Title: Prospective Observational Cohort Study to Describe the Use of Vectibix® in Combination With Chemotherapy in Routine Clinical Practice for Patients With Wild-type *KRAS* Metastatic Colorectal Cancer

Vectibix® (Panitumumab) Amgen Protocol Number 20120100

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Version 3

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Investigator's Agreement

I have read the attached protocol entitled Prospective Observational Cohort Study to Describe the Use of Vectibix® in Combination With Chemotherapy in Routine Clinical Practice for Patients With Wild-type *KRAS* Metastatic Colorectal Cancer, dated 25 July 2012, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable regulations/guidelines.

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

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Title: Prospective Observational Cohort Study to Describe the Use of Vectibix® in Combination With Chemotherapy in Routine Clinical Practice for Patients With Wild-type *KRAS* Metastatic Colorectal Cancer

Indication: Vectibix® in combination with FOLFOX for first-line treatment and in combination with FOLFIRI for second-line treatment in patients who have received first–line fluoropyrimidine-based chemotherapy (excluding irinotecan) for the treatment of patients with metastatic colorectal cancer (mCRC) with tumour expressing wild-type (non-mutated) Kirsten rat sarcoma viral oncogene homolog (*KRAS*)

Objectives

Study Objectives

Primary

- Describe the pattern of use of Vectibix® in combination with chemotherapy in subjects with wild-type *KRAS* metastatic colorectal cancer (mCRC): as first-line treatment in combination with FOLFOX or second-line treatment in combination with FOLFIRI in subjects who have received first–line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Secondary

- Describe key healthcare resource utilization indicators attributed to treatment and clinical management of mCRC.
- Describe key clinical indicators (demographics, disease characteristics, individual treatment goals co-morbidities and prior treatment history).
- Describe response to Vectibix® in routine clinical practice (including best response and conversion to resectability if available and by individual treatment goals if applicable).
- Provide overview of planned anti-cancer treatments initiated post Vectibix® discontinuation.

Hypotheses: A formal hypothesis will not be tested in this study. However, planned descriptive analyses will characterize the mCRC patient population who are treated in routine clinical practice, with Vectibix® as first-line treatment in combination with FOLFOX or second-line treatment in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Outcomes:
Primary

- Treatment patterns of Vectibix® and concomitant chemotherapy for mCRC, will be described, including information on:
  - Type of chemotherapy combined with Vectibix®
  - Starting dose and dose administration schedule of Vectibix® and chemotherapy
  - Cumulative dose, maximum dose, duration of exposure and total number of infusions received from the initiation of Vectibix® therapy and chemotherapy
  - Dose reductions and/or delays and reason(s) for dose reduction and delays of Vectibix® and/or concomitant chemotherapy
  - Discontinuation and reason(s) for discontinuation of Vectibix® and chemotherapy

Secondary

- The following will be described and tabulated:
  - Healthcare resource utilization including type of visit (inpatient, outpatient, ER, other) and reason for hospitalisation
  - Demographics, disease characteristics, co-morbidities, individual treatment goals and prior treatment history
  - Response to Vectibix®, if documented, including best response, conversion to resectability, and by individual treatment goals
  - Summaries of planned anti-cancer treatment initiated post Vectibix® discontinuation

Study Design

This is a multicenter, observational prospective cohort study in France and Germany. All treatment centres (inpatient and outpatient) with a focus on treating subjects with mCRC in participating countries will be prospectively defined for potential inclusion in the study. Centres will be selected to represent academic, oncology and specialist settings and to provide geographical diversity within each country. Eligible subjects will be enrolled and have retrospective data collected from Baseline (which occurs prior to the first dose of Vectibix®) up to the point of enrolment. All subsequent chemotherapy cycles and Vectibix® doses will be recorded prospectively. Each subject will have data collected until approximately 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up or up to 12 months from the first dose of Vectibix®, whichever occurs first.

In accordance with applicable data privacy laws in Germany and France, data will be obtained from routine clinical records and transcribed onto an electronic case report form (eCRF) which will be in three parts:

(i) Baseline
(ii) Follow-up throughout the observation period (based on physician preferences for follow up)
(iii) End of observation (EOO) – approximately 30 days after the end of Vectibix® treatment or 12 months from the initiation of Vectibix®, whichever occurs first (unless preceded by subject death, loss to follow up or withdrawal of consent)

Sample Size: Approximately 740 subjects with wild-type *KRAS* mCRC (up to 350 in France and up to 390 in Germany). Enrolment into the study will be capped by country according to these pre-specified numbers.

Study Participants: Subjects with KRAS wild-type mCRC treated with Vectibix® according to the indication specified in France and Germany that meet the eligibility criteria for this study.

Eligibility Criteria: The decision to prescribe treatments must have been freely undertaken by the clinician prior to consideration for the subject to be included in the study. Therefore, treatment administration will be independent and dissociated from participation in the study.

Inclusion Criteria

- Subject is ≥ 18 years of age at date of enrolment
- Histologically or cytologically confirmed carcinoma of colon or rectum
- Subject with metastatic carcinoma of colon or rectum
- Confirmed wild-type KRAS status of tumour
- Subjects whose care will be managed primarily by the enrolling physician and/ or all records will be available
- Tumour assessment (ie, CT/MRI) within 12 weeks (84 days) prior to first Vectibix® infusion.

- Subjects treated with at least one infusion of Vectibix® in combination with chemotherapy a maximum of 42 days before entering study: first-line in combination with FOLFOX or second-line in combination with FOLFIRI in subjects who have received first–line fluoropyrimidine-based chemotherapy (excluding irinotecan) for treatment of wild-type KRAS mCRC per approved prescribing information
- Subject or subject's legally acceptable representative has provided informed consent (for countries where required per local regulations)

Exclusion Criteria

- Ongoing or planned concurrent participation in any clinical study involving Investigational Product that has not been approved by the European Medicines Agency for any indication
- Ongoing or planned concurrent participation in any clinical study where the dosing of Vectibix® is determined by the protocol (participation in clinical trials on an approved drug and observational trials are permitted but these cannot mandate how mCRC should be treated)

Procedures:

This is a non-interventional study. Data will be collected where available and where the procedure is conducted per routine clinical practice

Baseline:

The following is a summary of key data to be collected at baseline.

- Physician's speciality
- Type of centre and treatment setting (inpatient vs. outpatient)
- Number of cancer patients seen per year by centre
- Date and confirmation of subject informed consent, where applicable by local regulations
- Subject demographics: sex, age
- Medical history: all significant co-morbidities, including information on cardiac, respiratory, metabolic function
- SADRs and ADRs to Amgen product
- Subject metastatic colorectal cancer (mCRC) history
  - Dated of primary CRC diagnosis and date of metastasis diagnosis
  - Site of primary tumour: rectum vs. colon, right vs. left colon
  - Synchronous vs metachronous mCRC
  - Sites of metastatic disease: liver, lung, other
  - Number of metastases overall and lesions by site
  - Tumour related symptoms (eg, pain, discomfort)
- Prior treatment history for CRC
  - All prior treatments for CRC and/or mCRC management including surgical procedures, radiotherapy, chemotherapy, biological therapy and/or other systemic anticancer therapy including initial Vectibix® plus chemotherapy infusions, other procedures, and dates of relapse and progression
- Subjects treatment goal
- Resection status
- Tumour *KRAS* status method and date of *KRAS* testing, if available. Data on other biomarkers, if conducted, will also be collected.
- ECOG performance status

- Physical examination (abbreviated) including height, body weight

The following key data will also be collected at baseline where available. This data must be generated prior to the subjects first dose of Vectibix®:

- All baseline laboratory tests performed prior to the subject receiving their first dose of Vectibix

Follow-up Observation Period

Follow-up data post initiation of Vectibix® treatment will be collected at the next patient visit (based on physician preferences for follow up), and throughout the observation period until 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up, or up to 12 months from the first dose of Vectibix®, whichever occurs first:

