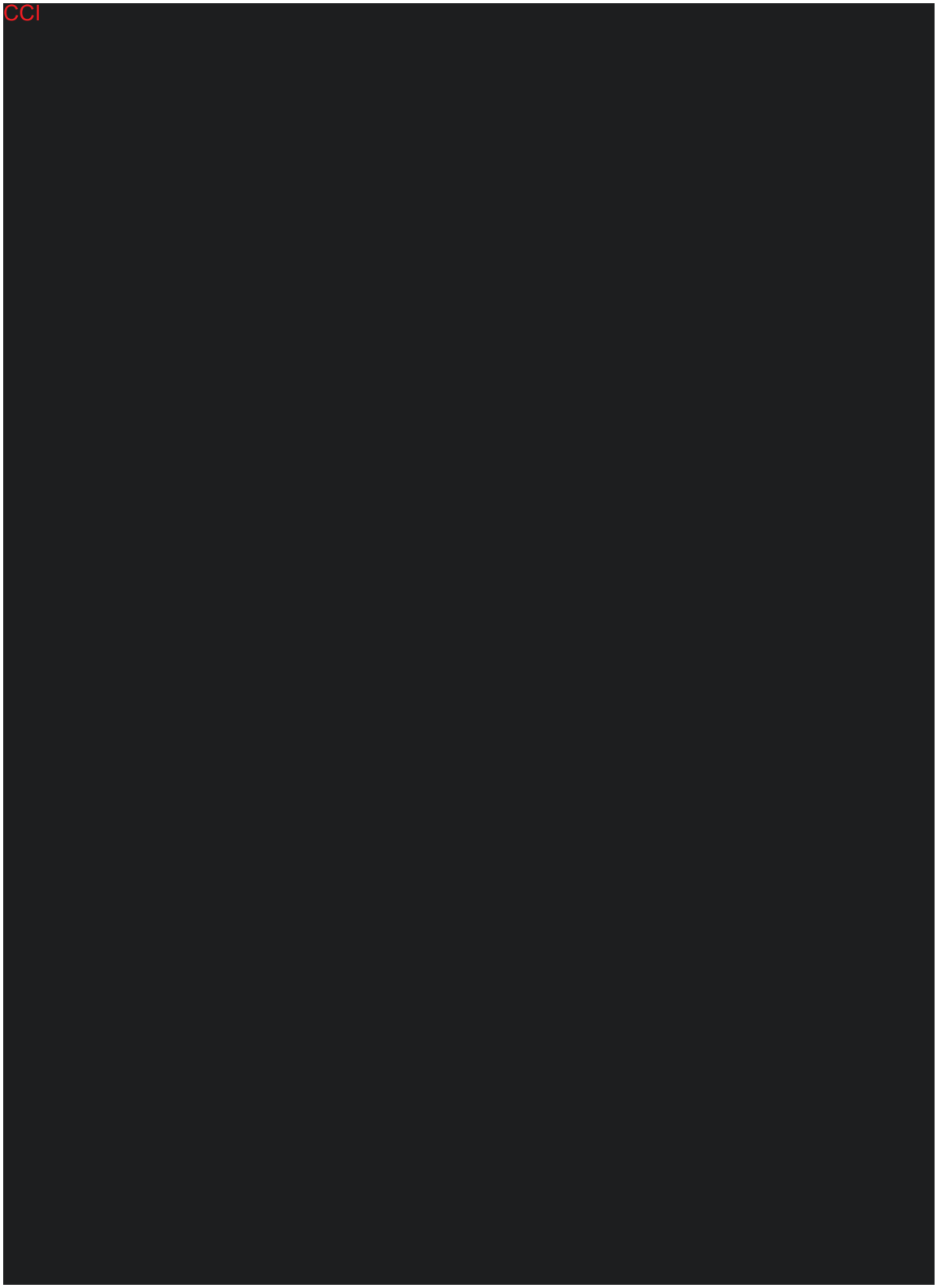
Appendix E. Schedule of Assessments

Data to be collected	Baseline[a]	Observation Period		
		Monthly follow-up date[b]	Safety follow up[c]	End of Study
Enrollment	x			
Demographics	x			
Targeted medical history	x			
Physical measurement	x	x		
Vital Signs	x	x		
Events (Observational study)		x	x	x
Concomitant medications	x	x	x	x
1st line of treatment	x	x		
2nd line of treatment		x		
Panitumumab administration	x	x		
Substance use	x			
Laboratories	x	x	x	
Reproductive status	x			
ECOG performance status	x	x		
Disease history	x			
Tumor evaluations	x	x	x	
Site characteristics	x			

[a]Baseline will be from 1 to maximum 12 months preceding enrolment in the study
[b]Data will be collected for 15 months
[c]This is 30 days after the end of 1st line of treatment

Appendix F. Functional Assessment of Cancer Therapy-EGFRI-18

CCI



Appendix G. Protocol Exempted Events

MedDRA System Organ Class	MedDRA Prefferd Term(s)
Infections and infestations	Conjunctivitis Urinary tract infection Localised infection Eye infection
Blood and lymphatic system disorders	Anaemia Leucopenia
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Hypocalcaemia Dehydration Hyperglycaemia Hypophosphataemia
Psychiatric disorders	Insomnia
	Anxiety
Nervous system disorders	Headache Dizziness
Eye disorders	Blepharitis Lacrimation increased Ocular hyperaemia Dry eye Eye pruritus
Cardiac disorders	Tachycardia Cyanosis
Vascular disorders	Deep vein thrombosis Hypotension Hypertension Flushing
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough Pulmonary embolism Epistaxis Interstitial lung disease[3] Bronchospasm Nasal dryness
Gastrointestinal disorders	Nausea Vomiting Abdominal pain Constipation Rectal haemorrhage Dry mouth Dyspepsia Aphthous ulcer Cheilitis Gastro-oesophageal reflux disease Chapped lips Dry lips
Musculoskeletal and connective tissue disorders	Back pain Pain in extremity

General disorders and administration site conditions	Fatigue Pyrexia Asthenia Mucosal inflammation Oedema peripheral Chest pain Pain Chills