EU RISK MANAGEMENT PLAN FOR AVASTIN®/BEVACIZUMAB

RMP Version to be assessed as part of this application:

RMP Version number: 34.0

Data lock point for this RMP: 5 September 2019

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
09-Dec-2020 23:17:13	Company Signatory (PV)	██████████
10-Dec-2020 14:54:50	Deputy QPPV	

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Rationale for submitting an updated RMP: The RMP has been updated to version 34.0 to remove studies incorrectly categorized as post-authorization safety studies (PASS) upon confirmation that none of these completed studies were previously classified as Category 1-3 PASS.

Summary of Significant Changes in this RMP:

Studies GOG-218, BO17707, AVF4095g, BO21990 (AVAglio), BO17707 (ICON7), GO25632 (MERiDiAN) are removed from the table of completed pharmacovigilance studies in Annex 2.

There are no safety concerns associated with bevacizumab. Therefore, there are no routine risk minimization measures.

Other RMP Versions under Evaluation:

Not applicable

Details of Currently Approved RMP:

RMP Version Number: 33.0

Approved with Procedure Number: EMEA/H/C/000582/IB/0113

Date of approval (opinion date): 08 June 2020

See page 1 for signature and date

████████████(Deputy QPPV for Dr. Birgitt Gellert,   Date
QPPV)

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PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or common name)	Bevacizumab
Pharmacotherapeutic group(s) (ATC Code)	L01XC07
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Avastin®
Marketing authorization procedure	Centrally authorized in the EEA
Brief description of the product including:	Chemical Class – Recombinant humanized monoclonal antibody
	Summary of mode of action: Bevacizumab selectively binds to, and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). It inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Hence, neutralizing the biologic activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor growth.
	Important information about its composition: Bevacizumab is produced by recombinant DNA technology in a Chinese Hamster ovary mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.
Hyperlink to the Product Information	*This cell should include a link or reference to the proposed PI in the eCTD sequence.* *If no updated PI is submitted with the procedure, the link should direct to the latest approved PI.*
Indication(s) in the EEA	Current: **Metastatic Colorectal Cancer (mCRC)** Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. **Metastatic Breast Cancer (mBC)** Bevacizumab in combination with paclitaxel (pac) is indicated for first-line treatment of

	adult patients with metastatic breast cancer.
	Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin® in combination with capecitabine.
	Advanced, metastatic or recurrent Non–Small Cell Lung Cancer (NSCLC)
	Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable part cell lung cancer other than predominantly squamous cell histology.
	Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non–small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.
	Advanced and/or metastatic Renal Cell Cancer (mRCC)
	Bevacizumab in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.
	Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
	Bevacizumab, in combination with carboplatin (C) and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
	Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor targeted agents.
	Bevacizumab, in combination with paclitaxel,

	topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
	Cervical Cancer Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.
	Proposed: Not applicable
Dosage in the EEA	Current: Metastatic carcinoma of the colon or rectum (mCRC) The recommended dose administered as an intravenous(IV) infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. Metastatic breast cancer (mBC) The recommended dose is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion. Non–small cell lung cancer (NSCLC) *First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy:* Avastin is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Avastin as a single agent until disease progression. The recommended dose is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an IV infusion. *First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib:* EGFR mutation testing should be performed prior to initiation of treatment with the combination of Avastin and erlotinib. It is important that a well-validated and robust methodology is chosen to avoid false negative

	or false positive determinations. The recommended dose of Avastin when used in addition to erlotinib is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.
	<u>Advanced and/or metastatic Renal Cell Cancer (mRCC)</u>
	The recommended dose is 10 mg/kg of body weight given once every 2 weeks as an IV infusion.
	<u>Epithelial Ovarian, Fallopian Tube and Primary Peritoneal cancer</u>
	Front-line treatment:
	Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.
	Treatment of platinum-sensitive recurrent disease:
	Avastin is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Avastin as single agent until disease progression. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
	Treatment of platinum-resistant recurrent disease:
	Avastin is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an IV infusion. When Avastin is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.
	<u>Cervical Cancer:</u>
	Avastin is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan. The recommended dose of Avastin

	is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.
	Proposed :Not applicable
Pharmaceutical form(s) and strengths	Current: Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials containing 4 mL or 16 mL of Avastin (25 mg/mL).
	Each Avastin 100 mg vial contains 100 mg of bevacizumab.
	Each Avastin 400 mg vial contains 400 mg of bevacizumab.
	Proposed : Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

EEA = European Economic Area, EGFR = Epidermal Growth Factor Receptor, FIGO = International Federation of Gynecology and Obstetrics, IV = Intravenous, mBC = metastatic breast cancer, mRCC = metastatic renal cell cancer, NSCLC = non-small cell lung cancer, VEGF = vascular endothelial growth factor

ABBREVIATIONS

GLOSSARY OF ABBREVIATIONS	
AEs	adverse events
CHF	congestive heart failure
CNS	central nervous system
CRC	colorectal cancer
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSR	Drug Safety Report
EGFR	Epidermal Growth Factor Receptor
EGFRmut+	EGFR mutation-positive
EGFRwt	EGFR wild-type
EMA	European Medicines Agency
ENCEPP	The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
EU	European Union
FACT-L	Functional Assessment of Cancer Therapy for Patients with Lung Cancer
FDA	Food and Drug Administration (USA)
GBM	glioblastoma multiforme
GI	gastrointestinal
GIP	gastrointestinal perforation
GOG	Gynecological Oncology Group
GPRD	General Practice Research Database
HER2	Human Epidermal Receptor 2
HR	hormone receptor
HRQoL	Health Related Quality of Life
IARC	International Agency for Research on Cancer
IV	intravenous
LVEF	left ventricular ejection fraction
MAH	Marketing Authorization Holder
mBC	metastatic breast cancer
mCC	metastatic cervical cancer
mCRC	metastatic colorectal cancer
MHRA	Medicines and Healthcare Products Regulatory Agency