- Vectibix® treatment pattern including:
  - Start and stop dates
  - Dose and schedule
  - Total number of infusions received
  - Dose reductions, dose delays, and reasons for dose reductions or delays
  - Reason for treatment discontinuation
- Concomitant anti-cancer therapy for mCRC including surgical procedures, radiotherapy, chemotherapy, biological therapy and/or other systemic anticancer therapy, and other procedures. Data to include:
  - Type of therapy
  - Start and stop dates
  - Dose, route, and frequency (if applicable)
  - Reason for cessation of therapy
- Tumour response follow up (eg, radiological imaging of sites of disease or investigator's assessment of tumour response)
- Resection status
- Healthcare resource utilization including type of visit (inpatient, outpatient, ER, other) and reason for hospitalisation
- Relevant concomitant medication
- SADRs and ADRs to Amgen product

End of Observation Visit

Documentation at the end of observation visit is required (defined as completion of 12-month observation period, death, withdrawal of consent, or loss to follow-up; whichever occurs first):

- Date and reason for ending study:
  - 12-month observation period reached
  - Discontinuation of Vectibix® treatment – date and reason for ending Vectibix® treatment
  - Death – date and primary cause of death to be recorded
  - Loss to follow-up
  - Withdrawal of informed consent
- Planned anti-cancer treatments initiated post Vectibix® discontinuation
- SADRs and ADRs to Amgen product

Statistical Considerations: The analysis of this study will be descriptive in nature. The data will be summarised for mCRC subjects with wild-type *KRAS* status who received Vectibix® as first-line treatment in combination with FOLFOX and separately for subjects who received Vectibix® in combination with FOLFIRI as second-line treatment in subjects who have received first–line fluoropyrimidine-based chemotherapy (excluding irinotecan). The data will be summarized by country. Selected sensitivity analyses may be performed if appropriate. For continuous outcomes, the mean, standard deviation, median, and range will be provided. For categorical variables, the frequency and percentage will be displayed. The percentage with two-sided 95% CI for the treatment pattern of Vectibix® (eg, cumulative proportion (over specified time period) of subjects with Vectibix® dose change) will be calculated. Duration of exposure, total number of infusions received, and the chemotherapy combined with Vectibix® will be summarized.

Rationale: The data being collected is to anticipate expected reimbursement agency requirements in Germany and France. The requirements focus on gaining a clear understanding of the real life use of Vectibix® in accordance with the new label, and so the objectives in this study have been defined to meet such requirements. This study will thus be conducted to gain understanding of Vectibix® use for the treatment of subjects with wild-type *KRAS* mCRC, in first-line in combination with FOLFOX or second-line in combination with FOLFIRI in routine clinical practice.

Figure 1. Sample Selection Flowchart

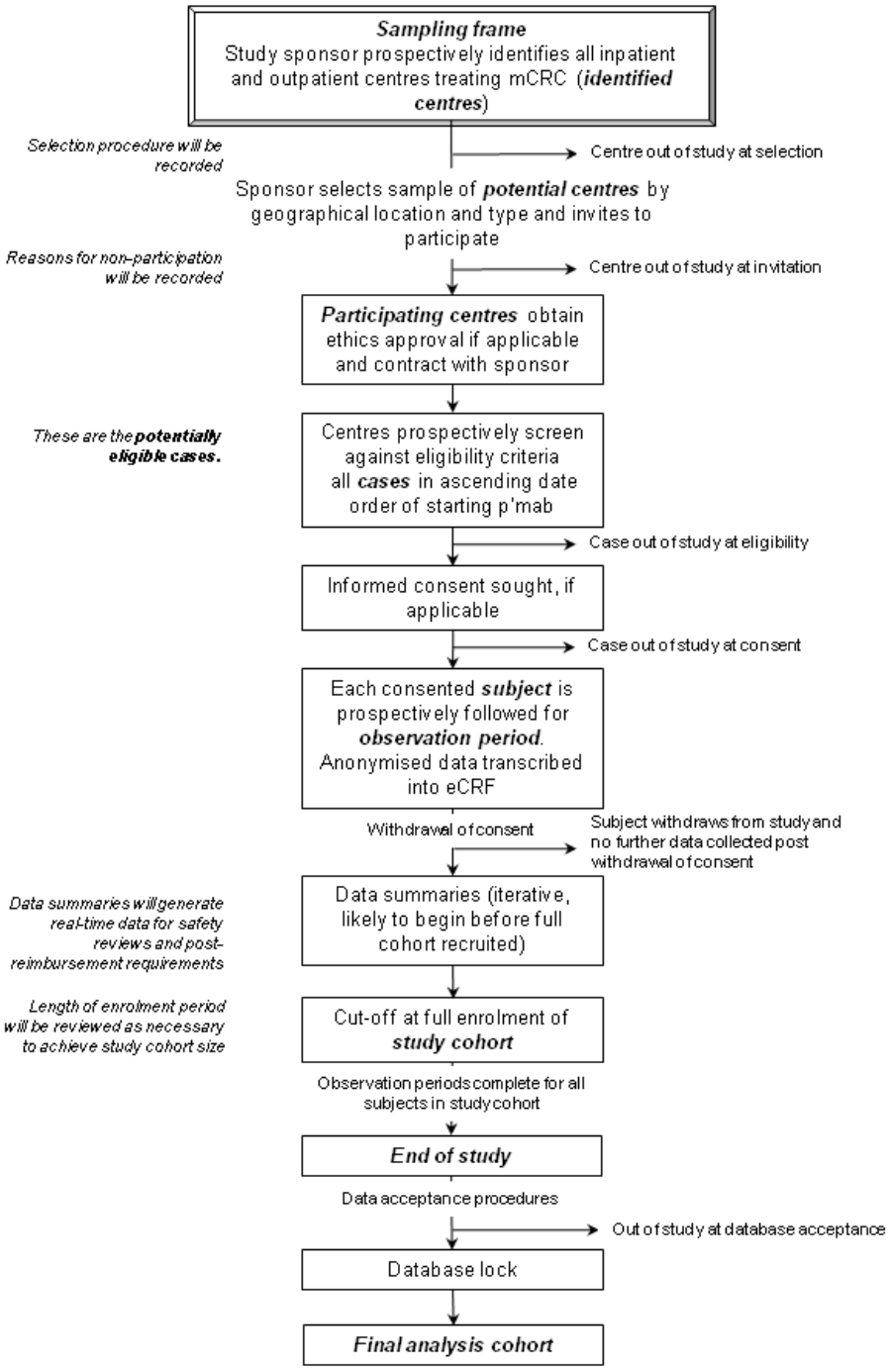

Figure 2. Study Design and Follow-up Schema

Eligibility criteria:
List of subsequent subjects with following characteristics:

- ≥ 18 years of age at date of enrolment
- Histologically or cytologically confirmed carcinoma of colon or rectum
- Subject with metastatic carcinoma of colon or rectum (mCRC)
- With known wild-type *KRAS* status
- subjects whose care will be managed primarily by the enrolling physician and/ or all records will be available
- Tumour assessment (ie, CT/MRI) within 12 weeks (84 days) prior to first Vectibix® infusion
- Subjects treated with at least one infusion of Vectibix® in combination with chemotherapy a maximum of 42 days before entering study:
  - 1st line with FOLFOX
  - 2nd line with FOLFIRI (where subject previously received 1st line fluoropyrimidine-based chemotherapy excluding irinotecan)
- Subject or subject's legally acceptable representative has provided informed consent (for countries where required per local regulations)

Day 1 = date of first dose of Vectibix® (prior to enrolment)

End of treatment = day of last dose of Vectibix®

End of Observation: Follow-up until approximately 30 days after the end of treatment, death, loss to follow-up, withdrawal of consent, or 12 months after first dose of Vectibix®, whichever occurs first

Baseline:
Collect data on:

- Subject demographic and tumor characteristics
- Disease and treatment history
- Co-morbidities
- Subjects performance status & physical exam
- Resection status
- KRAS status and other biomarkers
- laboratory parameters (taken before first dose of Vectibix®)
- ADR and SADRs to Amgen products

Follow-up:
Collect data on:

