Title: Protocol Medical Records Review to Describe the Patterns of KRAS Testing and Vectibix Use in Europe

Medical Record Review

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Product:	Vectibix (Panitumumab)
Study number:	20101120
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1. INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled Medical Records Review to Describe the Patterns of *KRAS* Testing and Vectibix Use in Europe, dated 08 November 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.

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)**

2. SYNOPSIS

Title: Medical Records Review to Describe the Patterns of *KRAS* Testing and Vectibix Use in Europe

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

Primary Objectives: The primary objective of this medical record review study is to estimate the prevalence of *KRAS* testing and impact of the *KRAS* test results on patterns of Vectibix use in patients with metastatic colorectal cancer (mCRC) treated with Vectibix following the changes of label about the risk of Vectibix use in mCRC patients with mutant *KRAS* tumors in selected European countries. The primary objectives include:

- To estimate the proportion of patients with mCRC treated with Vectibix who were tested to determine tumor *KRAS* status prior to treatment
- To characterize the results of above testing for *KRAS*: proportion that are mutant, wild-type, or unknown but tested
- To estimate the proportion of patients with mCRC treated with Vectibix who were concurrently treated with oxaliplatin-containing chemotherapy and received a *KRAS* test prior to first dose of Vectibix.
- To characterize the results of above testing of patients with mCRC treated concurrently with Vectibix and oxaliplatin-containing chemotherapy: proportion that are mutant, wild-type, or unknown but tested for *KRAS*

Secondary objectives include:

- To estimate the proportion of oncologists who agree to participate in the study
- To estimate the proportion of oncologists that conduct a *KRAS* testing prior to Vectibix prescription in patients with mCRC treated with Vectibix
- To estimate the proportion of laboratories that participate in the European Society of Pathology (ESP) Quality Assurance Scheme or are certified by an ESP approved accreditation body, among all laboratories that tested *KRAS* status on mCRC patients who were treated with Vectibix
- To estimate the proportion of laboratories that use a CE-marked or otherwise validated *KRAS* detection method, among all laboratories that tested *KRAS* status on mCRC patients who were treated with Vectibix.
- To characterize the results of *KRAS* testing in each round of chart abstraction to indicate if there are any differences in results between each round.

Hypotheses: This study is descriptive in nature and does not involve formal hypothesis testing. However, we will estimate the proportion of mCRC patients, treated with Vectibix, who were also tested for *KRAS* mutation status prior to treatment, and the associated 95% confidence interval (CI) for that proportion.

Study Design: Multi-country cross-sectional medical record review study

Study Endpoints: The objectives of this study will be addressed by estimating the following endpoints:

Primary Endpoints:

- Proportion of patients with mCRC and treated with Vectibix who were tested for *KRAS* status prior to receiving Vectibix administration

- Proportion of patients whose *KRAS* test result was mutant, wild-type or unknown in those who received a *KRAS* test before receiving treatment with Vectibix for mCRC
- Proportion of patients with mCRC and treated concurrently with Vectibix and oxaliplatin-containing chemotherapy who received a *KRAS* test prior to receiving Vectibix administration
- Proportion of patients whose *KRAS* test result was mutant, wild-type or unknown in those with mCRC and treated concurrently with Vectibix and oxaliplatin-containing chemotherapy who received a *KRAS* test prior to the administration of Vectibix treatment

Secondary Endpoints:

- Proportion of oncologists who agree to participate in the study
- Proportion of oncologists that conduct *KRAS* testing prior to Vectibix prescription in patients with mCRC treated with Vectibix
- Proportion of laboratories that participate in the ESP Quality Assurance Scheme or are certified by an ESP approved accreditation body, among all laboratories that tested *KRAS* status on mCRC patients who were treated with Vectibix
- Proportion of laboratories that use a CE-marked or otherwise validated *KRAS* detection method among all laboratories that tested *KRAS* status on mCRC patients who were treated with Vectibix
- The differences in the above endpoints between the rounds of medical chart abstraction in the respective country relative to the endpoints at the month of the first interview (Note that different sets of patients will be sampled at each of the three sampling occasions)

Sample Size: The analyses are at three levels, patient level, oncologist level and laboratory level. The oncologist level analysis includes a sample of approximately 50 oncologists, who agree to participate, in each round of the medical record review and a total of approximately 150 oncologists, who agree to participate, in all 3 rounds combined. Based on such a sample size, the half-width of a 95% CI is 0.13 and 0.08, around proportions of 0.7 and 0.9, respectively, in each round, and is 0.07 and 0.05 around proportions of 0.7 and 0.9, respectively, for all 3 rounds combined.

For the analysis at the patient level, medical records will be obtained from each oncologist, which will allow evaluation of approximately 150 medical records in each round of medical record review and approximately 450 medical records in all 3 rounds combined. Based on such a sample size and assuming an intra-class correlation coefficient for patients treated by the same oncologist of 0.2, the half-width of a 95% CI is 0.09 for proportions between 0.5 to 0.7, inclusive, and 0.06 around a proportion of 0.9 in each round, and is 0.05 for proportions of 0.5 to 0.7, inclusive, and 0.03 around a proportion of 0.9 for all 3 rounds combined.

Assuming that we obtain data on 25 laboratories in each round of the medical record review, and a total of 75 laboratories in all three rounds combined, the half-width of a 95% CI is 0.18 and 0.12 for proportions of 0.7 and 0.9, respectively, in each round, and is 0.10 and 0.07, for proportions of 0.7 and 0.9, respectively, for all three rounds combined.

Summary of Subject Eligibility Criteria: Oncologists satisfying all of the following eligibility criteria will be enrolled in the study:

- must be a practicing oncology specialist
- must have treated at least three new or continuing patients with mCRC per quarter
- must have prescribed Vectibix to new or continuing patients with mCRC in the previous 6 months.
- must not have participated in an earlier round of this study.
- must not have participated in Amgen study number 20101121
- must be the only oncologist who has participated at the same medical center for this round of the study

Medical records from patients satisfying all of the following eligibility criteria will be obtained from each eligible oncologist:

- must have received Vectibix for the treatment of mCRC during the 6-month period prior to the time when medical records are obtained
- must not have been in any experimental clinical trial at time of receiving Vectibix
- must not have participated in this study, in an earlier round

Where local laws require, written consent to allow access to the medical records, for the purpose of this study, will be obtained from eligible participating patients or from a legally acceptable representatives of deceased patients.

Procedures: The medical record review will be conducted for 3 rounds (in months 0, 12 (±3) and 24(±3), after the first medical record abstraction. Time 0 is equivalent to date of first chart review. Before each round, the sampling list will be created by Amgen. The number of oncologists sampled per country will be proportional to the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix. In each round of medical record review, potential participating oncologists will be sampled, by country, and reached through letter, telephone or email. Every attempt will be made to make sure there is adequate representation of different cancer centre types in each country in each round based on annual volume of mCRC patients seen based on centre size, academic status, specialist centres status and private versus public status. The oncologists will be introduced to the study plan, and their eligibility to participate in the study will be assessed using standardized screening questions. From each eligible participating oncologist, study staff will be asked to try to obtain medical records of patients who have most recently received Vectibix for the treatment of mCRC during the 6-months prior to completion of the feasibility questionnaire with the oncologist, and were not involved in any experimental clinical trial when treated with Vectibix. A written consent may be obtained from participating patients or relatives of deceased patients, consistent with local laws, to access their medical records for the purpose of this study Medical information will be abstracted from the obtained medical records using standardized forms Such medical information will include the occurrence and timing of treatment with Vectibix and oxaliplatin-containing chemotherapy, diagnosis of mCRC, and the occurrence, timing and results of *KRAS* tests. In addition, the oncologist will be asked to collect information from the pathology laboratory that performed the *KRAS* mutation test on the patient, using a standardized pathology data extraction form. The medical record and pathology data collection and abstraction will be conducted for 3 rounds in months 0, 12 (±3) and 24 (±3) after the first medical record abstraction, following the same process.

Statistical Analysis: The data analysis is descriptive in nature. The primary analysis will be conducted at three levels, patient level, oncologist and laboratory level.