GLOSSARY OF ABBREVIATIONS	
MI	myocardial infarction
mRCC	metastatic renal cell cancer
NCCN	National Comprehensive Cancer Network
NOAEL	no-observed-adverse-effect-level
NSCLC	non–small cell lung cancer
OF	ovarian failure
OS	overall survival
PFS	progression-free survival
PhV	pharmacovigilance
PK	pharmacokinetics
QoL	quality of life
RMP	Risk Management Plan
RMS	rhabdomyosarcoma
SEER	Surveillance, Epidemiology and End Results Program (NCI, USA)
SmPC	Summary of Product Characteristics
TKis	Tyrosine Kinase Inhibitors
VEGF	Vascular Endothelial Growth Factor
VTE	venous thromboembolic event

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1METASTATIC COLORECTAL CANCER

- Incidence:

According to data published by International Agency for Research on Cancer (IARC) in 2013, colorectal cancer (CRC) (ICD10: C18-21) was the second most frequently occurring new cancer in Europe, with an estimated 447,000 new cases (13% of all new cancers) occurring across 40 countries in 2012 (an age standardized rate of 44 cases per 100,000 per year for both sexes) (Ferlay et al. 2013). The age-standardized incidence rate is somewhat higher in males than in females (56 vs. 35 per 100,000 in 2012 in Europe). There is a nearly five-fold variation in incidence rates across Europe, with higher rates observed in European countries (e.g., Slovakia, Hungary, Czech Republic, Norway, Denmark, and the Netherlands), and the lowest rates in the Balkan countries (Bosnia, Herzegovina, Greece, Albania).

- Prevalence:

Data published by IARC in 2013 showed that CRC is the second most prevalent neoplasm in the world, with an estimated 5-year prevalence of around 3.2 million cases in 2008 (meaning there were an estimated 3.2 million people living with CRC in 2008 who had been diagnosed in the preceding 5 years) (Bray et al. 2013). Prevalence is higher in more developed than in less developed regions (crude 1-year prevalence: 72 vs. 14 cases per 100,000 population). IARC reported the 1-year crude prevalence per 100,000 population aged ≥ 15 in different geographic regions. It was reported as 76.1 for males and 60.3 for females in western Europe, 69.5 for males and 50.2 for females in southern Europe, 60.4 for males and 49.6 for females in northern Europe and 39.3 for males and 33.9 for females in central and eastern Europe.

- Demographics:

In almost all countries, age-standardized incidence rates are lower for women than for men (Parkin et al. 2005). It has been estimated that CRC incidence and mortality rates are around 35% higher in males than females and around 20% higher in black people than in white people (American_Cancer_Society. Cancer Facts & Figures 2010a). The median age at diagnosis is 68 years.

- The main existing treatment options:

Based on European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines, treatment options for metastatic colorectal cancer (mCRC) patients generally include regimens containing flurouracil, leucovorin, and/or oxaliplatin with or without bevacizumab. Targeted therapies are available for patients with tumors that overexpress EGFR (Van Cutsem et al. 2014).

- Risk factors for the disease:

Major risk factors include male gender, older age, family or personal history of CRC or colorectal polyps, Black race, chronic inflammatory bowel disease, e.g., ulcerative colitis and Crohn's disease, genetic syndromes (e.g., familial adenomatous polyposis and hereditary non-polyposis CRC), smoking, Type 2 diabetes mellitus and excessive alcohol consumption.

- Natural history of the indicated condition in the untreated population:

Mortality:

In Europe in 2012 around 215,000 people died from CRC, yielding an age-standardized death rate of 19.5 per 100,000 per year (25 per 100,000 in men, 15 per 100,000 in women) (Ferlay et al. 2013).

Outcome of the (untreated) target disease:

Because mCRC is not curable with current therapy, the goal of therapy in this setting is symptom palliation and to prolong progression-free survival (PFS) and overall survival (OS) while maintaining quality of life (QoL). At diagnosis, around 20% of patients have metastatic disease (http://seer.cancer.gov/statfacts/html/colorect.html).

- Important co-morbidities:

Hypertension (41.4%), diabetes (15.6%), previous solid tumor (14.3%), angina (12.1%), respiratory disease (11.7%), myocardial infarction (MI) (8.0%), congestive heart failure (CHF) (5.4%), stroke (5.3%), stomach/intestinal disease (4.7%), psychiatric disease (4.1%).(Piccirillo et al. 2008).

SI.2   METASTATIC BREAST CANCER

- Incidence:

IARC data published in 2013 shows that breast cancer (ICD10: C50) was the most frequently occurring new cancer in females in Europe, with an estimated 463,800 new cases (29% of all new cancers in females) occurring across 40 countries in 2012 (an age-standardized rate of 94 cases per 100,000 females per year) (Ferlay et al. 2013). There is a three-fold variation in incidence rates across Europe (49 to 148 cases per 100,000 per year), with a clear geographical pattern; higher rates were observed in Western European countries (notably Belgium, France and the Netherlands) and in Northern Europe (particularly the UK and Denmark, Iceland and Finland), while incidence rates in Eastern European countries were much lower. (Kothari et al. 2002; Gutierrez et al. 2008).

- Prevalence:

Data published by IARC in 2013 showed that female breast cancer is the most prevalent neoplasm worldwide, with an estimated 5-year prevalence of around 5.2 million cases in 2008 (meaning there were an estimated 5.2 million females living with breast cancer in 2008 who had been diagnosed in the preceding 5 years) (Bray et al. 2013). It ranks as

the most prevalent cancer in the vast majority of countries worldwide (145 of 184 countries assessed). Prevalence is higher in more developed than in less developed regions (crude 1-year prevalence: 118 vs. 30 cases per 100,000 population). IARC reported the 1-year crude prevalence per 100,000 population aged ≥15 in different geographic regions. It was reported as 165.4 in western Europe, 150.9 in northern Europe, 122.5 in southern Europe, and 76.3 in central and eastern Europe.