- Vectibix® and concomitant anti-cancer therapy usage
- Concomitant medication
- Healthcare Resource Utilization
- Tumor response
- Resection status
- ADR and SADRs to Amgen products

End of Observation Visit:

- Collect data on date and reason for ending study
- Planned anti-cancer treatments initiated post Vectibix® discontinuation
- ADR and SADRs to Amgen products

Glossary

Abbreviation or Term	Definition/Explanation
5-FU	5-fluorouracil
ADR	Adverse drug reaction
BSC	Best supportive care
CI	Confidence interval
CRC	Colorectal cancer
CRO	Contract Research Organisation
CRF	Case report form
CT	Computerized tomography
DRG	Diagnosis related group
ECOG	Eastern Cooperative Oncology Group
EOO	End of observation
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EDC	Electronic data capture
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Emergency room
FLFAS	First Line Full Analysis Set
FOLFOX	FOL (Folinic acid, Leucovorin) F (Fluorouracil – 5FU) OX (Oxaliplatin)
FOLFIRI	FOL (Folinic acid, Leucovorin) F (Fluorouracil – 5FU) IRI (Irinotecan)
ICH GCP	International Conference on Harmonization Good Clinical Practice
ICU	Intensive Care Unit
IEC	Independent ethics committee
IFL	Irinotecan, leucovorin (folinic acid), and fluorouracil
KRAS	Kirsten rat sarcoma viral oncogene homolog
mCRC	Metastatic colorectal cancer
MRI	Magnetic resonance imaging
NCI-CTC	National Cancer Institute Common Terminology Criteria
OS	Overall survival
PFS	Progression-free survival
RECIST	Response Evaluation Criteria In Solid Tumours
SADR	Serious adverse drug reaction
SLFAS	Second Line Full Analysis Set

Abbreviation or Term	Definition/Explanation
SmPC	Summary of Product Characteristics
VEGF	Vascular Endothelial Growth Factor
Source Data	Information from an original record or certified a copy of the original record containing patient information for use in observational research. The information may include, but is not limited to observations necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). Examples of source data include Subject ID.
Study day 1	Defined as the first day that Vectibix® was administered in combination with chemotherapy to the subject in routine clinical practice
End of observation (EOO) for individual subject	Defined as the last day that protocol-specified observation data is collected for an individual subject. Subjects will be followed-up until approximately 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up, or up to 12 months from the first dose of Vectibix®, whichever occurs first. This will also mark the end of study for a subject.
End of observation (EOO)	Defined as when the last subject is followed-up for the purposes of final collection of observation data. The study will end when the last subject remaining on the study either completes the 12-month observation period, dies, withdraws informed consent, or is lost to follow-up (whichever occurs first)
Individual treatment goals	Treatment goal for each subject in first-line treatment defined by their treating physician. These could include but are not limited to • Clear complete resection of metastasis (ie, option for curative resection) – “curative resection”; *or* • Need for maximum tumour shrinkage potentially enabling resection of metastatic disease limited to lung, liver and/or resectable sites – “maximum tumour shrinkage”; *or* • Tumour shrinkage and/or control of progressive disease of multiple disease location – “clinically relevant tumour shrinkage”; *or* • Disease control to prevent further progression – “disease control”.

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1. OBJECTIVES

Primary

To describe the pattern of use of Vectibix® in combination with chemotherapy in subjects with wild-type Kirsten rat sarcoma viral oncogene homolog (*KRAS)* metastatic colorectal cancer (mCRC): as first-line treatment in combination with FOLFOX or second-line treatment in combination with FOLFIRI in patients who have received first–line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Secondary:

- Describe key healthcare resource utilization indicators attributed to treatment and clinical management of mCRC
- Describe key clinical indicators (demographics, disease characteristics, individual treatment goals, co-morbidities and prior treatment history).
- Describe response to Vectibix®, if documented, including best response, conversion to resectability, and by individual treatment goals.
- Provide overview of planned anti-cancer treatments initiated post Vectibix® discontinuation.

2. BACKGROUND AND RATIONALE

2.1 Disease

Worldwide an estimated 1.24 million new cases of colorectal cancer were diagnosed in 2008, Colorectal cancer is the third most common cancer in men (664 000 cases, 10.0% of the total) and the second in women (571,000 cases, 9.4% of the total) worldwide (Ferlay, 2010). In 2008 there were an estimated 334,000 new cases of colorectal cancer in the European Union (EU27) (Ferlay, 2010). Of newly diagnosed patients, 15% to 25% have metastatic disease at diagnosis (Kindler and Shulman, 2001) and up to 50% of all patients eventually develop metastatic disease (Kindler and Shulman, 2001; McLeod et al, 2000). If diagnosis is made early, CRC is generally curable, with a 5-year survival rate over 90% (National Cancer Intelligence Network, 2009 and American Cancer Society, 2008). However, the 5-year survival rate in patients with metastatic disease is still very low: approximately 8% (Kindler and Shulman, 2001; Pazdur et al, 1999). A subset of patients with liver confined disease who are surgically resectable derive prolonged survival benefit. With present therapies this subset encompasses approximately 10-25% of all patients (Petrelli et al, 2005, Benoist et al, 2006, McLoughlin et al, 2006).

Given the availability of multiple effective cytotoxic agents, the development of targeted therapeutics, and the emergence of potential predictive biomarkers such as *KRAS*

(Normanno et al, 2009), the approach to the treatment of mCRC has undergone substantial evolution within the last ten years. Current treatment of mCRC is based on sequential lines of chemotherapy with or without a targeted therapy, but disease progression is an expected eventuality. Oxaliplatin- and irinotecan-based therapies are recognized as appropriate first- and second-line therapies for mCRC in patients with good performance status (National Comprehensive Cancer Network, 2010; Current French Clinical Guidance, 2009; German Clinical Guidance, 2008; UK National Institute for Health and Clinical Excellence, 2005). Studies have shown that in combination with 5-fluorouracil (5-FU), oxaliplatin and irinotecan-containing regimens are effective in both the initial and second-line setting regardless of the sequence of administration (National Comprehensive Care Network, 2010; Tournigand et al, 2004). The biologic therapies, bevacizumab (Avastin®, anti-VEGF is a registered trademark of Roche Pharma/Genentech, Inc.) and cetuximab (Erbitux®, anti-EGFR is a registered trademark of Merck KGaA, Bristol-Meyers Squibb and Eli Lilly), are also approved for the treatment of mCRC (note: in Europe and Canada cetuximab is approved for the treatment of patients with *KRAS* wild-type tumours) (Avastin® [bevacizumab] prescribing information, 2009; Avastin® [bevacizumab] Summary of Product Characteristics, 2009; Avastin® [bevacizumab] Product Monograph, 2009; Erbitux® [cetuximab] Summary of Product Characteristics, 2009; Erbitux® [cetuximab] Product Monograph, 2010).

In November 2011, the European Commission granted an extension of the indication for the use of Vectibix® (panitumumab) as follows:

> *Vectibix® is indicated for the treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC):*
>
> - *in first-line in combination with FOLFOX*
> - *in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).*
> - *as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.*

This approval was based on:

(i) Results of the PRIME study which evaluated the effect of panitumumab + FOLFOX versus FOLFOX alone in subjects with wild-type KRAS mCRC.

(ii) The 20050181 study which showed that adding panitumumab to FOLFIRI in subjects with wild-type KRAS mCRC resulted in increased PFS and response rate.

(iii) Other supportive clinical studies.

The original conditional marketing authorisation for Vectibix® was granted by the European Commission in December 2007 and prior to November 2011, Vectibix® was indicated in the EU as follows:

> *Vectibix® is indicated as monotherapy for the treatment of patients with EGFR expressing mCRC with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.*

This approval was based on a retrospective analysis from the first phase 3 trial (20020408) analyzed by *KRAS* status.