Patient Level Analysis

At the patient level, patient consent rate will be calculated as the proportion of eligible patients who gave consent, where needed, to participate out of all eligible patients. Medical record retrieval rate will be calculated as the proportion of obtained medical records out of all requested. Patient characteristics including age and gender when medical record is obtained will be described according to data abstracted from the obtained medical records. Descriptive statistics (frequency, proportion and 95% CI) for all study end points will be calculated based on data abstracted from medical records. In patient level analysis, standard errors will be estimated using mixed effects models (Leyland and Goldstein, 2001; Kish, 1987; Skinner et al., 1989). The patient level analysis will be conducted based on all abstracted charts and stratified by country, timing of chart abstraction (months 0, 12 (±3) and 24 (±3) after the first medical record abstraction), key patient characteristics such as age, gender, and oncologist characteristics such as years of practice and number of mCRC patients treated per quarter.

Oncologist Level Analysis

At the oncologist level, oncologist eligibility rate will be calculated as the proportion of eligible oncologists out of all screened oncologists. Oncologist consent rate will be calculated as the proportion of eligible oncologists who agreed to participate out of all eligible oncologists. Characteristics including country, size of medical facility, years of experience as an oncologist, number of mCRC patients presenting and being treated will be described for oncologists who are screened but not eligible, those who are eligible but do not agree to participate, and those who are eligible and agree to participate in the study. The frequency and proportion (and 95% CI) of oncologists from whom some or all of the obtained medical records reflect conduction of *KRAS* tests before prescribing treatment with Vectibix and reflect prescription of Vectibix treatment to patients whose *KRAS* test result is wild-type will be calculated. Also for oncologists who prescribe concurrent treatment of Vectibix and oxaliplatin-containing chemotherapy, the frequency and proportion (and 95% CI) of oncologists who conduct *KRAS* tests before the concurrent treatment as reflected in all or some of obtained charts, who prescribe the concurrent treatment only to patients who were tested as *KRAS* wild-type as reflected in all obtained charts or some of the obtained charts will be calculated. The oncologist level analysis will be conducted based on data from all participating oncologists and stratified by country, timing of chart abstraction (months 0, 12 (±3) and 24 (±3) after the first medical record abstraction) and key oncologist characteristics such as years of practice and number of mCRC patients treated per quarter.

Laboratory Level Analysis

At the laboratory level, success rate at obtaining laboratory information will be calculated as the proportion of laboratories that responded to the questionnaire out of all laboratories that an attempt was made to contact. We will estimate the proportion of laboratories that participate in the ESP QA scheme or are certified by an ESP approved accreditation body, as well as the proportion of laboratories that use a CE-marked or otherwise validated detection method for *KRAS* mutation testing.

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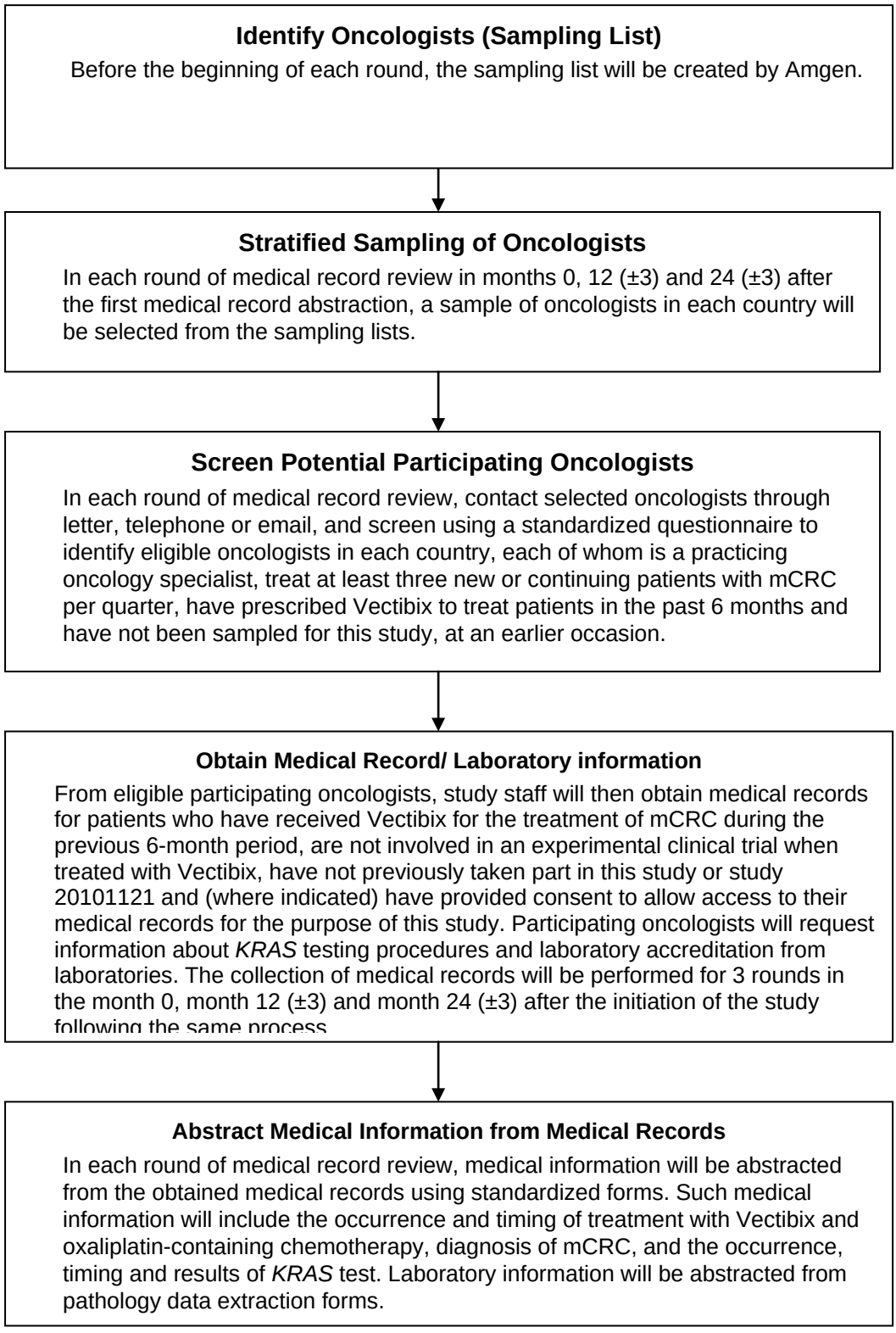
Figure 1. Study Design Schema



3. STUDY GLOSSARY

Abbreviation/Acronym	Definition
AE	Adverse Event
ADR	Adverse Drug Reaction
ASCO	American Society of Clinical Oncology
CE	Conformité Européenne
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ESP	European Society of Pathology
EU	European Union
FOLFIRI	FOL (Folinic acid, Leucovorin) F (Fluorouracil – 5FU) IRI
FOLFOX	FOL (Folinic acid, Leucovorin) F (Fluorouracil – 5FU) OX
IRB	Institutional Review Board
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
mCRC	Metastatic Colorectal Carcinoma
RMP	Risk Mitigation Plan
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
QA	Quality Assurance

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4. STUDY HYPOTHESIS, OBJECTIVES, AND AIMS

This medical record review study on the administration of Vectibix and the occurrence and results of tumor *KRAS* test in patients with metastatic colorectal cancer (mCRC) is part of the Vectibix post-marketing pharmacovigilance program and the risk mitigation plan (RMP) in the European Union (EU). The primary objective of this medical record review study is to describe the prevalence of *KRAS* testing and impact of the *KRAS* test results on patterns of Vectibix use in patients with mCRC treated with Vectibix. Specific objectives include:

Primary Objectives

- To estimate the proportion of patients with mCRC treated with Vectibix who were tested to determine tumor *KRAS* status prior to treatment
- To characterize the results of above testing for *KRAS*: proportion that are mutant, wild-type, or unknown but tested
- To estimate the proportion of patients with mCRC treated with Vectibix who were concurrently treated with oxaliplatin-containing chemotherapy and received a *KRAS* test prior to first dose of Vectibix.
- To characterize the results of above testing of patients with mCRC treated concurrently with Vectibix and oxaliplatin-containing chemotherapy: proportion that are mutant, wild-type, or unknown but tested for *KRAS*.

