Summary Table of Study Protocol

Title	POWER: Real World Data of 1st line Panitumumab Treatment in Combination With Chemotherapy in non Resectable Wild Type (WT) *RAS* Metastatic Colorectal Cancer (mCRC) Subjects in Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania, Russia an Observational Ambidirectional Study
Protocol version identifier	20170734, Version 1.0
Date of last version of the protocol	N/A
EU Post Authorization Study (PAS) Register No	N/A
Active Substance	Panitumumab
Medicinal Product	Panitumumab (Vectibix®)
Product Reference	EMEA/H/C/000741
Joint PASS	No
Research Question and Objectives	To obtain characteristics of subjects with WT *RAS* non resectable mCRC receiving panitumumab in combination with chemotherapy as a 1st line treatment, and to describe the patterns of treatment, including 1st and 2nd line therapies.
Countries of Study	Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania, Russia
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Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Europe B.V.
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Investigator's Agreement

I have read the attached protocol entitled "POWER: Real World Data of 1st line panitumumab treatment in combination with chemotherapy in non resectable WT *RAS* metastatic colorectal cancer (mCRC) subjects in Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania, Russia an Observational Ambidirectional Study", dated *08 August 2018* and agree to abide by all provisions set forth therein.

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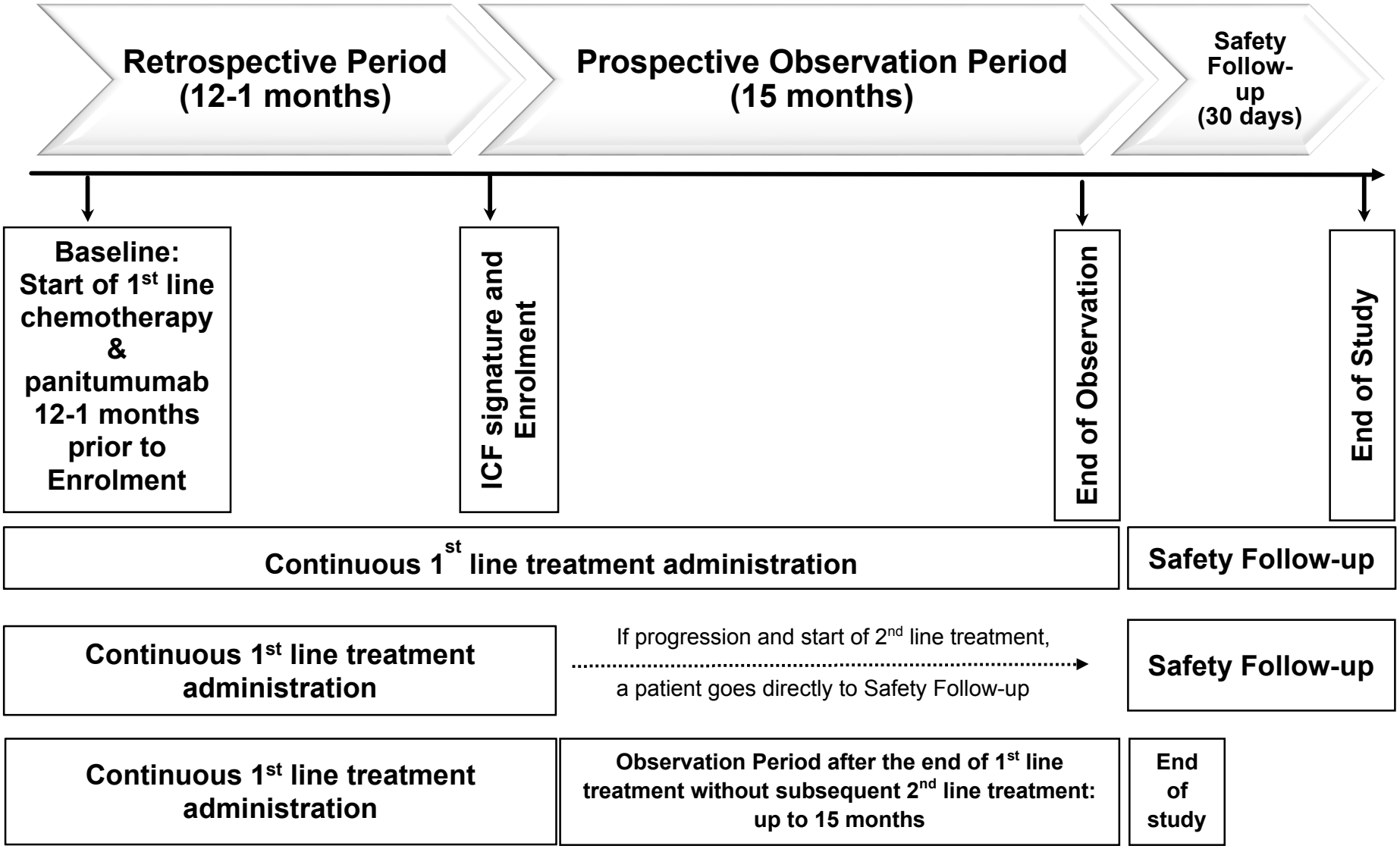
Signature