2.2 Vectibix® (Panitumumab) Background

Vectibix® (Panitumumab) is a high-affinity (k_d 5 x 10^{-11} M), human immunoglobulin G2 (IgG2) monoclonal antibody directed against human EGFR (Davis et al, 1999; Yang et al, 1999). Panitumumab blocks EGFR binding of epidermal growth factor (EGF), transforming growth factor-alpha (TGFα), amphiregulin, betacellulin, epiregulin, and heparin-binding EGF.

2.2.1 Vectibix® (Panitumumab) Clinical Experience in mCRC – Safety

The clinical safety profile of panitumumab as monotherapy and in combination with chemotherapy is based on results from clinical studies in subjects with a variety of solid tumours. These studies indicated that panitumumab is generally well tolerated. Twenty of these studies involved subjects with mCRC (n = 2588 receiving panitumumab as a single agent or in combination). In these subjects, dermatologic-related toxicities were the most frequently reported adverse events (93% of subjects), with most events being mild to moderate. Relatively few subjects (2%) permanently discontinued panitumumab due to dermatologic adverse events. Infusion reactions to panitumumab (defined as any reported allergic reaction, anaphylactoid reaction, chills, fever, or dyspnoea, occurring within 24 hours of the first dose that were not otherwise designated as either anaphylactoid or allergic reaction) were infrequent (3% of subjects; < 1% serious); premedication was not mandated in study protocols. Panitumumab immunogenicity, as measured by enzyme-linked immunosorbent assay (ELISA) and Biacore assay, was very low. Compared with subjects who did not develop antibodies, no relationship

between the presence of anti-panitumumab antibodies and the safety of panitumumab was observed, although the small sample size limits these analyses.

In an analysis of 4 mCRC monotherapy studies (20020408, 20030194, 20030167, and 20030250), no significant differences in the adverse event profile of panitumumab were observed between subjects with wild-type *KRAS* and subjects with mutant *KRAS* when adjusted for duration of exposure.

The clinical safety profile of panitumumab in combination with chemotherapy is based on results from 9 clinical studies with data from 1536 subjects, including 585 subjects who received panitumumab in combination with oxaliplatin-based chemotherapy and 951 subjects who received panitumumab in combination with irinotecan-based chemotherapy. These data primarily consist of results from Studies 20050203 and 20050181.

The safety results of the two pivotal studies (20050203, first-line treatment with oxaliplatin and 20050181, second-line treatment with irinotecan) indicate a tolerable safety profile for panitumumab when administered in combination with chemotherapy to subjects with wild-type *KRAS* mCRC as initial and second-line therapy.

In subjects treated with oxaliplatin, the rate of grade 3 or 4 adverse events and serious adverse events was higher for panitumumab plus chemotherapy relative to chemotherapy alone, primarily due to toxicities known to be associated with panitumumab; however, the rate of discontinuation of chemotherapy was similar between treatments arms, suggesting that these events were clinically manageable. In subjects with mutant KRAS tumours, the negative effect in the panitumumab + FOLFOX arm relative to chemotherapy alone was greater for subjects receiving FOLFOX than for those receiving FOLFIRI.

In subjects treated with irinotecan, the subject incidence of grade 3 or 4 adverse events and serious adverse events was higher for panitumumab plus chemotherapy relative to chemotherapy alone, although the overall subject incidences were lower in both treatment arms than those observed in subjects who received oxaliplatin. Events were consistent with the effects of panitumumab and the underlying chemotherapy and were manageable. A negative effect was not seen in subjects with mutant *KRAS* tumours who received panitumumab in combination with irinotecan-based chemotherapy; however, there was also no evidence of benefit.

Vectibix® should not be administered in combination with chemotherapy and bevacizumab. A randomised, open-label, multicentre study of 1,053 patients evaluated the efficacy of bevacizumab and oxaliplatin- or irinotecan-containing chemotherapeutic regimens with and without Vectibix® in the first-line treatment of metastatic colorectal cancer. Shortened progression free survival time and increased deaths were observed in the patients receiving Vectibix® in combination with bevacizumab and chemotherapy. A greater frequency of pulmonary embolism, infections (predominantly of dermatologic origin), diarrhoea, electrolyte imbalances, nausea, vomiting and dehydration was also observed in the treatment arms using Vectibix® in combination with bevacizumab and chemotherapy. An additional analysis of efficacy data by *KRAS* status did not identify a subset of patients who benefited from Vectibix® in combination with oxaliplatin- or irinotecan-based chemotherapy and bevacizumab. A trend towards worse survival was observed with Vectibix® in the wild-type *KRAS* subset of the bevacizumab and oxaliplatin cohort, and a trend towards worse survival was observed with Vectibix® in the bevacizumab and irinotecan cohort regardless of *KRAS* mutational status.

National Cancer Institute Common Terminology Criteria (NCI-CTC) grade 3-5 pulmonary embolism occurred at a higher rate in subjects treated with Vectibix® (7% vs. 4%) and included fatal events in three (< 1%) subjects treated with Vectibix®.

As a result of the toxicities experienced, subjects randomized to Vectibix®, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study, compared with those randomized to bevacizumab and chemotherapy.

In a single-arm study of 19 subjects receiving Vectibix® in combination with irinotecan, leucovorin (folinic acid), and fluorouracil (IFL), the incidence of NCI-CTC grade 3-4 diarrhoea was 58%; in addition, grade 5 diarrhoea occurred in one subject. In a single-arm study of 24 subjects receiving Vectibix® plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhoea was 25%.

Severe diarrhoea and dehydration, which may lead to acute renal failure and other complications, have been observed in subjects treated with Vectibix® in combination with chemotherapy.

Refer to the current Vectibix® [panitumumab] Summary of Product Characteristics (SmPC) for further details regarding the safety of panitumumab as monotherapy and in combination with chemotherapy in mCRC.

2.2.2 Vectibix® (Panitumumab) Clinical Experience in mCRC – Efficacy

Results from a multicenter, randomized (1:1), controlled phase 3 study (Study 20020408) of panitumumab plus best supportive care (BSC) vs. BSC alone demonstrated a statistically significant improvement in the primary efficacy endpoint of progression-free survival in subjects with metastatic colorectal cancer (mCRC) who had disease progression during or after prior standard fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy, ie, a 46% reduction in the rate of disease progression or death compared with BSC alone. Furthermore, 10% of subjects in the panitumumab plus BSC group and no subject in the BSC alone group had an objective response according to modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria by central review (all partial responses). An additional 26% of subjects in the panitumumab plus BSC group and 10% of subjects in the BSC alone group had a best response of stable disease.

Results from 5 supportive mCRC studies (20025405, 20030167, 20030250, 20030194, and 20050216) confirmed the anti-tumour activity of panitumumab (as measured by objective response rates) in subjects with mCRC who failed prior irinotecan and/or oxaliplatin therapy. In addition, after completion of Study 20020408, a prespecified statistical analysis plan was defined to evaluate *KRAS* status in relation to outcomes; this plan was finalized prior to any *KRAS* testing. This analysis of Study 20020408 showed that *KRAS* mutation status serves as a predictive biomarker of response in the setting of panitumumab monotherapy in subjects with mCRC who have failed prior therapy. These data suggest that improvements in progression-free survival (PFS) and objective response rate are restricted to subjects with *KRAS* wild-type tumours.

Results from 2 phase 3, pivotal studies (20050203 and 20050181) provide efficacy data on panitumumab in combination with chemotherapy as initial or second-line treatment in the mCRC setting. Both of these studies were open-label, randomized trials of panitumumab plus chemotherapy versus chemotherapy alone. Oxaliplatin-based chemotherapy (FOLFOX) and irinotecan-based chemotherapy (FOLFIRI) were selected for these studies because they were among the standard of care in this setting when these trials were designed.

Results from the 20050203 and 20050181 pivotal studies demonstrated that in subjects with wild-type *KRAS* tumour status, panitumumab resulted in a statistically significant and clinically relevant improvement in PFS when combined with chemotherapy relative to chemotherapy alone in Study 20050203 (FOLFOX) (median of 10.0 vs. 8.6 months; hazard ratio 0.799; 95% confidence interval (CI): 0.674, 0.946; log-rank test p = 0.0092) and Study 20050181 (FOLFIRI) (median of 6.7 vs. 4.9 months; hazard ratio 0.820; 95% CI: 0.692, 0.972; log-rank test p = 0.0231).