Secondary Objectives

- To estimate the proportion of oncologists who agree to participate in the study
- To estimate the proportion of oncologists that conduct *KRAS* testing prior to Vectibix prescription in pati*ents* with mCRC treated with Vectibix
- To estimate the proportion of laboratories that participate in the European Society of Pathology (ESP) Quality Assurance (QA) scheme or are certified by an ESP approved accreditation body, among all laboratories that tested *KRAS* status on mCRC patients who were treated with Vectibix
- To estimate the proportion of laboratories that use a CE-marked or otherwise validated *KRAS* detection method among all laboratories that tested *KRAS* status on mCRC patients who were treated with Vectibix
- To characterize the results of *KRAS* testing in each round of chart abstraction that will be carried out at 0, 12 (±3) and 24 (±3) months to indicate if there are any differences in results between rounds.

5. BACKGROUND AND RATIONALE

5.1 Indication for Vectibix

Vectibix was first approved in the EU in December 2007 as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Vectibix is not indicated for the treatment

of colorectal cancer with *KRAS* mutations since data from mCRC clinical trials have not shown a treatment benefit for Vectibix in patients with these mutations (Amado 2008).

In June 2011, CHMP recommended an extension of the approved indication to include treatment in first line in combination with FOLFOX and in second line in combination with FOLFIRI in patients who have received first –line fluoropyrimidine-based chemotherapy (excluding irinotecan) in patients with wild-type mCRC. The final recommended indication, which has been forwarded to the European Commission for decision, will therefore be:

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.

The CHMP also recommended that a new contraindication for the use of Vectibix in combination with oxaliplatin-containing therapy in patients with mutant *KRAS* tumors be included in section 4.3 of the Vectibix Summary of Product Characteristics (SmPC). This recommendation is based on recent data which indicate that patients with mutant *KRAS* tumors who are concurrently treated with oxaliplatin-containing chemotherapy have negative outcomes (Douillard et al 2010, Bokemeyer et al 2011). Further information on the requirements to determine *KRAS* mutational status prior to Vectibix treatment was also included in sections 4.2 and 4.4 of the SmPC.

5.2 Rationale for the Medical Record Review Study

To ensure the appropriate administration of Vectibix for the treatment of mCRC with wild-type *KRAS*, it is important to understand how patients with mCRC are being treated with Vectibix, with regard to the administration of *KRAS* test and knowledge of the test results in real-world practice. With the emergence of recent data on use of EGFR monoclonal antibodies in mCRC patients with mutant *KRAS* tumors and related label changes in Europe, it is also critical to monitor changes in the pattern of Vectibix treatment. In addition, the optimal use of Vectibix requires accurate *KRAS* mutation testing. The main requirement for conclusive *KRAS* genotyping is the ability to discriminate any one of several *KRAS* codon 12 and 13 mutations from the non-mutated (wild-type) *KRAS* gene. Barriers to this include the differences in detection limits for

distinct mutations, as well as the variability between different *KRAS* genotyping methods. The ESP has set forth a number of initiatives to validate and standardize *KRAS* mutation testing: the ESP QA program for *KRAS* testing. Therefore, Amgen is committed to conduct a multiple cross-sectional medical record review and laboratory review study based on medical records/laboratory information collected from a sample of oncologists in Europe. The countries included in this study are likely to be representative of the EU, and will include the largest markets for Vectibix in the EU.

5.3 Study Hypothesis

This study is descriptive in nature and does not involve formal hypothesis testing. However, we will estimate the proportion of mCRC patients, treated with Vectibix, who were tested for *KRAS* mutation status prior to treatment, and the associated 95% confidence interval (CI) for that proportion.

6. METHODS

6.1 Study Design

The medical record review will be conducted for 3 rounds in months 0, 12 (±3), and 24 (±3) after the first medical record abstraction. Before each round, the sampling list will be created by Amgen. The number of oncologists sampled per country will be proportional to the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix. Potential oncologists will be contacted by letter, telephone or email. The oncologists will be introduced to the study, and their eligibility to participate in the study will be assessed using a standardized questionnaire. Eligible oncologists must be practicing oncology specialists who have treated at least three patients with mCRC per quarter have prescribed Vectibix to treat patients with mCRC in the previous 6 months, have not previously taken part in this study, and be the only oncologist from the participating center taking part in the study in this round. The number of oncologists sampled per country will be proportional to the number of oncology centers per country. In each round of medical record review, potential participating oncologists will be sampled, by country, and reached through letter, telephone or email. Every attempt will be made to make sure there is adequate representation of different cancer centre types in each country in each round based on annual volume of mCRC patients seen, centre size, academic status, specialist centres status and private versus public status. From each eligible participating oncologist, study staff will then obtain medical records for patients who have received Vectibix for the treatment of mCRC, during the 6-month period prior to the time of contact with the

relevant oncologist, and are not involved in an experimental clinical trial when treated with Vectibix. A written consent may be obtained from participating patients to access their medical records or from relatives of deceased patients, depending on local laws. Medical information will be abstracted from the medical records using standardized forms. Such medical information will include the occurrence and timing of treatment with Vectibix and oxaliplatin-containing chemotherapy, diagnosis of mCRC, and the occurrence, timing and results of *KRAS* testing. The oncologist will also be asked to collect information from the pathology laboratory that performed the *KRAS* mutation test on the patient, using a standardized pathology data extraction form the medical record and pathology information collection and abstraction will be conducted for each round in months 0, 12 (±3) and 24(±3) after the first medical record abstraction, following the same process.

6.2 Study Setting

Medical records will be collected from eligible participating oncologists in participating European countries.

6.3 Unit of Analysis

Analysis for this study will be conducted at 3 levels, patient level, oncologist level and laboratory level. Descriptive statistics will be calculated at each level to evaluate the prevalence of *KRAS* testing and test results (mutant, wild-type and unknown) in patients with mCRC and treated with Vectibix and patients with mCRC and treated concurrently with Vectibix and oxaliplatin-containing chemotherapy. In the patient level analysis, standard errors will be estimated using mixed effects models (Leyland and Goldstein, 2001; Kish, 1987; Skinner et al., 1989).

6.4 Sampling Methods

6.4.1 Selecting the Sampling Frame

The study population consists of practicing oncologists enrolled from several European countries. To identify these oncologists, lists of oncologists (and their contact information) will be created by Amgen before each round. The number of oncologists sampled per country will be proportional to the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix. To ensure an oncologist will not participate in the study twice, oncologists who have participated (including those who refuse to participate) in a previous round of medical record review study will not be included in the sampling for the following rounds. The sampled oncologists will be

contacted by the vendor through letter, telephone or email and screened with regard to the following eligibility criteria using a standardized questionnaire

- must be a practicing oncology specialist
- must have treated at least three new or continuing patients with mCRC per quarter
- must have prescribed Vectibix to treat new or continuing patients with mCRC in the past 6 months
- must not have participated in an earlier round of this study
- must not have participated in Amgen study number 20101121
- must be the only oncologist who has participated at the same medical center for this round of the study

The sampling and screening of potential participating oncologists will be proportional to the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix. The same process of sampling, contact, and screening of oncologists will be conducted 3 times in months 0, 12 (±3), and 24 (±3) after the first medical record abstraction.

6.4.2 Selection of Medical Records

From each eligible participating oncologist, study staff will then obtain medical records from patients who satisfy all the following eligibility criteria.

- must have received Vectibix for the treatment of mCRC during the 6-month period prior to the time when medical records are obtained
- must not have been in any experimental clinical trial at the time of receiving Vectibix
- must provide written consent (or by patient's legally acceptable representative) to allow access to their medical records (for countries where required per local law/regulations)
- must not have taken part in this study before

Consistent with local laws, each oncologist will complete a paper screening log and list all patients who were treated with Vectibix in the last 6 months. The oncologist will then contact patients to obtain written consent (if this is required by local laws) to allow the use of their medical records for the purpose of this study. The oncologist will contact patients according to when patients received their first dose of Vectibix, with patients with the most recent first dose dates contacted first. If the selected patient declines to provide written consent, the next most recently treated patient will be selected from among eligible patients treated by the same oncologist. The process to obtain patient's consent will continue until a consented patient is identified. If none of the patients of a participating oncologist meets the eligibility criteria or consents to provide medical

records, another oncologist will be selected to replace this oncologist and meet the sample size requirement.

Depending on site resource, oncologists (or designee) will complete data abstraction forms for eligible participating patients relevant to the administration of the Vectibix treatment, which at least covers but is not necessarily limited to the time span from 3 months before to 3 months after the 1st dose of the episode of Vectibix treatment. The availability of diagnostic information on the presence of colorectal carcinoma, metastases, and their location, *KRAS* status, treatment with Vectibix, treatment with oxaliplatin and other chemotherapeutic agents, treatment with other biologics, and type of surgical procedures will be recorded.