Name of Coordinating Investigator

Date (DD Month YYYY)

Figure 1. Study Design Schema



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2. List of Abbreviations and Terms

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

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

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

3. Responsible Parties

Clinical Study Sponsor:	Amgen Ltd. 240 Cambridge Science Park, Milton Road, Cambridge, UK
Key Sponsor contacts:	PPD Therapeutic Area Head Oncology/Haematology, Europe North East - Medical Amgen (Europe) GmbH Suurstoffi 22, CH-6343 Rotkreuz Switzerland

4. Abstract

Study Title

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

Study Background and Rationale

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

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

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

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

Research Question and Objective(s)

- Primary Objective(s)

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

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

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

Study Design/Type

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

Study Population or Data Resource

The study population will consist of subjects (≥18 years old) with initially non resectable WT *RAS* mCRC receiving panitumumab in combination with chemotherapy as 1st line treatment. The observations will be conducted in the selected European countries, including but not limited to Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovenia, Romania and Russia. Study period will last 12 months of enrolment plus max.16 months of observation (min. 1 month of retrospective plus max. 15 months of prospective observation), plus 30 days of Safety Follow-up.

Summary of Subject Eligibility Criteria

Inclusion Criteria

- Subject who received first infusion of panitumumab in combination with chemotherapy as 1st line treatment between 1 and 12 months before enrolment and who continues treatment with panitumumab in combination with chemotherapy at the time of enrolment
- Subject with a record of WT RAS CRC diagnosis as per standard clinical practice
- Subject with metastatic carcinoma of the colon or rectum with at least one metastatic site recorded
- Subject with initially non resectable mCRC at the start of panitumumab plus chemotherapy treatment

- Subject who was diagnosed with a tumour, assessed by CT/MRI etc. prior to panitumumab plus chemotherapy initiation
- Histologically or cytologically confirmed carcinoma of the colon or rectum as the primary site
- Subject ≥ 18 years of age on the date of enrolment
- Subjects whose care will be managed primarily by the enrolling physician and/ or all records will be available from initiation of 1st line panitumumab plus chemotherapy treatment to end of safety follow up
- Subject or subject's legally acceptable representative has provided informed consent if applicable per local regulations

Exclusion Criteria

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

Safety Follow-up

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

Variables

– *Outcome Variable(s)*

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

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

The optional exploratory outcomes to be assessed will include type of proactive and reactive measures of skin toxicity and type of treatment applied. Biomarkers status will be evaluated if possible.

– *Exposure Variable(s)*

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

– *Other Covariate(s)*

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

Study Sample Size

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

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

Data Analysis

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

5. Amendments and Updates

None