In both phase 3 studies, the primary analysis of overall survival (OS) showed a trend towards improvement with panitumumab plus chemotherapy relative to chemotherapy alone in subjects with wild-type *KRAS* tumours (absolute difference in median OS of 4.2 months and 2.0 months in Studies 20050203 (FOLFOX) and 20050181 (FOLFIRI), respectively), but did not demonstrate a statistically significant difference between treatment arms. The incidence of subsequent anti-EGFR therapy was higher in subjects receiving chemotherapy alone compared with those receiving panitumumab plus chemotherapy; these imbalances between treatment arms may have influenced the analysis of OS. In Study 20050203, PFS and OS were shorter in subjects with mutant *KRAS* tumours in the panitumumab plus FOLFOX arm compared with the FOLFOX alone arm. In Study 20050181, the addition of panitumumab to FOLFIRI had no positive or negative effect on PFS, OS, or objective response rate in subjects with mutant *KRAS* tumours. In subjects with wild-type *KRAS* tumours, panitumumab resulted in a higher objective response rate (ie, confirmed complete or partial response) when combined with chemotherapy relative to chemotherapy alone in Study 20050203 (57% vs. 48%) and Study 20050181 (36% vs. 10%). In addition, 3 phase 2 studies (20060314, 20050184, and 20060277) supported the efficacy data for the use of panitumumab in combination with either oxaliplatin- or irinotecan-based chemotherapy as initial or second-line treatment for subjects with mCRC. Results of the phase 2 studies for PFS, OS, and objective response were generally consistent with the phase 3 studies. Improvement in objective response rate and PFS were observed for subjects with wild-type *KRAS* tumours compared with those with mutant *KRAS* tumours in these phase 2 studies.

Refer to the current Vectibix® [panitumumab] SPC for further details regarding the efficacy of panitumumab as monotherapy and in combination with chemotherapy in mCRC.

2.3 Rationale

The data which will be collected is to anticipate expected reimbursement agency requirements in Germany and France. The requirements focus on gaining a clear understanding of the real life use of Vectibix® in accordance with the new label, and so the objectives in this study have been defined to meet such requirements. This study will therefore be conducted to gain understanding of Vectibix® use for the treatment of subjects with wild-type *KRAS* mCRC, in first-line in combination with FOLFOX or second-line in combination with FOLFIRI in subjects who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

2.4 Hypotheses

The analysis of data in this study will be descriptive in nature therefore no formal hypotheses will be tested. The data will describe a realistic characterization of the mCRC patient population in routine clinical practice, treated with Vectibix® as first-line treatment in combination with FOLFOX or second-line treatment in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

3. STUDY DESIGN

This is a multicenter, observational, prospective cohort study in France and Germany.

All treatment centres (inpatient and outpatient) with a focus on treating subjects with mCRC in participating countries will be prospectively defined for potential inclusion in the study. Centres will be selected to represent academic, oncology, specialist and private settings, and to provide geographical diversity within each country. A subject log will be maintained and details of all patients not enrolled will be recorded, as permitted by local regulations, including reason for non-enrolment.

Subjects with wild-type *KRAS* mCRC receiving Vectibix® treatment in combination with chemotherapy as first-line treatment in combination with FOLFOX or second-line treatment in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) will be eligible for entry to the study.

Enrolled subjects must have received at least one infusion of Vectibix® in combination with chemotherapy a maximum of 42 days before entering study. Retrospective data will be collected from Baseline (which occurs prior to the first dose of Vectibix®) up to the

point of enrolment. Subsequent chemotherapy cycles and Vectibix® doses will be recorded prospectively.

Each subject will have data collected until approximately 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up, or up to 12 months from the first dose of Vectibix®, whichever occurs first.

Data will be obtained from routine clinical records and transcribed onto an electronic case report form (eCRF) which will be in three parts:

(i) Baseline visit
(ii) Follow-up visit – or next patient visit throughout the observation period based on physician preference for follow up.
(iii) End of observation– approximately 30 days after the end of Vectibix® treatment or 12 months from the initiation of Vectibix®, whichever occurs first (unless preceded by subject death, loss to follow up or withdrawal of consent).

3.1 Number of Centres

Approximately 50-100 centres will participate in this study in total. A large number of centres are necessary to ensure we capture sufficient patients as the change in the label for Vectibix® in Europe is relatively recent. Centres that do not enrol subjects within 3 months of centre initiation may be closed if it is likely that they will not be able to enrol a sufficient number of subjects in the required timeframe. We aim to include a wide selection of hospital types that include large specialist referral centres as well as smaller general hospitals and each country will be required to include a representative sample of different types of hospitals (academic, specialist, general hospitals, private etc). In Germany many patients may also be treated in an outpatient oncology clinic setting so we represent these centres too.

3.2 Number of Subjects

Participants in this observational study shall be referred to as “subjects”. This study will enrol approximately 740 subjects (up to 350 in France and up to 390 in Germany) in total. Enrolment into the study will be capped by country according to these numbers.

3.3 Estimated Study Duration

3.3.1 Study Duration for Participants

The duration of observation will vary for each subject. Subjects will be followed-up until approximately 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up, or up to 12 months from the first dose of Vectibix®, whichever occurs first.

It is anticipated that subject enrolment will be ongoing for 12 months.

Including the 12-months observation period for each subject, it is anticipated the study duration will be approximately 24 months.

3.3.2 End of Study

The end of the study for an individual subject is defined as the last day that protocol-specified observation data is collected for an individual subject. Subjects will be followed-up until approximately 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up, or up to 12 months from the first dose of Vectibix®, whichever occurs first.

The end of study is defined as when the last subject is followed-up for the purposes of final collection of observation data. The study will end when the last subject remaining on the study either completes the 12-month observation period, dies, withdraws informed consent, or is lost to follow-up, whichever occurs first.

3.4 Subject Eligibility

Before any study-specific data are recorded, the appropriate written informed consent must be obtained if required. The decision to prescribe treatments must have been freely undertaken by the clinician prior to consideration for the subject to be included in the study. Therefore, treatment administration will be independent and dissociated from participation in the study.

3.5 Inclusion Criteria

3.5.1 Subject is ≥18 years of age at date of enrolment

3.5.2 Histologically or cytologically confirmed carcinoma of colon or rectum

3.5.3 Subject with metastatic carcinoma of colon or rectum

3.5.4 Confirmed wild-type KRAS status of tumour

3.5.5 Subjects whose care will be managed primarily by the enrolling physician and/ or all records will be available

3.5.6 Tumour assessment (ie, CT/MRI) within 12 weeks (84 days) prior to first Vectibix® infusion

3.5.7 Subjects treated with at least one infusion of Vectibix® in combination with chemotherapy a maximum of 42 days before entering study: first-line in combination with FOLFOX or second-line in combination with FOLFIRI in subjects who have received first–line fluoropyrimidine-based chemotherapy (excluding irinotecan) for treatment of wild-type KRAS mCRC per approved prescribing information

3.5.8 Subject or subject's legally acceptable representative has provided informed consent (for countries where required per local regulations)

3.6 Exclusion Criteria

3.6.1 Ongoing or planned concurrent participation in any clinical study involving Investigational Product that has not been approved by the European Medicines Agency for any indication

3.6.2 Ongoing or planned concurrent participation in any clinical study where the dosing of Vectibix® is determined by the protocol (participation in clinical trials on an approved drug and observational trials are permitted but these cannot mandate how mCRC should be treated)

3.7 Subject Enrolment

All subjects or legally acceptable representatives must personally sign and date the consent form before enrolment, where consent is required. A subject is considered as enrolled upon completion of this requirement. All subjects who enter into the study will be allocated a unique subject identification number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study. Investigators will be expected to maintain a log of all potential study candidates that includes limited information about the potential candidate including reason for subjects not being enrolled (eg, subject ineligible or refused to participate).

3.8 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. There are no proscribed therapies and investigators may treat their subjects according to clinical practice.