The medical record/pathology data collection will be conducted in months 0, 12 (±3) and 24 (±3) after the first medical record abstraction, following the same process.

6.5 Data Collection

It is the responsibility of the oncologist to ensure that the data entered is as accurate and complete as possible. The oncologist or designee will enter the anonymised data from the medical records into the EDC system.

6.5.1 Abstraction Form

Medical information related to the treatment with Vectibix and performance of *KRAS* tests will be abstracted from medical records using standardized electronic forms to comprehensively collect information related to *KRAS* testing and the test results, relevant information including but not limited to 3 months before and 3 months after the 1st dose of the episode of Vectibix treatment will be abstracted. To ensure all questions are well targeted and correctly understood, two pilot medical record abstractions will be conducted in each country in the 1st round of medical record review. The completed forms will be reviewed and the medical record abstraction form may be modified as needed according to the outcome of the pilot abstraction. If significant revisions are made to the medical record abstraction form, two additional medical records per country will be obtained to meet the sample size requirement.

6.6 Study Limitations

As this study involves multiple providers from different countries, the quality and quantity of medical information available from paper or electronic medical records may vary by clinics, hospitals, and the person performing the abstraction. Medical records from some providers may not contain information for all hospitalizations, encounters with specialists,

or lab results. Additionally, medical records may not be obtained from all patients or oncologists.

The sampling lists generated for each round may sample oncologists with differences in their levels of experience or medical facility type from one round to the next. As a result, the characteristics of oncologists who are eligible and participate in each round may differ, which may mean that inter-round differences in responses to questions could be associated with the differences between the oncologists participating in each round.

Selection bias may result from declination to participate from otherwise eligible oncologists or failure to obtain medical records from eligible patients for reasons associated with the occurrence or results of *KRAS* tests. For instance, if oncologists who do not conduct *KRAS* tests before prescribing Vectibix treatment are less likely to participate or if medical records reflecting absence of *KRAS* tests before Vectibix treatment are less likely to be obtained, the study results may over-estimate the proportion of patients who receive *KRAS* tests before Vectibix treatment.

Because the study only includes oncologists who treat at least three patients with mCRC per quarter, the study result may be less generalizable to less experienced oncologists. These inclusion criteria may also increase the possibility that oncologists and patients at larger centers are preferentially selected relative to oncologists and patients at smaller centers. It is possible that oncologists at larger centers have more experience in KRAS testing than some oncologists at smaller centres. We will evaluate the effect of center size by comparing the results of the data extraction between patients from larger centers and patients from smaller centers. Also oncologists eligible for the study may decline to participate for various reasons and thus medical records from the participating oncologists may not be generalizable to all eligible oncologists in each country. For instance, oncologists who are at higher level positions or involved in other administrative, research or teaching activities may be less likely to participate because of their busy schedule. To investigate the representativeness of the sample in each country and the extent of potential non-generalizability introduced by the eligibility criteria and rejection to participate, characteristics (including country, size of medical facility, years of experience as an oncologist, number of mCRC patients presenting and being treated) of oncologists who are not eligible, those who are eligible but do not consent to participate, and those who are eligible and consent to participate will be compared.

7. ETHICAL AND REGULATORY OBLIGATIONS

7.1 Protection of Human Subjects

The protocol of the current study and consent form where relevant will be submitted to relevant local Institutional Review Board (IRB) or Ethical Review Board in each country for review and approval. If required by local laws, individual written consent forms from each participating oncologist and each participating patient must be obtained. All patient identification data will be removed from the medical records. Paper copies of medical records will be stored appropriately with accessibility restricted to relevant study personnel. Electronic medical records data will be stored in password-protected computers which are only accessible to relevant study personnel.

7.2 Safety Data Collection, Recording, and Reporting

7.2.1 Safety Event Definitions

7.2.2 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition
- Events occurring from a medication error or overdose of a product(s), whether accidental or intentional
- Events occurring from abuse of a product(s)
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)
- Any lack or loss of intended effect of the product(s)

7.2.3 Adverse Drug Reactions (ADRs)

An adverse event in the medical record that is clearly stated to be related to an Amgen product is an adverse drug reaction.

7.2.4 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

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

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

7.2.5 Serious Adverse Drug Reactions (SADRs)

A serious adverse event in the medical record that is clearly stated to be related to an Amgen product is a serious adverse drug reaction (SADR).

7.2.6 Definition of Other Safety Findings

Other Safety Findings include:

- Medication errors, overdose, misuse, abuse (whether accidental or intentional) or all reports of uses outside the terms for authorized use of the product (including off label use) involving an Amgen product, regardless of whether associated with an AE or ADR
- Pregnancy (occurring in female patients while taking Amgen products and female partners of male patients taking Amgen products) and lactation exposure regardless of whether associated with an AE or ADR
- Transmission of infectious agents regardless of whether associated with an AE or ADR

7.2.7 Definition of 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. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints may include but are not limited to issues related to:

- Appearance (e.g. broken, cracks, color, particles, odor)
- Labeling (e.g. missing, torn, smudged)

- Durability (e.g. stability issues)
- Open packaging
- Device damage (e.g. pre-filled syringe with bent needle)
- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or incomplete delivery (e.g. defective delivery system [syringe])

7.2.8 Reportable Events and Reporting Timeframes

- All clearly documented SADRs, product complaints and other safety findings, including pregnancy (including female patients taking Amgen products and female partners of male patients taking an Amgen product) and/or lactation, are to be reported to Amgen Global Safety within 1 business day of awareness.
- ADRs that do not meet serious criteria are to be collected in the study database and must be reported in the final study report.
- Oncologists may be requested to provide follow-up information concerning adverse drug reactions

8. DATA MANAGEMENT AND QUALITY-CONTROL PROCEDURES

The quality control for the medical record abstraction process will be implemented according to the standard procedures that have been agreed upon by Amgen. Completeness and quality of information abstracted from medical records will be checked by Amgen. Relevant inquiries from Amgen regarding the quality of abstracted medical information will be addressed. Medical record retrieval rate will be calculated as the proportion of medical records abstracted out of all requested. Proportion of missing or incomplete abstractions will be calculated in all abstracted charts and by reasons for being missing or incomplete. Results from the medical record review will be entered into an electronic dataset. All electronic data files will be de-identified and stored in password-protected computers.

9. STATISTICAL CONSIDERATIONS

9.1 Study Size

The analyses are at three levels, laboratory level, oncologist level and patient level. Sampling will take place at the oncologist level. Assuming that we sample 25 laboratories in each round of the medical record review and a total of 75 in all 3 rounds combined, the half-width of the 95% CI around a range of proportions from 0.5 to 0.9 is shown in Table 1.

The oncologist level analysis includes a sample of approximately 50 oncologists, who agree to participate, in each round of medical record review and a total of approximately 150 oncologists, who agree to participate, in all 3 rounds combined. Based on such

sample sizes for the oncologist level analysis, the half-width of the 95% CI around a range of proportions from 0.5 to 0.9 is shown in Table 2.

For the analysis at patient level, medical records will be obtained from each oncologist, which will allow evaluation of approximately 150 medical records in each round of medical record review and approximately 450 medical records in all 3 rounds combined. Based on such a sample size, and assuming an intra-class (intra-practice) correlation coefficient of 0.3, 0.2 or 0, for the patient level analysis, the half-width of the 95% CI around a range of proportions from 0.5 to 0.9 is shown in Table 3.