- Demographics:

Approximately 94% of all new breast cancer cases in the US occur in women over the age of 40, with a median age at diagnosis of 61. In the US, White women have a higher incidence of breast cancer after the age of 40, while Black women have a higher incidence before age 40 and are more likely to die at any age compared to White women (American_Cancer_Society. Breast Cancer Facts & Figures 2007-2008. Atlanta, 2008).

- The main existing treatment options:

Treatment options for breast cancer patients differ by hormone receptor (HR) and Human Epidermal Receptor 2 (HER2) status. Based on NCCN guidelines, patients with recurrent or metastatic breast cancer (HR+, HER2−) should receive sequential rounds of endocrine therapy until progression or unacceptable toxicity. Chemotherapy should be initiated if there is no clinical benefit following three sequential rounds of endocrine therapy or if the patient develops symptomatic visceral disease. In patients who are HR-negative and HER2-negative, chemotherapy is the preferred treatment choice. Preferred chemotherapy regimens are anthracycline or taxane based, although other options such as anti-metabolites (capecitabine or gemcitabine) and microtubule inhibitors (vinorelbine or eribulin) are considered acceptable. There is no compelling evidence that combination regimens are superior to sequential agents, but both approaches are considered acceptable by the NCCN. If bone disease is present, treatment regimens should include denosumab, zoledronic acid, or pamidronate.

ESMO guidelines differ slightly from NCCN guidelines and suggest that in the absence of contraindications or patient concerns, anthracycline- or taxane- based regimens, preferably as single agents should be considered as first-line treatment for HER2-negative metastatic breast cancer patients who have not previously received these treatments in the adjuvant setting (Cardoso et al. 2014). Capecitabine and vinorelbine are acceptable alternatives. Each regimen (except anthracyclines) should be given until disease progression or unacceptable toxicity.

- Risk factors for the disease:

Major risk factors include female gender, older age, early menarche, late menopause, older age at first childbirth, nulliparity, family history of breast cancer, mutations in BRCA1 and BRCA2 genes, certain benign breast lesions, e.g., atypical ductal hyperplasia and atypical lobular hyperplasia, history of chest radiotherapy, combined hormone therapy post menopause and excessive alcohol consumption.

- Natural history of the indicated condition in the untreated population:

Mortality: In Europe in 2012 around 131,000 females died from breast cancer, yielding an age-standardized death rate of 23 per 100,000 per year (Ferlay et al. 2013). The five-year survival figure for women with all stages of the disease is estimated at approximately 89% in the US and 76% in Europe (Coleman et al. 2003; American_Cancer_Society. Global Cancer Facts & Figures 2007).

Outcome of the (untreated) target disease: Because metastatic breast cancer is not curable with current therapy, the goal of therapy in this setting is symptom palliation and to prolong PFS and OS while maintaining QoL. Median survival after first metastatic recurrence treated with chemotherapy is approximately 18–20 months, but ranges from a few weeks to many years, depending on various prognostic factors identified, including Human Epidermal Growth Factor Receptor 2 (HER2), menopausal and HR status, and age.

- Important co-morbidities:

Hypertension (34.5%), previous solid tumor (12.4%), diabetes (10.4%), respiratory disease (8.2%), psychiatric disease (5.8%), angina (4.2%), obesity (3.9%), MI (3.1%), stroke (2.8%), and stomach/intestinal disease (2.4%) (Piccirillo et al. 2008).

SI.3 NON–SMALL CELL LUNG CANCER

- Incidence:

Data published by IARC showed that there were over 1.8 million new cases of lung cancer worldwide in 2012 (http://globocan.iarc.fr) with an age-standardized rate of 23.1 per 100,000 population. In Europe, approximately 410,000 new cases (12% of all incident cancer cases) of lung cancer were diagnosed in 2012 (age-standardized rate 41.9 per 100,000 population) for both sexes. Lung cancer is the second most common cancer in men (16% of all new cases) and third most common cancer in women (7.4%) in Europe, with approximately 291,000 new cases for men (age-standardized rate: 68.3 per 100,000 population) and 119,000 new cases diagnosed in women (age-standardized rate: 21.6 per 100,000 population). In men, the highest incidence of lung cancer was in Central and Eastern European countries (i.e., Hungary, former Yugoslav Republic of Macedonia, Serbia and Poland) and lowest in Northern Europe (i.e., Finland and Sweden). The opposite trend was seen for women with higher incidence rates in Northern Europe and lower rates in Eastern Europe (Ferlay et al. 2013).

- Prevalence:

Data published by IARC in 2013 showed that lung cancer is the fourth most prevalent neoplasm worldwide, with an estimated 5-year prevalence of around 1.89 million cases in 2008 (meaning there were an estimated 1.89 million individuals living with lung cancer in 2008 who had been diagnosed in the preceding 5 years (1.26 million men and 626,000 women) (Bray et al. 2013). Prevalence is higher in more developed than in less developed regions (crude 1-year prevalence: 46.5 vs. 10 cases per 100,000 population

for men and 21.9 vs. 4.5 cases per 100,000 population for women). IARC reported the 1-year crude prevalence per 100,000 population aged ≥15 in different geographic regions. It was reported as 42.8 for males and 9.3 for females in central and eastern Europe, 30.4 for males and 21.0 for females in northern Europe, 50.0 for males and 11.8 for females in southern Europe and 47.7 for males and 18.5 for females in western Europe.