4. STUDY PROCEDURES

This study is non-interventional and will not alter the clinical management of subjects. No clinic visits other than those routinely scheduled will be required. Data to be recorded on the eCRF should be taken from clinical records collected in the course of normal clinical practice. No additional procedures other than those in line with routine standard of care will be performed and all medical data collected for the study are expected to be a part of standard medical records.

The investigator at each centre is responsible for ensuring that all required data is recorded.

Participating centres will assess the eligibility of patients visiting their clinic against the protocol inclusion exclusion criteria, any eligible subjects may be invited to participate in the study. After informed consent is obtained, where applicable by local law,

retrospective data will be collected from Baseline (which occurs prior to the first dose of Vectibix®) up to the point of enrolment. All subsequent chemotherapy cycles and Vectibix® doses will be recorded prospectively.

Baseline

After a subject has been enrolled, baseline (before administration of Vectibix® in combination with chemotherapy) data from that subject's medical records will be abstracted onto the eCRF by the investigator, or designee. If the investigator states a preference for paper CRF, then this option will be made available. Baseline values will be considered as those obtained most recently prior to initiation of Vectibix® in combination with chemotherapy. Baseline data will include the following (where available and recorded as standard clinical practice):

- Physician's speciality
- Type of centre and treatment setting (inpatient vs outpatient)
- Number of cancer patients treated per year by centre
- Date and confirmation of written informed consent, where applicable by local regulations
- Subject demographics: sex, age
- Medical history: all significant co-morbidities, including information on cardiac, respiratory, metabolic function
- SADRs and ADRs to Amgen product
- Subject metastatic colorectal cancer (mCRC) history:
  - Date of primary CRC and date of metastasis diagnosis
  - Site of primary tumour: rectum vs. colon, right vs. left colon
  - Synchronous vs metachronous mCRC
  - Sites of metastatic disease: liver, lung, other
  - Number of metastases overall and lesions by site
  - Tumour related symptoms (eg, pain, discomfort)
- Prior treatment history for CRC
  - All prior treatments for CRC and/or mCRC management including surgical procedures, radiotherapy, chemotherapy, biological therapy and/or other systemic anticancer therapy including initial Vectibix® plus chemotherapy infusions, other procedures, and dates of relapse and progression
- Subjects treatment goal
- Resection status
- Method and date of *KRAS* testing, if available. Data on other biomarkers, if conducted, will also be collected.
- ECOG performance status

- Physical examination (abbreviated) including height, body weight.

The following key data will also be collected at baseline where available. This data must be generated prior to the subjects first dose of Vectibix® :

- All baseline laboratory tests performed prior to the subject receiving their first dose of Vectibix

Follow-up Observation Period

Data obtained after the initiation of Vectibix® in combination with chemotherapy, and subsequently during the remainder of the 12-month observational period will similarly be abstracted onto the eCRF (or paper CRF) based on physician preferences for follow up.

Follow-up data post initiation of Vectibix® treatment will be collected at the next patient visit (based on physician preferences for follow up) throughout the observation period until 30 days after the end of Vectibix® treatment, death, withdrawal of consent, loss to follow-up, or up to 12 months from the first dose of Vectibix®, whichever occurs first. This data will include the following (where available and recorded as standard clinical practice):

- Vectibix® treatment pattern including:
  - start and stop dates
  - dose and schedule
  - total number of infusions received
  - dose reductions, dose delays, and reasons for dose reductions or delays
  - reason for treatment discontinuation
- Concomitant anticancer therapy for mCRC including surgical procedures, radiotherapy, chemotherapy, biological therapy and/or other systemic anticancer therapy and other procedures. Data to include:
  - type of therapy
  - start and stop dates
  - dose, route, and frequency (if applicable)
  - reason for cessation of therapy
- Tumour response follow up (radiological imaging of sites of disease, investigator's assessment of tumour response)
- Resection status
- Healthcare resource utilization including type of visit (inpatient, outpatient, ER, other) and reason for hospitalisations
- Relevant concomitant medication
- SADRs and ADRs to Amgen product

End of Observation Visit

Documentation at the end of observation period is required (defined as completion of 12-month observation period, discontinuation of Vectibix® treatment, death, withdrawal of consent, or loss to follow-up [whichever occurs first]):

- Date and reason for ending study:
  - 12-month observation period reached
  - Discontinuation of Vectibix® treatment – date and reason for ending Vectibix® treatment
  - Death – date and primary cause of death to be recorded
  - Loss to follow-up
  - Withdrawal of informed consent
- Planned anti-cancer treatments initiated post Vectibix® discontinuation
- SADRs and ADRs to Amgen product

4.1 Removal of Subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her 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. Any subject may withdraw consent to participate in the study at any time during the study. Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Reasons for removal from observation might include but is not limited to:

- withdrawal of consent
- administrative decision by the investigator or Amgen
- death
- lost to follow-up

4.2 Replacement of Subjects

No replacement of subjects will be permitted.

4.3 Internal Validity of Study Design

4.3.1 Selection Bias

We do anticipate some degree of selection bias within our study. Since we are not recruiting patients until they have been dosed with Vectibix® at least once, there is a

small group of patients who we will not be sampling ie, those who do not commence treatment, or cease treatment very soon after the first dose, usually because of death or disease progression. Therefore the response rate may be inflated slightly and other collected data impacted. Note that in Germany we may only be able to obtain limited data from deceased patients. However generally for most patients this will not limit inclusion of patient data into the study as the study is mainly prospective in design and patients will be alive at study enrolment (where consent is required). Should subjects die during the course of the study it may become more difficult to obtain complete follow up information if the notes are then subsequently filed elsewhere and we need informed consent to obtain them.

4.3.2 Reliability and Validity

Abstractors will be trained to not make interpretations of data. The CRF will be developed to avoid interpretation and only abstract data as documented in the record. Measures will be put in place in order to ensure that the data are as reliable as possible. There will be frequent data transfers throughout the study period and data checks to test data quality.

4.4 External validity

We shall represent different types of hospitals and outpatient departments (academic, specialist, general hospitals etc) in this study. We will be performing frequent data extractions to review any inconsistencies within the data and minimize the effect of bias. Centre selection bias is a potential threat to representativeness of the subject population included in the study. We aim to include a wide selection of hospital types that include large specialist referral centres as well as smaller general hospitals and each country will be required to include a representative sample of different types of hospitals (academic, specialist, general hospitals, etc). In Germany many patients may also be treated in an outpatient oncology clinic setting so we represent these centres too.

5. STATISTICAL CONSIDERATIONS

5.1 Study Size

This study will enrol approximately 740 subjects (up to 350 in France and up to 390 in Germany) in total. Enrolment into the study will be capped by country according to these numbers. Statistical properties of the study size are described in Section 5.3. These samples sizes are consistent with previous submissions to reimbursement agencies.

5.2 Study Outcomes, Subsets, and Covariates

5.2.1 Outcomes

Primary:

- Treatment pattern of Vectibix® and concomitant chemotherapy for mCRC will be described, including information on
  - Type of chemotherapy combined with Vectibix® in the first or second line setting
  - Starting dose and dose administration schedule of Vectibix® and chemotherapy
  - Cumulative dose, maximum dose, duration of exposure and total number of infusions received from the initiation of Vectibix® therapy and chemotherapy
  - Dose reductions and delays and reason(s) for dose reduction and delays of Vectibix® and/or concomitant chemotherapy
  - Discontinuation and reason(s) for discontinuation of Vectibix® and chemotherapy

Secondary:

- The following will be described and tabulated
  - Healthcare resource utilization, including type of visit (inpatient, outpatient, ER, other) and reason for hospitalisation
  - Demographics, disease characteristics, co-morbidities, individual treatment goals and prior treatment history
  - Response to Vectibix®, if documented, including best response, conversion to resectability, and by individual treatment goals
  - Summaries of planned anti-cancer treatment post initiation post Vectibix® discontinuation

5.2.2 Analysis Subsets

First Line FOLFOX Analysis Set (FLFAS): all enrolled subjects who have received at least one infusion of Vectibix® in combination with FOLFOX as first-line treatment, a maximum of 42 days before entering study.