Table 1. Half-width of 95% Confidence Intervals for Different Proportions (Laboratory Level Analysis)

Proportion	Half-width of 95% Confidence Interval	
	Sample size of 25	Sample size of 75
~0.5	0.20	0.11
0.6	0.19	0.11
~0.7	0.18	0.10
0.8	0.16	0.09
~0.9	0.12	0.07

Table 2. Half-width of 95% Confidence Intervals for Different Proportions (Oncologist Level Analysis)

Proportion	Half-width of 95% Confidence Interval	
	Sample size of 50	Sample size of 150
0.5	0.14	0.08
0.6	0.14	0.08
0.7	0.13	0.07
0.8	0.11	0.06
0.9	0.08	0.05

Table 3. Half-width of 95% Confidence Intervals for Different Proportions (Patient Level Analysis)

Proportion	Half-width of 95% Confidence Interval					
	Sample size of 150			Sample size of 450		
	CC*=0	CC*=0.2	CC*=0.3	CC*=0	CC*=0.2	CC*=0.3
0.5	0.08	0.09	0.10	0.05	0.05	0.06
0.6	0.08	0.09	0.10	0.05	0.05	0.06
0.7	0.07	0.09	0.09	0.04	0.05	0.05
0.8	0.06	0.08	0.08	0.04	0.04	0.05
0.9	0.05	0.06	0.06	0.03	0.03	0.04

* Assumed intra-class correlation coefficient for patients who are treated by the same oncologist

9.2 Data Analysis

We will conduct no formal hypothesis testing. The primary analysis will be conducted at three levels, patient level, oncologist level and laboratory level. We would expect that patients of a single oncologist will be more alike than patients of other oncologists. As observations from patients of the same oncologist will not be independent of each other, we will account for the correlation structure of the data during analysis.

- Patient Level Analysis

At the patient level, patient consent rate will be estimated as the proportion of eligible patients who consent to participate out of all eligible patients. Medical record retrieval rate will be estimated as the proportion of obtained medical records out of all requested. Patient characteristics including age and gender when medical record is obtained will be described according to data abstracted from the obtained medical records. Descriptive statistics (frequency, proportion and 95% CI) for all study end points will be estimated

based on data abstracted from medical records and pathology data extraction forms, including:

- proportion of patients with mCRC and treated with Vectibix who were tested for *KRAS* status prior to receiving Vectibix administration
- proportion of patients whose *KRAS* test result was mutant, wild-type or unknown in those who received a *KRAS* test before receiving treatment with Vectibix for mCRC
- proportion of patients with mCRC and treated concurrently with Vectibix and oxaliplatin-containing chemotherapy who received a *KRAS* test prior to receiving Vectibix administration
- proportion of patients whose *KRAS* test result was mutant, wild-type or unknown in those with mCRC and treated concurrently with Vectibix and oxaliplatin-containing chemotherapy who received a *KRAS* test prior to the administration of Vectibix treatment
- the differences in the above end points between rounds and country

In patient level analysis, we will use random effects models (two level multilevel models) to estimate the standard errors of the proportions. That is, patients will be modeled as level 1 units clustered within oncologists as level 2 units (Leyland and Goldstein, 2001). The patient level analysis will be conducted based on all abstracted charts and stratified by country, timing of chart abstraction (months 0, 12 (±3) and 24 (±3) after the first medical record abstraction), key patient characteristics such as age, gender, and oncologist characteristics such as years of practice and number of mCRC patients treated per quarter.

- Oncologist Level Analysis

At the oncologist level, oncologist eligibility rate will be calculated as the proportion of eligible oncologists out of all screened oncologists. Oncologist consent rate will be calculated as the proportion of eligible oncologists who consent to participate out of all eligible oncologists. Characteristics including country, size of medical facility, years of experience as an oncologist, number of mCRC patients presenting and being treated will be described for oncologists who are screened but not eligible, those who are eligible but do not consent to participate, and those who are eligible and consent to participate in the study. The frequency and proportion (and 95% CI) of oncologists from whom some or all of the obtained medical records reflect conduction of *KRAS* tests before prescribing treatment of Vectibix and reflect prescription of Vectibix treatment to patients whose *KRAS* test result is wild-type will be calculated. In oncologists who prescribe concurrent treatment of Vectibix and oxaliplatin-containing chemotherapy, we will estimate the frequency and proportion (and 95% CI) of oncologists who conduct *KRAS*

test before the concurrent treatment as reflected in all or some of obtained charts, and the frequency and proportion (and 95% CI) of oncologists who prescribe the concurrent treatment only to patients who were tested as *KRAS* wild-type as reflected in all or some of the obtained charts. In the oncologist level analysis, standard errors will be estimated based on the normal approximation to the binomial distribution (using the central limit theorem). The oncologist level analysis will be conducted based on data from all participating oncologists and stratified by country, timing of chart abstraction (months 0, 12 (±3) and 24 (±3) after the first medical record abstraction), and key oncologist characteristics such as years of practice and number of mCRC patients treated per quarter.

- Laboratory Level Analysis

At the laboratory level, success rate at obtaining laboratory information will be calculated as the proportion of laboratories that respond to our questionnaire out of all laboratories that we attempted to contact. We will calculate the frequency and proportion (and 95% CI) of laboratories that participate in the ESP QA scheme or are certified by an ESP approved accreditation body, as well as the frequency and proportion (and 95% CI) of laboratories that use a CE-marked or otherwise validated detection method for *KRAS* mutation testing. Standard errors will be estimated based on the normal approximation to the binomial distribution.

- Sensitivity Analyses

We may encounter missing data; in that we may not obtain information from some laboratories, some oncologists may not answer some questions, and we may not be able locate some information in the patients' charts. Missing data (Little and Rubin, 2002) will be identified and an attempt will be made to characterize missing values and their potential impact.

10. COMMUNICATION OF STUDY RESULTS

Interim reports summarizing results of the medical record review in each round will be submitted to the CHMP when the analysis and results summarization are completed after each round of medical record review. Each interim report will include data from the current round of medical record review and cumulative data from all previous abstractions. Final study reports summarizing all study results will also be submitted to CHMP after the completion of the final round of medical record review.

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Amendment Number 4

Protocol Title: Medical Records Review to Describe the Patterns of KRAS Testing and Vectibix Use in Europe

Amgen Protocol Number: 20101120

Product: Vectibix (Panitumumab)

Amendment Date: 08 November 2012

Rationale:

We have made a number of changes to this protocol to allow us to operationalise it more easily. Primarily we would like to make our eligibility criteria for oncologists less strict to ensure that we can include sufficient number of oncologists and patients in each round. We would propose not to specify which countries are participating in each round so that we have the flexibility to add more countries as required in subsequent rounds to increase the number of eligible oncologists who can participate in this study that are representative of the EU. We also would like to allow ourselves some flexibility to start rounds 2 or 3 slightly earlier or later than 12 months after the previous round so we have more time to collect data if necessary. We also propose some wording changes to allow us to collected data from deceased patients with the appropriate consent as required by local laws. Specifically, tis protocol is being amended for the following reasons:

- To remove reference to specific countries in Europe that participate in each round of this study to allow the study team to add or subtract more countries into subsequent rounds. This is to allow us to sample physicians from a higher number of underlying eligible physicians. Due to slower than expected uptake of reimbursement and sales of Vectibix in Europe, the number of eligible physicians is lower than expected than when this protocol was originally written.

- We have removed reference to specific ranges of numbers of oncologists and centers required by countries. Rather we have added wording to reflect that the numbers of oncologists sampled per country will be proportional to the use of Vectibix in that country. We have also added extra text to reinforce our commitment to ensuring that there is adequate representation of different cancer centre types in each country.
- To allow more flexibility in starting the rounds earlier or later, we have proposed changes to allow the study team to begin rounds 2 and 3 within 3 months of the 12 month interval originally stated. There were delays to the first patient enrolled in round 1 due: to slow ethics approvals in some countries ; lower than expected number of physicians interested in participating; lower than expected eligible numbers of physicians; delays in initiating contracts with some hospital sites. By allowing a 3 month flexibility window we can start round 2 earlier to make up for lost time and allow us to deliver the fine report on time in December 2014.
- We have added “approximately” to the numbers expected in each round of physicians and patient charts abstracted as we anticipate difficulty in being certain that the numbers included in each round will be so precise and may fluctuate slightly. However overall we believe the general numbers included in each round will be similar.
- We have relaxed some of the eligibility criteria for physicians to allow us to include some physicians who do not treat as many patients with mCRC and also who do not prescribe so much Vectibix. Based on feedback from our affiliate and from our expert clinicians, the original eligibility criteria that were set are too strict and will not allow to include a sufficient number of physicians in subsequent rounds.
- We have changed wording from “sampled” to “participated” in some sections which refer to oncologists included in this study as it is only those who have participated who will be excluded from subsequent rounds or from participating in study 20101121.