- Demographics:

Lung cancer predominately occurs in older individuals (median age at diagnosis of 70), with the probability of developing lung cancer being very low until age 39 in both sexes. Lung cancer is more common in men than in women. The risk of developing lung cancer remains higher among men in all age groups after age 40 years. Women have a higher incidence of localized disease at presentation and of adenocarcinoma and typically are younger when they present with symptoms. Lung cancer incidence rates are similar among African American and White women; however, lung cancer occurrence is approximately 45% higher among African American men than among white men.

EGFRmut-positive patients have a similar median age at diagnosis compared with EGFR-wild type patients. However, EGFR mutations are more common in women (31%–72% of EGFRmut-positive patients are women) (D'Angelo et al. 2011; Arcila et al. 2012; Rosell et al. 2009; Wang et al. 2012), never smokers (32%–77%) (Wang et al. 2012; Rosell et al. 2009; Arcila et al. 2012; D'Angelo et al. 2011; Gahr et al. 2013), and patients with adenocarcinomas (49%–99%) (Dong et al. 2013; Takahashi et al. 2010; Huang et al. 2011; Rosell et al. 2009).

- The main existing treatment options:

Current NCCN and ESMO guidelines recommend consideration of tyrosine kinase inhibitors (TKIs), as a first-line therapy for advanced disease in patients whose tumors harbor EGFR activating mutations (D'Addario, Fruh et al. 2010; Beasley and Milton 2011; Reck, Popat et al. 2014).

Patients for whom an EGFR TKI is not indicated, platinum-based doublet chemotherapy in combination with bevacizumab remain a treatment option for first-line treatment of metastatic non-squamous non–small cell lung cancer (NSCLC). For patients who respond to therapy, preferred maintenance therapies include bevacizumab, pemetrexed, or gemcitabine (NCCN 2014). For most patients, four cycles of chemotherapy are recommended, with a maximum of six cycles (Reck et al. 2014)

- Risk factors for the disease:

Major risk factors for NSCLC include: smoking tobacco, exposure to asbestos, radon, halogen ether, inorganic arsenic, chromium, nickel, copper, cadmium, vinyl chloride, and radioisotope exposure; pre-existing non-malignant lung diseases, like Chronic

Obstructive Pulmonary Disease (COPD), idiopathic pulmonary fibrosis and tuberculosis, family history of lung cancer and history of chest radiotherapy. Major risk factors for EGFRmut-positive NSCLC include: female gender, patients who do not currently smoke or have never smoked, patients with adenocarcinomas and Asian race/ethnicity.

- Natural history of the indicated condition in the untreated population:

Mortality Lung cancer is the most common cause of cancer death worldwide with 1.6 million deaths in both sexes (1.1 million men and 491,000 women) (http://globocan.iarc.fr). In Europe in 2012, approximately 354,000 people died from lung cancer, yielding an age-standardized death rate of 35.2 per 100,000 per year (59.1 per 100,000 for men and 17.2 per 100,000 in women) (Ferlay et al. 2013). Lung cancer is the leading cause of cancer death in men in all European countries except Sweden, and although it is the third leading cause of cancer deaths in women, it is becoming the most common cause of death (overtaking breast cancer) in a growing number of countries.

Outcome of the (untreated) target disease: NSCLC represents about 85% of all lung cancers and the most common histologies are adenocarcinoma (40–45%), epidermoid or squamous carcinoma (30–35%), and large cell carcinoma (<10%) (http://www.cancer.org). Lung cancer is commonly diagnosed at an advanced stage, presenting as metastatic disease in approximately 57% of all cases (http://seer.cancer.gov/statfacts/html/lungb.html).

- Important co-morbidities:

Hypertension (37.7%), respiratory disease (28.5%), previous solid tumor (18.0%), angina (14.2%), diabetes (11.2%), MI (9.9%), stroke (5.3%), CHF (5.1%), stomach/intestinal disease (5.0%), psychiatric disease (4.8%) (Piccirillo et al. 2008).

SI.4   METASTATIC RENAL CELL CARCINOMA
- Incidence:

In Europe, in 2012, there were approximately 115,200 new cases of kidney cancer (71,700 cases in men and 43,400 cases in women), yielding an age-standardized incidence rate of 12.1 new cases per 100,000 population for both sexes. The incidence rate is higher in men compared with women (age-standardized rate of 17.2 vs. 8.1 per 100,000, respectively) (Ferlay et al. 2013). There are no obvious geographical variations in incidence rates for males or females.

- Prevalence:

Data published by IARC reported an estimated 5-year prevalence of approximately 750,000 kidney cancer cases in 2008 world-wide (meaning there were an estimated 750,000 individuals living with kidney cancer in 2008 who had been diagnosed in the preceding 5 years (Bray et al. 2013). Prevalence is higher in more developed than in less developed regions (crude 1-year prevalence: 17.2 vs. 1.6 cases per 100,000 population for men and 9.5 vs. 0.9 cases per 100,000 population for women).

IARC reported the following 1-year crude prevalence per 100,000 population aged ≥ 15 in different geographic regions. It was reported as 21.5 for males and 11.0 for females in western Europe, 14.3 for males and 8.5 for females in northern Europe, 13.9 for males and 8.2 for females in central and eastern Europe, and 13.7 for males and 7.0 for females in southern Europe.

- Demographics:

The median age at diagnosis for kidney cancer patients is 64 years. Kidney cancer is more common in African Americans and American Indian and Alaska Native populations. Men have approximately a two-fold higher risk of developing and dying from kidney cancer compared to women.

- The main existing treatment options:

Main treatment options in patients with metastatic disease include 3 agents that target angiogenesis (sunitinib, bevacizumab, and pazopanib) and a mammalian target of rapamycin (mTOR)–targeted therapy (temsirolimus) that have been approved as front-line agents.