Second Line FOLFIRI Analysis Set (SLFAS): all enrolled subjects who have received at least one infusion of Vectibix® in combination with FOLFIRI as second-line treatment and have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan), a maximum of 42 days before entering study.

FLFAS and SLFAS are the primary analysis sets for all analyses. Selected sensitivity analyses may be performed to assess the impact of using other analysis sets.

The data will be summarized by country to fulfil local post reimbursement requirements.

5.2.3 Covariates

Certain pre-treatment factors (covariates) may be found to affect the pattern of Vectibix® usage, hence subgroup analysis will be used to investigate the covariates listed below with a view to a numerical evaluation of their influence.

The following covariates may be used to conduct the subgroup analyses for all subjects:

- ECOG performance status: ≤1 vs. 2
- Location of primary tumour: colon vs. rectum, right or left
- Number of sites of metastatic lesions: 1 vs. 2 vs. ≥3 and per organ (liver, lung, other etc)
- Location of sites of metastatic disease: liver only vs. other sites ± liver
- Prior adjuvant therapy: yes vs. no (regimen and date last adjuvant treatment administered)
- Type of centre
- Individual treatment goals (including resectability)
- The following covariates may be used to conduct the subgroup analyses for SLFAS:
- Categories of prior systemic therapy mCRC: chemotherapy only vs. chemotherapy plus targeted therapy
- Prior anti-EGFR therapy for mCRC : yes vs. no
- Prior anti-VEGF therapy for mCRC: yes vs. no
- Prior oxaliplatin-based chemotherapy for mCRC: yes vs. no
- Prior irinotecan-based chemotherapy for mCRC: yes vs. no

5.3 Sample Size Considerations

The analysis of this study will be descriptive in nature. Consequently, the sample size has not been assessed in terms of statistical power but with regards to what precision might be expected when examining categorical data such as type of anticancer therapy and discontinuation of Vectibix®. Proportions and confidence intervals will be most useful if reported in subgroups rather than overall. For instance the majority (perhaps 60%) of subjects recruited will be receiving first line treatment; their treatment patterns are expected to be different from second line subjects. Similarly, first line subjects with potentially resectable tumours (around 20%) will have different treatment patterns to those with unresectable tumours. Thus, we will have three important subgroups (the number of resectable subjects in the second line is expected to be negligible), consisting of 12% (line 1 potentially resectable), 48% (line 1 unresectable) and 40% (line 2) of the subjects in each country.

Table 1 below lists the expected precision of binomial estimates (in terms of half-width of a 95% confidence interval) using the planned sample sizes in the above scenarios. The expected precision in most of the subsets will be smaller than 10% but could be as high around 15% in Line 1 potentially resectable subjects.

Table 1. Expected Precision for the Proportion of Treatment Patterns

Expected Proportion of Treatment Pattern	Half-width of 95% CI for Proportion of Subjects with a Treatment Pattern			
	France (350 subjects)			
	Line 1 resectable (n=42)	Line 1 unresectable (n=168)	Line 2 resectable (n=140)	All subjects (n=350)
0.1	9.1%	4.5%	5.0%	3.1%
0.3	13.9%	6.9%	7.6%	4.8%
0.5	15.1%	7.6%	8.3%	5.2%

Expected Proportion of Treatment Pattern	Half-width of 95% CI for Proportion of Subjects with a Treatment Pattern			
	Germany (390 subjects)			
	Line 1 resectable (n=47)	Line 1 unresectable (n=187)	Line 2 resectable (n=172)	All subjects (n=390)
0.1	8.6%	4.3%	4.5%	3.0%
0.3	13.1%	6.6%	6.8%	4.5%
0.5	14.3%	7.2%	7.5%	5.0%

5.4 Access to Individual Subject Treatment Assignments by Amgen or Designees

Randomization and unblinding procedures are not applicable to this study design.

5.5 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned. Early stopping rules will not be applied due to the observational nature of this research program.

5.6 Planned Methods of Analysis

5.6.1 General Approach/Considerations

The analysis of this study will be descriptive in nature. The data will be summarized for subjects with metastatic colorectal cancer (mCRC) with tumour expressing wild-type (non-mutated) *KRAS* who received Vectibix® in combination with FOLFOX as first-line

treatment and subjects who received Vectibix® in combination with FOLFIRI as second-line treatment and received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). The data will be summarized by country to fulfil local post reimbursement requirements. For continuous outcomes, the mean, standard deviation, median, and range will be provided. For categorical variables, the frequency and percentage, with two-sided 95% CI, will be displayed for the treatment pattern of Vectibix®. Summary tables and analyses will be based on FLFAS and SLFAS and corresponding local tumour response analysis sets.

For each outcome parameter, the covariates listed in Section 5.2.3 will be assessed in a logistic or general linear model. 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.

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

5.6.2 Analysis of Key Study Outcomes

5.6.2.1 Primary Outcomes

Pattern of Chemotherapy

The type of chemotherapy combined with Vectibix®, including start and stop dates, dose, route, frequency and reason for cessation of chemotherapy will be summarized.

Summary of Vectibix® Exposure

Starting dose and dose administered after initiation of Vectibix® will be summarized.

Cumulative dose, maximum dose, duration of exposure and number of infusions received will be summarized for the entire follow-up observation period from initiation of Vectibix®. For each subject, cumulative dose will be calculated by summing the doses of all Vectibix® infusions received across the entire observation period (ie, from initiation of Vectibix® to last dose of Vectibix®). The total number of infusions received will be calculated by summing the number of Vectibix® infusions received across the entire observation period. Similarly, duration of exposure will be calculated as the number of months between the date of the first and last Vectibix® infusions administered during the observation period (Note: a subject is considered exposed to Vectibix® if he/she received at least one infusion, irrespective of the duration of subsequent exposure). The maximum dose will be calculated as the highest Vectibix® dose administered across the

entire observation period. The number and percentage of subjects experiencing Vectibix® dose reductions and delays, along with the reasons for reductions and delays will be summarized.

Vectibix® Discontinuation

The number and percentage of subjects who discontinue Vectibix® during the observational period, along with the reasons for discontinuation will be summarized.

5.6.2.2 Secondary Outcomes

(i) **Healthcare Resource Utilization**

Hospitalizations will be summarized including the type of hospitalization (outpatient, inpatient, ER, ICU, standard of care), the duration of hospitalization (days) as well as the reason for the hospitalization. Disease monitoring will also be summarized by type of visit (eg, GP or Specialist). Specialist visits as well as tumour assessment and methods (type of scans) occurrence and frequency will be summarized using descriptive statistics.

Baseline Characteristics Description of the Subject

Descriptive statistics will be used to summarize subject demographic and baseline characteristics including age, sex, height, body weight, performance status, co-morbidities and prior treatment history. The duration of follow-up will also be summarized.

Response Rate

Response to Vectibix®, if documented, including best response, conversion to resectability will be summarized using the local tumour response analysis set.

Anti-cancer Treatment initiated post Vectibix® discontination

Documented planned anti-cancer treatments initiated post Vectibix® discontinuation will be summarized as for categorical variables. Vectibix®Vectibix®

6. STUDY LIMITATIONS

(See also Section 4.3 and Section 4.4)

There are two potential limitations regarding subject selection:

(i) Centre level refusals

(ii) Patient level refusals, again

We shall review carefully refusals at the centre and patient level and, if appreciable, qualify the results accordingly.