- We would like to resubmit our protocol to local ethics committees as required by local laws to allow us to collect data from dead patients. We feel that this is required as many patients on Vectibix only have a few months to live, and at present we do not have ethical approval to include data from dead patients in our study. Therefore we added appropriate wording in our protocol to reflect this.
- We have changed the wording that we had originally inserted to explain how we would be developing our sampling lists. We do not feel such detailed explanation is necessary. We now know that the Cegedim lists were not very specific to oncologists and require a lot of work to clean and make more specific to oncologists likely to treat mCRC patients. In addition, we now know that ESMO will not release individual physician contact details unless ESMO itself is charged with carrying out the study for us.
- We have changed some of the wording in the limitations section to indicate that lack of experience of KRAS testing may be related to centre size, rather than lack of knowledge amongst physicians in smaller centres.
- To update the study team details as team members have changed.
- The safety reporting sections have been updated to reflect the latest safety collection and reporting requirements of the EU Pharmacovigilance Directive

Description of Changes

A number of typographical and formatting errors have been corrected throughout the protocol. The study Glossary, Section 3 has also been update to reflect new acronyms.

Section: First page of the protocol.

Sponsor information has been updated. The first and last key contacts have been replaced

Replace:

Andrew Roddam, BSc, DPhil
Director and International Lead, Centre for Observational Research, Amgen Limited, 1 Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DH, UK
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With:

Robert Pack PhD
Clinical Research Study Manager
Global Study Management
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Section: Synopsis: Secondary objectives - 5th bullet

Replace

- To characterize the results of *KRAS* testing in the three rounds of chart abstraction that will be carried out at 0, 12 and 24 months to indicate if there are any differences in results from each of the three rounds.

With

- To characterize the results of *KRAS* testing in **each** round of chart abstraction to indicate if there are any differences in results between each round.

Section: Synopsis: Study Endpoints:

Replace

Study Endpoints: The objectives of this study will be addressed by estimating the following **statistics primary and secondary** endpoints

With

Study Endpoints: The objectives of this study will be addressed by estimating the following endpoints:

Section: Synopsis: Secondary Endpoints - 5th Bullet

Replace

> The differences in the above endpoints in the 12th month and 24th month after the first medical record abstraction in the respective country relative to the endpoints at the month of the first interview (Note that different sets of patients will be sampled at each of the three sampling occasions)

With

- The differences in the above endpoints between the **rounds** of medical **chart** abstraction in the respective country relative to the endpoints at the month of the first interview (Note that different sets of patients will be sampled at each of the three sampling occasions)

Section: Synopsis: Sample Size - first and second paragraph

Replace

The analyses are at three levels, patient level, oncologist level and laboratory level. The oncologist level analysis includes a sample of 50 oncologists, who agree to participate, in each round of the medical record review and a total of 150 oncologists, who agree to participate, in all 3 rounds combined

With

The analyses are at three levels, patient level, oncologist level and laboratory level. The oncologist level analysis includes a sample of **approximately** 50 oncologists, who agree to participate, in each round of the medical record review and a total of **approximately** 150 oncologists, who agree to participate, in all 3 rounds combined

Replace:

For the analysis at the patient level, **3 or more** medical records will be obtained from each oncologist, which will allow evaluation of **at least** 150 medical records in each round of medical record review and **at least** 450 medical records in all 3 rounds combined.

With

For the analysis at the patient level, medical records will be obtained from each oncologist, which will allow evaluation of **approximately** 150 medical records in each round of medical record review and **approximately** 450 medical records in all 3 rounds combined

Section: Synopsis: Summary of Subject Eligibility Criteria - First Paragraph 2nd 3rd 4th & 6th Bullets

Replace

- must have treated at least **5** new or continuing patients with mCRC per quarter
- must have prescribed Vectibix to **treat at least 5** new or continuing patients with mCRC in the previous 6 months.
- must not have **been sampled** in an earlier round of this study.
- must be the only oncologist **sampled** at the same medical center for this round of the study

With

- must have treated at least **three** new or continuing patients with mCRC per quarter
- must have prescribed Vectibix to new or continuing patients with mCRC in the previous 6 months.
- must not have **participated** in an earlier round of this study.

- must be the only oncologist **who has participated** at the same medical center for this round of the study

Section: Synopsis: Summary of Subject Eligibility Criteria - Second Paragraph, 3rd Bullet

Replace

- must not have **been taken part** in this study, in an earlier round

With

- must not have **participated** in this study, in an earlier round

Section: Synopsis: Summary of Subject Eligibility Criteria - Third Paragraph

Replace

A written consent to allow access to the medical records for the purpose of this study may be required from eligible participating patients, depending on the laws of the local country.

With

Where local laws require, written consent to allow access to the medical records, for the purpose of this study, **will be obtained** from eligible participating patients **or from a legally acceptable representative of deceased patients.**

Section: Synopsis: Procedures

Replace

The medical record review will be conducted for 3 rounds in months 0, 12, and 24 after the first medical record abstraction. Time 0 is equivalent to date of first chart review. Before **the beginning of the study**, the sampling list will be created by Amgen **by merging lists of oncologists (and their contact information) to be collected from Cegedim, the European Society of Medical Oncology (ESMO), from major cancer centers, and oncology clinics in 5 countries of Europe, including France, Germany, Italy, Spain and the Czech Republic.** The number of oncologists sampled per country will be proportional to **oncology centers per** country. **The minimum and maximum for the number of oncologists in each country for each round of medical record review are proposed to be: 10-20 for France and Germany; 5-10 for Italy, Spain and Czech Republic, such that 50 oncologists participate in each round of the study. We will attempt to sample the numbers of oncologists in each country according to these ranges.** In each round of medical record review, potential participating oncologists will be randomly sampled, by country, and reached through letter, telephone or email.

With

The medical record review will be conducted for 3 rounds (in months 0, 12 **(±3)** and 24**(±3),** after the first medical record abstraction. Time 0 is equivalent to date of first chart review. Before **each round**, the sampling list will be created by Amgen. The number of oncologists sampled per country will be proportional to **the use of Vectibix in each** country **and the number of oncology centres known to prescribe Vectibix.** In each round of medical record review, potential participating oncologists will be sampled, by country, and reached through letter, telephone or email. **Every attempt will be made to make sure there is adequate representation of different cancer centre types in each country in each round based on annual volume of mCRC patients seen**

based on centre size, academic status, specialist centres status and private versus public status.

Replace

From each eligible participating oncologist, study staff will be asked to try to obtain **at least 3** medical records of patients who have most recently received Vectibix for the treatment of mCRC during the 6-months prior to **making contact** with the oncologist, and were not involved in any experimental clinical trial when treated with Vectibix. A written consent may be obtained from participating patients, consistent with local laws, to access their medical records for the purpose of this study. Medical information will be abstracted from the obtained medical records using standardized forms

With

From each eligible participating oncologist, study staff will be asked to try to obtain medical records of patients who have most recently received Vectibix for the treatment of mCRC during the 6-months prior to **completion of the feasibility questionnaire** with the oncologist, and were not involved in any experimental clinical trial when treated with Vectibix. A written consent may be obtained from participating patients **or relatives of deceased patients,** consistent with local laws, to access their medical records for the purpose of this study Medical information will be abstracted from the obtained medical records using standardized forms

Replace

The medical record and pathology data collection and abstraction will be conducted for 3 rounds in months 0, 12 and 24 after the first medical record abstraction, following the same process.

With

The medical record and pathology data collection and abstraction will be conducted for 3 rounds in months 0, 12 **(±3)** and 24 **(±3)** after the first medical record abstraction, following the same process.

Section: Synopsis: Statistical Analysis: Patient Level Analysis

Replace

The patient level analysis will be conducted based on all abstracted charts and stratified by country, timing of chart abstraction (months 0, 12, and 24 after the first medical record abstraction),

With

The patient level analysis will be conducted based on all abstracted charts and stratified by country, timing of chart abstraction (months 0, 12**, (±3)** and 24 **(±3)** after the first medical record abstraction),

Section: Synopsis: Statistical Analysis: Oncologist Level Analysis

Replace

The oncologist level analysis will be conducted based on data from all participating oncologists and stratified by country, timing of chart abstraction (months 0, 12, and 24 after the first medical record abstraction)

With

The oncologist level analysis will be conducted based on data from all participating oncologists and stratified by country, timing of chart abstraction (months 0, 12 **(±3)** and 24 **(±3)** after the first medical record abstraction)

Section: Figure 1. Study Design Schema

Identify Oncologists (Sampling List)

Oncologists and their contact information will be obtained from Cegedim, the European Society for Medical Oncology (ESMO), and from major oncology clinics and cancer centers in each of the five European countries, including France, Germany, Italy, Spain and the Czech Republic.