Renal cell cancers (RCC) are being diagnosed at an earlier stage, and nephron-sparing surgery and thermal ablation are gaining acceptance as a treatment of choice for smaller tumors. Radical nephrectomy is the standard for larger and central tumors.

- Risk factors for the disease:

Major risk factors include cigarette smoking, obesity, hypertension, non-aspirin non-steroidal anti-inflammatory drugs used over a long duration of time, long term dialysis that leads to an increased incidence of cystic disease of the kidney, renal transplant recipients that develop acquired renal cystic disease of the native kidney, exposure to cadmium and trichloroethylene, and certain genetic diseases (e.g., Von Hippel-Lindau disease).

- Natural history of the indicated condition in the untreated population:

Mortality: In Europe in 2012, approximately 49,000 people died from kidney cancer, yielding an age-standardized death rate of 4.7 per 100,000 per year (Ferlay et al. 2013). The mortality rate was more than double in men compared to women (7.2 vs. 2.8 per 100,000, respectively). Approximately 31,300 men and 17,700 women died from kidney cancer in Europe in 2012.

Outcome of (untreated) targeted disease:

The relative 5-year survival rate of metastatic kidney cancer is 12%.

- Important co-morbidities:

Information on specific comorbidities in RCC patients was not identified. In a large, population-based, study of renal cancer patients in Denmark, approximately 40% had a

Charlson Comorbidity Index greater than zero. Additionally, an increase in the comorbidity index predicted decreased 1- and 5-year OS (Lund et al. 2009).

SI.5 OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CANCER
- Incidence:

Ovarian cancer is one of the most common gynecological cancers in Europe and the United States. The incidence of ovarian cancer varies by geographic region, with the highest rates observed in North America, Europe, and other developed countries (http://globocan.iarc.fr). Based on data published by IARC, there were 65,500 new cases of ovarian cancer, yielding an age-standardized incidence rate of 13.1 cases per 100,000 women in Europe (Ferlay et al. 2013). The incidence rates are highest in Central/Eastern (14.8 per 100,000) and Northern Europe (14.9 per 100,000), compared to Southern (12.0 per 100,000) and Western Europe (10.4 per 100,000) (Ferlay et al. 2013). Incidence rates in the highest-risk areas (i.e., Northern Europe) have declined since the 1980s, while rates are increasing in low-risk areas (i.e., Southern Europe) (Bray et al. 2005).

Based on the results of two phase III trials of platinum based therapies in stage III and IV ovarian cancer patients, 60% to 70% of patients who respond to first-line platinum-based therapy will have a recurrence (du Bois et al. 2003; Ozols et al. 2003). Approximately 20% of women will experience a recurrence within six months of initial platinum therapy, and will be considered platinum resistant (Shaboodien et al. 2013).

Fallopian tube cancer

Primary fallopian tube cancer accounts for less than 1% of all cancers in the female genital tract (Kosary 2007a). In Nordic countries, the incidence of primary fallopian tube cancer ranges from 4.3 to 6.5 cases per million (Riska et al. 2012).

Primary peritoneal cancer

No population-based estimates for the incidence of primary peritoneal cancer in European countries were identified.

- Prevalence

Ovarian cancer: Data published by IARC estimates a 5-year prevalence of approximately 550,000 ovarian cancer cases world-wide in 2012. There is a nearly four-fold difference in 1-year prevalence estimates for developed countries compared with less developed countries (24.1 vs. 6.6 per 100,000, respectively) (Bray et al. 2013). IARC reported the 1-year crude prevalence estimates per 100,000 population in different geographic regions. It was reported as 14.6 in central and eastern Europe, 16.6 in northern Europe, 12.6 in southern Europe and 14.3 in western Europe.

Fallopian tube cancer: No population-based prevalence estimates for European countries were identified. However, the estimated prevalence of fallopian tube cancer in the United States, based on the 2011 complete prevalence estimates from the Surveillance, Epidemiology and End Results Program (NCI, USA)(SEER), is approximately 7,719 cases.

Primary peritoneal cancer: No population-based prevalence estimates for European countries were identified. However, the estimated prevalence of primary peritoneal cancer in the United States, based on the 2011 complete prevalence estimates from SEER, is approximately 4,267 cases.

- Demographics:

The median age at diagnosis for ovarian cancer is 63 years, with peak incidence occurring at age 60 (Holschneider and Berek 2000). Women who develop ovarian cancer are most commonly White and peri- or post-menopausal (http://seer.cancer.gov/statfacts/html/ovary.html). The demographics for fallopian tube and primary peritoneal cancer are similar to that of epithelial ovarian cancer.

- The main existing treatment options:

The standard of care for ovarian cancer includes surgical exploration for primary staging and for cytoreduction or debulking. If the disease appears to be confined to the pelvis, comprehensive surgical staging is indicated. The volume of residual disease at the completion of surgery represents one of the most powerful prognostic factors. According to the 2013 NCCN ovarian cancer guidelines, residual disease of less than 1 cm is evidence of optimal cytoreduction, although the greatest possible effort should be made to remove all obvious disease.

Standard therapy for all patients with advanced disease following surgery is a taxane/platinum combination, usually carboplatin and either paclitaxel or docetaxel for a minimum of 6 cycles; Standard postoperative chemotherapy is combination therapy with platinum and paclitaxel. Cisplatin and paclitaxel or carboplatin and paclitaxel are accepted alternatives. Randomized studies have proven that both regimens result in equivalent survival rates. However, because of a more tolerable toxicity profile, the combination of carboplatin and paclitaxel is preferred (NCCN 2013).

- Risk factors for the disease:

Major risk factors include: older age, nulliparity, older age at first birth, post-menopausal treatment with estrogens or clomiphene, family history of breast cancer or CRC and mutations in BRCA1 and BRCA2 genes.