Another potential limitation is that medical practice may be affected by participation in the study (Hawthorne effect). This could affect the initial treatment decision for subjects who start treatment after a centre has been initiated. The main limitations in this study relate to the ability to include a sufficient sample of patients that meet the eligibility criteria and that are being treated with Vectibix® according to the label specified. We shall be including a large number of centres to allow us to capture an adequate study population that represents patients being prescribed Vectibix® in France and Germany according to the label. The results should therefore be generalizable to patients on Vectibix® in these two countries and in addition to countries nearby that have similar health care systems. As the study design is mainly prospective, this will minimize missing data. There is a risk that there will be some incomplete data and that it will not be possible to go back to the medical records to complete it adequately so that incomplete data may need to be excluded from the analysis. We will be performing frequent data extractions to review any inconsistencies within the data.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

7.1 Adverse Events and Adverse Drug Reactions

7.1.1 Definition of Adverse Events and Adverse Drug Reactions

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The Investigator is responsible for ensuring that any adverse events observed by the Investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

A suspected ADR is an adverse event that is considered related to the medicinal product by the treating physician.

7.1.2 Reporting Procedures for Adverse Drug Reactions

Data on suspected ADRs will be collected and reported in this study but not adverse events that are not considered related to Amgen medicinal product.

The investigator is responsible for ensuring that any suspected ADRs observed by the Investigator or reported by the subject are documented in a subject's medical record as possibly related to an Amgen medicinal product, and that those occurring between baseline and the end of observation visit are reported using the applicable form (eg, ADR Summary CRF) within 30 calendar days of discovery or notification.

The investigator must assign the following ADR attributes:

- ADR diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution,
- Severity,
- Assessment of relatedness to Vectibix ®, and
- Action taken.

The investigator may be asked to provide follow-up information on the reported adverse drug reaction.

7.2 Serious Adverse Events and Serious Adverse Drug Reactions

7.2.1 Definition of Serious Adverse Events and Serious Adverse Drug Reactions

A serious adverse event (SAE) is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A suspected SADR is an SAE that is considered related to the medicinal product according to the treating physician.

An adverse event would meet the criterion of "requires hospitalisation," if the event necessitated an admission to a health care facility (eg, overnight stay).

If an Investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

7.2.2 Reporting Procedures for Serious Adverse Reactions

Data on suspected SADRs will be collected and reported in this study but not SAEs that are not considered related to Amgen medicinal product.

The Investigator is responsible for ensuring that all suspected SADRs observed by the Investigator or reported by the subject that occur between baseline and the end of observation period are reported to Amgen within 1 business day of discovery or notification.

The investigator is responsible for ensuring that any identified suspected SADRs documented in a subject's medical record as possibly related to Amgen medicinal product and occurring between baseline and the end of observation period, are reported to Amgen Global Safety via a Serious Adverse Drug Reaction form. Suspected SADRs and all amendments to SADRs must be reported to Amgen within 1 business day of identification. Initial suspected SADR information and all follow-up information must be recorded on the SADR form and submitted to Amgen Global Safety. Investigators may be requested to provide follow-up information concerning suspected SADRs.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, Investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations and good clinical practice.

7.3 Pregnancy Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking an Amgen medicinal product report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, Investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 30 days after the last dose of Amgen medicinal product.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 7 business days of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet. The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol- required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, Investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 30 days after the last dose of Amgen medicinal product.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 7 business days of the site receiving notification. Report a lactation case on the Lactation Notification Worksheet.

Please see Appendix A and Appendix B for examples of the forms that should be used to report pregnancy and lactation.

8. ETHICAL AND REGULATORY OBLIGATIONS

This study will comply with all applicable laws, regulations, and guidance.

8.1 Informed Consent

In accordance with applicable data privacy laws the following is applicable where required by local regulations/guidelines/law:

An initial generic informed consent form will be provided for the investigator to prepare the informed consent document to be used at his or her centre if required. Updates to the template will be communicated by letter from the Amgen study manager or designee to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the observational study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, and anticipated benefits, and potential hazards of the study and before any data collection is performed. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the observational study.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the study. If the subject does not have a primary care physician and the investigator

will be acting in that capacity, the investigator should document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

8.2 Independent Ethics Committee (IEC)

The following is applicable where required by local regulations/guidelines/law:

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study.

The investigator must submit and, where necessary, obtain approval from the IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC of deviations from the protocol or SADR occurring at the centre and other adverse drug reactions reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC renewal throughout the duration of the study, where applicable. Copies of the investigator's reports and the IEC continuance of approval must be sent to Amgen.

8.3 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 year of birth on the demographics CRF.
- For SADRs reported to Amgen, subjects should be identified by their, age and 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, analyzing, 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.

9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. Where applicable per local governing law and/or regulations, if Amgen amends the protocol, agreement from the investigator to adhere to the amendment must be obtained through signature on the protocol amendment. Otherwise, no agreement from the Investigator is required.

The IEC must be informed of all amendments and give approval, where applicable per local regulations/ guidelines/ laws. 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 study contract. The investigator should notify the IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

9.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed CRF, informed consent forms (where required by local regulations), and subject identification list
- Study files containing the protocol with all amendments, SPC, copies of pre-study documentation, and all correspondence to and from the IEC and Amgen

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Study Agreement.

9.3 Study Monitoring and Data Collection

The Amgen representative 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 observational study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

Full details of the study monitoring requirements will be described in a separate study monitoring plan.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, 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). Inspection of centre facilities and 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:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of data across all subjects and centres, a data management review will be performed on subject data received at Amgen. During this review, subject data will be 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 data management review process, data queries and/or centre notifications will be created in the electronic data capture (EDC) system database for centre resolution and closed by Amgen reviewer.

- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the centre notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the study database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit—week 4 and early termination) and clarifying "other, specify" if data are provided (eg, physical examination). Each investigative centre will be provided a list of the types of corrections applied to study data at the initiation of the study and at study closeout.

9.4 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

10. COMMUNICATION OF 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. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), 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. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

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Appendix A. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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 DOB:** mm___/ dd___/ yyyy____

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 LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

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

If yes, provide date of delivery: mm___/ dd___/ yyyy____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011

Page 1 of 1

Appendix B. Lactation Notification Worksheet

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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 Date of Birth:** mm_____/dd_____/yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

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

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

5. Breast Feeding Information

Currently breast feeding? ☐ 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:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product prior to conception, during pregnancy, and during lactation. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: _____ Page 1 of 1

Amendment 1

Protocol Title: Prospective Observational Cohort Study to Describe the Use of Panitumumab in Combination With Chemotherapy in Routine Clinical Practice for Patients With Wild-type KRAS Metastatic Colorectal Cancer

Amgen Protocol Number 20120100

Amendment Date: 11 September 2012

Rationale:

This protocol has been amended to include a number of administrative changes, as follows:

Safety wording

Safety wording changes has been made to conform to the recent changes to the EU PV requirements for determinations of expectedness and expedited reporting of AEs.

Sponsor contacts. The following sponsor contacts have replaced due to the appointment of new staff to support this study:

Pam Ward has been replaced by Lis Mable

Aliki Taylor has been replaced by Margarita de la Orden

Missed placed text

Some text relating to non-participating sites should not have been part of the protocol and has now been deleted.

Description of Changes

Section: *7.2.2* Reporting Procedures for Serious Adverse Reactions. Last paragraph of this section (page 39)

Delete: **Determination of expectedness for Amgen products will be based on the contents of the Investigator's Brochure and the regional prescribing information for products being studied for an approved use.**

Section: First page of the protocol. Key Sponsor Contact(s). The first and last key contacts have been replaced

Replace:

Aliki Taylor
Observational Research Director
Amgen Ltd
1 Uxbridge Business Park
Uxbridge, UB8 1DH
United Kingdom
Phone: +44 (0) 1895-525-482

With:

Margarita de la Orden
Observational Research **Senior Manager**
Amgen Ltd
1 Uxbridge Business Park
Uxbridge, UB8 1DH
United Kingdom
Phone: +44 (0) 1895-525-**583**

and

Pamela Ward
Clinical Program Operations Manager
Amgen Ltd
1 Uxbridge Business Park
Uxbridge, UB8 1DH
United Kingdom

With

Lis Mable
Clinical Research Study Manager
Amgen Ltd
240 Cambridge3Science Park
Milton Road, Cambridge, CB4 0WD
United Kingdom

Section 3: Study Design (page 23) in the middle of the first paragraph

Delete: **Details on all centres that are selected but do not participate will be recorded, including primary reason for non-participation**