Stratified **Random** Sampling of Oncologists

In each round of medical record review in months 0, 12, and 24 after the first medical record abstraction, a **random** sample of oncologists in each **of the five countries** will be selected

Screen Potential Participating Oncologists

In each round of medical record review, contact selected oncologists through letter, telephone or email, and screen using a standardized questionnaire to identify eligible oncologists in each country, each of whom is a practicing oncology specialist, treat at least **5** new or continuing patients with mCRC per quarter, have prescribed Vectibix to treat **at least 5** patients in the past 6 months and have not been sampled for this study, at an earlier occasion.

Obtain Medical Record/ Laboratory information

From eligible participating oncologists, study staff will then obtain medical records for **at least 3** patients who have received Vectibix for the treatment of mCRC during the previous 6-month period, are not involved in an experimental clinical trial when treated with Vectibix, have not previously taken part in this study or study 20101121 and (where indicated) have provided consent to allow access to their medical records for the purpose of this study. Participating oncologists will request information about *KRAS* testing procedures and laboratory accreditation from laboratories. The collection of medical records will be performed for 3 rounds in the month 0, month 12 and month 24 after the initiation of the study following the same process.

With

Identify Oncologists (Sampling List)

Before the beginning of each round, the sampling list will be created by Amgen.

Stratified Sampling of Oncologists

In each round of medical record review in months 0, 12 **(±3)** and 24 **(±3)** after the first medical record abstraction, a sample of oncologists in each **country** will be selected **from the sampling lists.**

Screen Potential Participating Oncologists

In each round of medical record review, contact selected oncologists through letter, telephone or email, and screen using a standardized questionnaire **to identify eligible** oncologists in each country, each of whom is a practicing oncology specialist, treat at least **three** new or continuing patients with mCRC per quarter, have prescribed Vectibix to treat patients in the past 6 months and have not been sampled for this study, at an earlier occasion.

Obtain Medical Record/ Laboratory information

From eligible participating oncologists, study staff will then obtain medical records for patients who have received Vectibix for the treatment of mCRC during the previous 6-month period, are not involved in an experimental clinical trial when treated with Vectibix, have not previously taken part in this study or study 20101121 and (where indicated) have provided consent to allow access to their medical records for the purpose of this study. Participating oncologists will request information about *KRAS* testing procedures and laboratory accreditation from laboratories. The collection of medical records will be performed for 3 rounds in the month 0, month 12 **(±3)** and month 24 **(±3)** after the initiation of the study following the same process

Section: 4 Secondary Objective - 5th Bullet

Replace

- To characterize the results of *KRAS* testing **in the three** round**s** of chart abstraction that will be carried out at 0, 12 and 24 months to indicate if there are any differences in results **from each of the three** rounds.

With

- To characterize the results of *KRAS* testing in **each** round of chart abstraction that will be carried out at 0, 12 **(±3)** and 24 **(±3)** months to indicate if there are any differences in results **between** rounds.

Section: 5.2 Rationale for the Medical Record Review Study

Replace

information collected from a sample of oncologists in **5** Europe**an countries, including France, Germany, Italy, Spain and the Czech Republic.** These countries are likely to be representative of the EU, and **are amongst** the largest markets for Vectibix in the EU.

With

information collected from a sample of oncologists in Europe. **The** countries **included in this study** are likely to be representative of the EU, and **will include** the largest markets for Vectibix in the EU.

Section: 6.1 Study Design

Replace

The medical record review will be conducted for 3 rounds in months 0, 12, and 24 after the first medical record abstraction. **Before the beginning of the study, the sampling list will be created by Amgen by merging lists of oncologists (and their contact information) to be collected from Cegedim, the ESMO, from major cancer centers and oncology clinics in 5 countries of Europe, including France, Germany, Italy, Spain and the Czech Republic. In each round of medical record review, potential participating oncologists will be randomly sampled from all identified oncologists.**

With

The medical record review will be conducted for 3 rounds in months 0, 12 **(±3),** and 24 **(±3)** after the first medical record abstraction. **Before each round, the sampling list will be created by Amgen. The number of oncologists sampled per country will be proportional to the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix.**

Replace

Eligible oncologists must be practicing oncology specialists who have treated at least **5** patients with mCRC per quarter, have prescribed Vectibix to treat **at least 5** patients with mCRC in the previous 6 months,

With

Eligible oncologists must be practicing oncology specialists who have treated at least **three** patients with mCRC per quarter have prescribed Vectibix to treat patients with mCRC in the previous 6 months,

Replace

The minimum and maximum for the number of oncologists in each country for each round of medical record review are proposed to be: 10-20 for France and Germany; 5-10 for Italy, Spain and Czech Republic, such that 50 oncologists participate in each round of the study. We will attempt to sample the numbers of oncologists in each country according to these ranges.

With

In each round of medical record review, potential participating oncologists will be sampled, by country, and reached through letter, telephone or email. Every attempt will be made to make sure there is adequate representation of different cancer centre types in each country in each round based on annual volume of mCRC patients seen, centre size, academic status, specialist centres status and private versus public status.

Replace

From each eligible participating oncologist, study staff will then obtain **3 or more** medical records for patients who have received Vectibix for the treatment of mCRC,

With

From each eligible participating oncologist, study staff will then obtain medical records for patients who have received Vectibix for the treatment of mCRC,

Replace

A written consent may be obtained from participating patients to access their medical records, depending on local laws.

With

A written consent may be obtained from participating patients to access their medical records **or from relatives of deceased patients**, depending on local laws.

Replace

pathology data extraction form The medical record and pathology information collection and abstraction will be conducted for **3** round**s** in months 0, 12 and 24 after the first medical record abstraction, following the same process.

With

pathology data extraction form the medical record and pathology information collection and abstraction will be conducted for **each** round in months 0, 12 **(±3)** and 24**(±3)** after the first medical record abstraction, following the same process.

Section: 6.2 Study Setting

Replace

Medical records will be collected from eligible participating oncologists in **5 European** countries **including France, Germany, Italy, Spain and the Czech Republic.**

With

Medical records will be collected from eligible participating oncologists in **participating European** countries.

Section: 6.4.1 Selecting the Sampling Frame

Replace

The study population consists of practicing oncologists enrolled from **5** European countries. To identify these oncologists, lists of oncologists (and their contact information) will **be collected by Amgen from Cegedim, ESMO, as well as from major oncology clinics and cancer centers in each country. Potential participating oncologists will be randomly sampled from all identified oncologists to ensure the sample is representative of all oncologists in each country.** To ensure an oncologist will not participate in the study twice, oncologists **sampled** (including those who refuse to participate) in a previous round of medical record review study will not be included in the sampling for the following rounds.

With

The study population consists of practicing oncologists enrolled from **several** European countries. To identify these oncologists, lists of oncologists (and their contact information) will be **created by Amgen before each round. The number of oncologists sampled per country will be proportional to the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix.** To ensure an oncologist will not participate in the study twice, oncologists who **have participated** (including those who refuse to participate) in a previous round of medical record review study will not be included in the sampling for the following rounds.

Section: 6.4.1 Selecting the Sampling Frame - 2nd 3rd 4th & 6th Bullet

Replace

- must have treated at least **5** new or continuing patients with mCRC per quarter
- must have prescribed Vectibix to treat **at least 5** new or continuing patients with mCRC in the past 6 months
- must not have **been sampled** in an earlier round of this study
- must be the only oncologist **sampled** at the same medical center for this round of the study

With

- must have treated at least **three** new or continuing patients with mCRC per quarter
- must have prescribed Vectibix to treat new or continuing patients with mCRC in the past 6 months

- must not have been **participated** in an earlier round of this study
- must be the only oncologist **who has participated** at the same me medical center for this round of the study

Section: 6.4.1 Selecting the Sampling Frame - last paragraph

Replace

The sampling and screening of potential participating oncologists will be proportional to **oncology centers per country, we suggest that the minimum and maximum number of oncologists in each country for each round of medical record review will be: 10-20 for France and Germany; 5-10 for Italy, Spain and Czech Republic, such that 50 oncologists participate in each round of the study. We will attempt to sample the numbers of oncologists in each country according to these ranges. A sampling log will be maintained to record number of screened oncologists.** The same process of sampling, contact, and screening of oncologists will be conducted 3 times in months 0, 12, and 24 after the first medical record abstraction.