Individuals with a BRCA1 gene mutation have approximately 40–85% cumulative risk of breast cancer by the age of 70 and a 25–65% risk of developing epithelial ovarian cancer. Those with a BRCA2 gene mutation have a 40–85% lifetime risk of developing

breast cancer and a 15–20% risk of developing epithelial ovarian cancer (Pruthi et al. 2010). In addition, women with a family history of ovarian cancer have a three to seven-fold increased risk of developing ovarian cancer (Salzberg et al. 2005).

The risk of ovarian cancer is two to three times higher in women who have not had children and is modestly increased among those with early menarche (age <11 years) or menopause at age 55 years or older (Salzberg et al. 2005). Women who have been pregnant have a 40-60% decreased risk for developing ovarian cancer compared with nulliparous women (Salzberg et al. 2005). One pregnancy lowers ovarian cancer risk by as much as one third and the reduction in risk increases with each additional pregnancy (Hunn and Rodriguez 2012). In addition, use of oral contraceptives for more than 10 years and breastfeeding are also associated with a decreased risk for ovarian cancer (Salzberg et al. 2005).

- Natural history of the indicated condition in the untreated population:

Mortality:
Ovarian cancer: Ovarian cancer has a higher fatality-to-case ratio than any other gynaecologic malignancy (Holschneider and Berek 2000). It is the fifth leading cause of cancer mortality among European women (Ferlay et al. 2013). In Europe, the age-adjusted 2012 mortality rate is 7.6 deaths per 100,000 women per year (42,700 deaths), with the highest rates in Northern Europe (8.7 per 100,000) and the lowest rates in Southern Europe (6.4 per 100,000) (Ferlay et al. 2013).

Fallopian tube cancer: The five-year survival by stage is approximately 81% for stage I, 65% for stage II, 54% for stage III, and 36% for stage IV, based on the data available in the United States (Wethington et al. 2008). The relative 5-year survival by age at diagnosis (years) is as follows: 40–49 (73.9%), 50–59 (61.8%), 60–69 (64.6%), 70–79 (58.8%) and >80 (61.2%) (Kosary 2007a). No population-based mortality estimates for European countries were identified.

Primary peritoneal cancer: The prognosis of peritoneal cancer is poor, and is similar to that of advanced ovarian cancer (Jaaback et al. 2006). No population-based mortality estimates for European countries were identified.

Outcome of the (untreated) target disease: Due to asymptomatic early-stage disease, most women who are diagnosed with ovarian cancer already have metastatic disease. The relative 5-year survival of patients with distant disease is 27.4%.

Important co-morbidities:
Hypertension (51.8%), coronary artery disease or atherosclerosis (18.5%), osteoarthritis (13.4%), diabetes (13.3%) CHF (11.9%), and COPD (10.3%) (Chia et al. 2013).

SI. 6 CERVICAL CANCER

- Incidence:

Worldwide, cervical cancer is the fourth most common cancer in women, with approximately 528,000 new cases diagnosed in 2012. The majority of cervical cancer cases are diagnosed in less developed countries (445,000 cases) compared with developed countries (83,000 cases) (http://globocan.iarc.fr).

According to data published by IARC, there were approximately 58,300 cases of cervical cancer in Europe in 2012 (Ferlay et al. 2013). The age-standardized incidence rate was 13.4 per 100,000 per year. The rates were highest in Central/Eastern Europe (19.2 cases per 100,000), whereas Northern, Western, and Southern Europe had very similar and lower rates (9.9, 8.7 and 10.0 cases per 100,000, respectively).

- Prevalence:

Data published by IARC indicate that cervical cancer is the 6th most prevalent cancer worldwide, with an estimated 5-year prevalence of approximately 1.55 million women (meaning there were 1.55 million women living with cervical cancer in 2008 who had been diagnosed in the preceding 5 years) (Bray et al. 2013). The prevalence is slightly higher in less developed countries compared with more developed regions (crude 1-year prevalence: 17.7 vs 12.1 per 100,000). IARC reported 1-year prevalence estimates per 100,000 in different geographic regions. It was reported as 19.6 in central and eastern Europe, 10.0 in northern Europe, 11.3 in southern Europe and 9.6 in western Europe.

- Demographics:

The median age of diagnosis of cervical cancer is 49 and is most frequently diagnosed among women aged 35–44 (http://seer.cancer.gov/statfacts/html/cervix.html). Cervical cancer is more common in Black and Hispanic women compared with white women (incidence rates of 9.4, 10.2 and 7.8 per 100,000, respectively). Mortality from cervical cancer is nearly double in Black women (4.1 per 100,000) compared with White women (2.1 per 100,000).

- The main existing treatment options:

There are few treatment options available to metastatic cervical cancer (mCC) patients and chemotherapy is considered palliative and given to relieve symptoms and improve QoL (Colombo et al. 2012). Preferred chemotherapy regimens, based on NCCN and ESMO guidelines include cisplatin and paclitaxel-based regimens. NCCN guidelines include individualized radiation therapy for control of pelvic disease and other symptoms.

- Risk factors for the disease:

Major risk factors include persistent infection with a carcinogenic type of human papillomavirus (HPV), Human Immunodeficiency Virus (HIV) infection, and family history of cervical cancer. Among women with an HPV infection, risk factors for developing

cervical cancer include the following: smoking, multiparity, long-term oral contraceptive use, and lack of cervical cancer screening tests.

- Natural history of the indicated condition in the untreated population:

Mortality: Globally there were an estimated 266,000 deaths from cervical cancer in 2012, accounting for 7.5% of all female cancer deaths (http://globocan.iarc.fr). Most cervical cancer deaths (87%) occur in developing countries. Mortality varies 18-fold between different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe, and Australia/New Zealand to more than 20 per 100,000 in places like Eastern Africa (27.6).

In Europe, there were approximately 24,400 deaths from cervical cancer in 2012, with an age-standardized mortality rate of 4.9 per 100,000 (Ferlay et al. 2013). The highest mortality rate was seen in Central/Eastern Europe (8.0 per 100,000) and the lowest in Western Europe (2.4 per 100,000). Mortality rates have been declining in Europe, ranging from −5.9% per year in Switzerland to −2.0% in Croatia and Spain (Karim-Kos et al. 2008).

Outcome of the (untreated) target disease:
Few treatment options are available for mCC and most are palliative. Localized cervical cancer can be treated and has a 5-year survival rate of 91%. Screening for cervical cancer has led to a decline in the incidence in developed countries. However, in low-resource areas, the incidence of cervical cancer continues to increase. Lack of screening also leads to an increase in the proportion of cases that present at later stages, where currently, cures are not possible.

- Important co-morbidities:

Based on a cohort of cervical cancer patients treated with cisplatin, topotecan or paclitaxel in the US MarketScan claims database from 2007–2012, common comorbidities within 30 days of mCC diagnosis included hypertension (24%), anemia (21%), hydronephrosis (14%), dehydration (12%), lymphadenopathy (12%), lung disorder (12%), neutropenia (11%), dyspnoea (11%), and urinary tract infection (11%).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

1. WOUND HEALING

A bevacizumab treatment-related delay in wound healing was observed in two wound healing models (linear incision and circular wound) in the rabbit. No effect on wound healing was seen in a linear incision model in the cynomolgus monkey, indicating that the effect can be variable.

Relevance to human usage: Yes

Discussion:

Angiogenesis, in general, and Vascular Endothelial Growth Factor (VEGF) are implicated in wound healing. The inhibition of angiogenesis following administration of bevacizumab could adversely affect wound healing in humans. In clinical trials as well as in the post-marketing setting, treatment with bevacizumab has been observed to be associated with an increased risk of wound healing complications.

2. EMBRYO-FETAL DEVELOPMENT:

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all tested doses of 10-100 mg/kg. The maternal no-observed-adverse-effect level (NOAEL) was 10 mg/kg, while the fetal NOAEL was < 10 mg/kg (five doses over 12 days).

Relevance to human usage: Yes

Discussion:

Angiogenesis has been shown to be critically important to fetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy. Cases of fetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics, have been observed in the post-marketing setting.

3. PHYSEAL DYSPLASIA

Angiogenesis, in general, and VEGF are critically implicated in embryogenesis and growth. Pre-clinical reports indicated that bevacizumab disturbed physeal bone development in juvenile monkeys, potentially relevant to growing children. It should be noted; however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

Relevance to human usage: No

Discussion:

Not applicable. Physeal dysplasia is a histopathological term. When used in a clinical context it has a congenital connotation and is not reflective of use of bevacizumab in children.

4. OVARIAN FUNCTION:

Perturbation of ovarian function was observed. Inhibition of ovarian function was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with bevacizumab for either 13 or 26 weeks. The doses associated with this effect were greater than or equal to 4 times the human therapeutic dose or greater than or equal to 2-fold above the expected human exposure based on average serum concentrations in female monkeys.

Relevance to human usage: Yes

Discussion:

Angiogenesis, in general, and VEGF are implicated in ovarian function. Cases of ovarian failure (OF) have been observed in patients treated with bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of women; however, the long-term effects of treatment with bevacizumab on fertility are unknown.

5. NEPHROTOXICITY:

No nephrotoxic safety concerns were identified in pre-clinical toxicity studies.

Relevance to human usage: No

Discussion:

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5–1.9 times baseline level), both with and without proteinuria, are associated with the use of Avastin. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with Avastin.

6. HEPATOTOXICITY:

No hepatotoxic safety concerns were identified in the pre-clinical toxicity studies.

Relevance to human usage: No

Discussion:

The effect of bevacizumab on hepatic function will continue to be monitored by assessment of the incoming safety data from ongoing trials and by routine pharmacovigilance (PhV) activities.

7. CARDIOTOXICITY:

No evidence of cardiotoxicity was observed in repeat-dose toxicity studies in cynomolgus monkeys treated Intravenous (IV) with up to 50 mg/kg of bevacizumab for 26 weeks.

Relevance to human usage: No

Discussion

The study BO17920 was completed in May 2011. The results of QTc evaluations in 1109 adjuvant colon cancer patients enrolled in study BO17920 indicated no obvious imbalances in delta QTc between the treatment arms. Based on the data obtained, the analysis and the independent expert assessment, Genentech/Roche believes that these data address questions regarding the impact of bevacizumab on the QT interval and fulfil the Avastin post-marketing commitment to several regulatory agencies.

Conclusion

None of the safety concerns from non-clinical data are considered as important identified, important potential risks, or missing information.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Clinical trial exposure data are presented below for each indication by duration of exposure, age group and gender, dose and ethnic or racial origin respectively in Table 5 to Table 32. In addition, exposure data pooled for all indications is presented in Table 1 to Table 4.