With

The sampling and screening of potential participating oncologists will be proportional to **the use of Vectibix in each country and the number of oncology centres known to prescribe Vectibix.** The same process of sampling, contact, and screening of oncologists will be conducted 3 times in months 0, 12 **(±3),** and 24 **(±3)** after the first medical record abstraction.

Section: 6.4.2 Selection of Medical Records - first paragraph

Replace

From each eligible participating oncologist, study staff will then obtain **3 or more** medical records from patients who satisfy all the following eligibility criteria.

With

From each eligible participating oncologist, study staff will then obtain medical records from patients who satisfy all the following eligibility criteria.

Section: 6.4.2 Selection of Medical Records - 3rd Bullet

Replace

- must provide written consent to allow access to their medical records **(only if local laws require it)**

With

- must provide written consent **(or by patient's legally acceptable representative)** to allow access to their medical records (**for countries where required per local law/regulations)**

Section: 6.4.2 Selection of Medical Records - Second paragraph

Replace

The oncologist will then contact **3or more** patients to obtain written consent (if required)

With

The oncologist will then contact patients to obtain written consent (if **this is** required **by local laws**)

Section: 6.4.2 Selection of Medical Records - Forth paragraph

Replace

The medical record/pathology data collection will be conducted in months 0, 12, and 24 after the first medical record abstraction, following the same process.

With

The medical record/pathology data collection will be conducted in months 0, 12 **(±3)** and 24 **(±3)** after the first medical record abstraction, following the same process.

Section: 6.6 Study Limitations - Second Paragraph

Replace

The **random** sampling lists generated for each round may sample oncologists with differences in their levels of experience or medical facility type from one round to the next.

With

The sampling lists generated for each round may sample oncologists with differences in their levels of experience or medical facility type from one round to the next.

Section: 6.6 Study Limitations - Forth Paragraph

Replace

Because the study only includes oncologists who treat at least **5** patients with mCRC per quarter, the study result may be less generalizable to less experienced oncologists.

With

Because the study only includes oncologists who treat at least **three** patients with mCRC per quarter, the study result may be less generalizable to less experienced oncologists.

Replace

It is possible that oncologists at larger centers **are more knowledgeable** than **the** oncologists at **large.**

With

It is possible that oncologists at larger centers **have more experience in KRAS testing** than **some** oncologists at **smaller centres**.

Section: 7.1 Protection of Human Subjects

Replace

The protocol of the current study will be submitted to relevant local Institutional Review Board (IRB) or Ethical Review Board in each country for review and approval.
As required by local laws, individual consent from each participating oncologist and each participating patient **may** be obtained.

With

The protocol of the current study **and consent form where relevant** will be submitted to relevant local Institutional Review Board (IRB) or Ethical Review Board in each country for review and approval. **If** required by local laws, individual **written** consent **forms** from each participating oncologist and each participating patient **must** be obtained.

Section: 7.2.1 Safety Event Definitions & 7.2.2 Reportable Events and Reporting Timeframes

The complete safety reporting sections, as stated above, have been updated to reflect the latest safety collection and reporting requirements of the EU Pharmacovigilance Directive.

Replace

7.2.1. Adverse Events

7.2.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.

An adverse drug reaction (ADR) is an adverse event that is considered related to the medicinal product.

7.2.1.2. Reporting Procedures for Adverse Events

Any clearly documented ADRs for an identifiable subject (patient) related to any Amgen products should be collected and reported on the data collection form.

7.2.2. Serious Adverse Events

7.2.2.1. Definition of Serious Adverse Events

A serious adverse event (SAE) is any adverse drug reaction as defined above that:

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

other significant medical hazard

A serious adverse drug reaction (SADR) is a serious adverse event that is considered related to the medicinal product.

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

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

7.2.2.2. Reporting Procedures for Serious Adverse Events

All SADRs related to Amgen products shall be reported to Amgen Global Safety within one business day of discovery or notification. Initial SADR information and all follow-up information must be recorded on the SADR form and faxed to Amgen Global Safety. Oncologists may be requested to provide follow-up information concerning adverse drug reactions.

With:

7.2.1 Safety Event Definitions

7.2.1.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition
- Events occurring from a medication error or overdose of a product(s), whether accidental or intentional
- Events occurring from abuse of a product(s)
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

- Any lack or loss of intended effect of the product(s)

7.2.1.2 Adverse Drug Reactions (ADRs)

An adverse event in the medical record that is clearly stated to be related to an Amgen product is an adverse drug reaction.

7.2.1.3 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

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

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.
"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

7.2.1.4 Serious Adverse Drug Reactions (SADRs)

A serious adverse event in the medical record that is clearly stated to be related to an Amgen product is a serious adverse drug reaction (SADR).

7.2.1.5 Definition of Other Safety Findings

Other Safety Findings include:

- Medication errors, overdose, misuse, abuse (whether accidental or intentional) or all reports of uses outside the terms for authorized use of the product (including off label use) involving an Amgen product, regardless of whether associated with an AE or ADR
- Pregnancy (occurring in female patients while taking Amgen products and female partners of male patients taking Amgen products) and lactation exposure regardless of whether associated with an AE or ADR
- Transmission of infectious agents regardless of whether associated with an AE or ADR

7.2.1.6 Definition of 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. This includes all components distributed with the product(s) such as packaging, product containers, delivery system, labeling, inserts, etc.

Product Complaints may include but are not limited to issues related to:

- Appearance (e.g. broken, cracks, color, particles, odor)
- Labeling (e.g. missing, torn, smudged)
- Durability (e.g. stability issues)
- Open packaging
- Device damage (e.g. pre-filled syringe with bent needle)
- Inability of customer to understand product labeling
- Inability of customer to deliver the product successfully, including partial or incomplete delivery (e.g. defective delivery system [syringe])

7.2.2 Reportable Events and Reporting Timeframes

- All clearly documented SADRs, product complaints and other safety findings, including pregnancy (including female patients taking Amgen products and female partners of male patients taking an Amgen product) and/or lactation, are to be reported to Amgen Global Safety within 1 business day of awareness.

- ADRs that do not meet serious criteria are to be collected in the study database and must be reported in the final study report.
- Oncologists may be requested to provide follow-up information concerning adverse drug reactions

Section: 9.1 Study Size - second paragraph

Replace

The oncologist level analysis includes a sample of 50 oncologists, who agree to participate, in each round of medical record review and a total of 150 oncologists,

With

The oncologist level analysis includes a sample of **approximately** 50 oncologists, who agree to participate, in each round of medical record review and a total of **approximately** 150 oncologists,

Section: 9.1 Study Size - Third paragraph

Replace

For the analysis at patient level, **3 or more** medical records will be obtained from each oncologist, which will allow evaluation of 150 **or more** medical records in each round of medical record review and 450 **or more** medical records in all 3 rounds combined.

With

For the analysis at patient level, medical records will be obtained from each oncologist, which will allow evaluation of **approximately** 150 medical records in each round of medical record review and **approximately** 450 medical records in all 3 rounds combined.

Section: 9.2 Data Analysis - Patient level – Firth Bullet

Replace

- the differences in the above end **points in months 12 and 24 relative to month 0 after the first medical record abstraction**

With

- the differences in the above end points **between rounds and country**

Section: 9.2 Data Analysis - Patient level – second paragraph

Replace

The patient level analysis will be conducted based on all abstracted charts and stratified by country, timing of chart abstraction (months 0, 12, and 24 after the first medical record abstraction),

With

The patient level analysis will be conducted based on all abstracted charts and stratified by country, timing of chart abstraction (months 0, 12 **(±3)** and 24 **(±3)** after the first medical record abstraction),

Section: 9.2 Data Analysis – Oncologist level – bottom of first paragraph

Replace

The oncologist level analysis will be conducted based on data from all participating oncologists and stratified by country, timing of chart abstraction (months 0, 12, and 24 after the first medical record abstraction),

With

The oncologist level analysis will be conducted based on data from all participating oncologists and stratified by country, timing of chart abstraction (months 0, 12 **(±3)** and 24 **(±3)** after the first medical record abstraction),

Section: 10 Communication of Study Results - First Paragraph

Replace

Interim reports summarizing results of the medical record review in **the months 0, 12, and 24 after the first medical record abstraction,** will be submitted to the CHMP when the analysis and results summarization are completed after each round of medical record review.

With

Interim reports summarizing results of the medical record review in **each** round will be submitted to the CHMP when the analysis and results summarization are completed after each round of medical record review.