1.   <u>ALL INDICATIONS</u>

Table 1   Duration of Exposure

```
expo_dur2b_rm07  Summary of Clinical Exposure (21d Safety Follow-up) by Duration [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS     Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
```

	<= 6 months N = 3692	>6 - 12 months N = 3405	>12 - 24 months N = 2485	>24 - 36 months N = 201	>36 months N = 37
Total					
Mean	0.284	0.734	1.264	2.364	3.863
Median	0.293	0.715	1.191	2.330	3.603
Min-Max	0.00 - 0.50	0.51 - 1.00	1.00 - 2.00	2.01 - 3.00	3.01 - 6.46
Sum	1047.20	2498.67	3140.64	475.09	142.94
n	3691	3405	2485	201	37

```
n represents number of patients contributing to summary statistics.
Breast Cancer:      AV02100 AV02119 AV03693 AV03694 BO17708 BO20231 GO25632  ||  Cervical Cancer: ML01230
Colorectal Cancer: AV00780 AV02107 AV02192 AV03200 NO16966                   ||  Glioblastoma:      AV03708 BO21990
Lung Cancer:        AV00757 AV04599 BO17704 JO25567  Ovarian Cancer:  AV03390 AV04095 BO17707 ML01187 MO22224
Renal Cancer:       BO17705
DM11 06MAY2016:18:28:51
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Table 2 Age Group and Gender

expo_age2b_rm07 Summary of Clinical Exposure (21d Safety Follow-up) by Age Group and Gender [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
        AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
        BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only

	18-39 N = 559	40-64 N = 6441	>=65 N = 2819	Missing N = 1
Female				
Mean	0.733	0.788	0.725	0.370
Median	0.626	0.712	0.653	0.370
Min-Max	0.01 - 3.75	0.01 - 6.46	0.02 - 5.12	0.37 - 0.37
Sum	338.66	3891.67	1420.63	0.37
n	462	4941	1960	1
Male				
Mean	0.793	0.690	0.631	-
Median	0.671	0.589	0.523	-
Min-Max	0.02 - 3.22	0.00 - 3.13	0.01 - 3.60	-
Sum	76.87	1032.80	541.64	-
n	97	1497	859	0
Total				
Mean	0.743	0.765	0.696	0.370
Median	0.635	0.690	0.600	0.370
Min-Max	0.01 - 3.75	0.00 - 6.46	0.01 - 5.12	0.37 - 0.37
Sum	415.54	4926.36	1962.27	0.37
n	559	6440	2819	1

n represents number of patients contributing to summary statistics.
Breast Cancer: AV02100 AV02119 AV03693 AV03694 BO17708 BO20231 GO25632 || Cervical Cancer: ML01230
Colorectal Cancer: AV00780 AV02107 AV02192 AV03200 NO16966 || Glioblastoma: AV03708 BO21990
Lung Cancer: AV00757 AV04599 BO17704 JO25567 || Ovarian Cancer: AV03390 AV04095 BO17707 ML01187 MO22224
Renal Cancer: BO17705
DM11 06MAY2016:18:21:17   (1 of 1)

Table 3   Dose

exp_dose2b_rm07 Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS Center: ALL CENTERS
Safety Population - Bevacizumab Patients only

	2.5 MG/KG/WEEK N = 2690	5 MG/KG/WEEK N = 7130	Total N = 9820
Total			
Mean	0.731	0.749	0.744
Median	0.709	0.638	0.657
Min-Max	0.01 - 2.43	0.00 - 6.46	0.00 - 6.46
Sum	1967.35	5337.19	7304.54
n	2690	7129	9819

n represents number of patients contributing to summary statistics.
Breast Cancer: AV02100 AV02119 AV03693 AV03694 BO17708 BO20231 GO25632 || Cervical Cancer: ML01230
Colorectal Cancer: AV00780 AV02107 AV02192 AV03200 NO16966 || Glioblastoma: AV03708 BO21990
Lung Cancer: AV00757 AV04599 BO17704 JO25567 || Ovarian Cancer: AV03390 AV04095 BO17707 ML01187 MO22224
Renal Cancer: BO17705
DM11 06MAY2016:18:32:05

Table 4   Ethnic or Racial Origin

exp_race2b_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin and Gender [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only

	ASIAN N = 664	BLACK N = 458	CAUCASIAN N = 8198	OTHER N = 224	MISSING N = 276
Female					
Mean	0.862	0.703	0.766	0.722	0.732
Median	0.761	0.583	0.693	0.598	0.635
Min-Max	0.03 - 4.14	0.01 - 5.83	0.01 - 6.46	0.06 - 3.01	0.06 - 2.69
Sum	457.95	260.96	4633.91	121.38	177.14
n	531	371	6052	168	242
Male					
Mean	0.893	0.641	0.666	0.570	0.511
Median	0.769	0.526	0.561	0.468	0.345
Min-Max	0.06 - 2.97	0.04 - 2.07	0.00 - 3.60	0.02 - 2.02	0.06 - 1.62
Sum	118.73	55.81	1428.01	31.89	16.87
n	133	87	2144	56	33
Total					
Mean	0.868	0.692	0.740	0.684	0.706
Median	0.761	0.548	0.654	0.552	0.578
Min-Max	0.03 - 4.14	0.01 - 5.83	0.00 - 6.46	0.02 - 3.01	0.06 - 2.69
Sum	576.68	316.77	6062.86	153.27	194.96
n	664	458	8197	224	276

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design.
Breast Cancer: AV02100 AV02119 AV03693 AV03694 BO17708 BO20231 GO25632 || Cervical Cancer: ML01230
Colorectal Cancer: AV00780 AV02107 AV02192 AV03200 NO16966 || Glioblastoma: AV03708 BO21990
Lung Cancer: AV00757 AV04599 BO17704 JO25567 || Ovarian Cancer: AV03390 AV04095 BO17707 ML01187 MO22224
Renal Cancer: BO17705
DM11 06MAY2016:19:22:22   (1 of 1)

2. <u>METASTATIC COLORECTAL CANCER</u>

Table 5 Duration of Exposure

```
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
             AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
             BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS      Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : COLORECTAL CANCER
```

	<= 6 months N = 876	>6 - 12 months N = 703	>12 - 24 months N = 299	>24 - 36 months N = 6
Total				
Mean	0.268	0.743	1.357	2.099
Median	0.267	0.720	1.248	2.084
Min-Max	0.01 - 0.50	0.51 - 1.00	1.00 - 2.00	2.02 - 2.27
Sum	234.37	522.31	405.88	12.59
n	876	703	299	6

```
n represents number of patients contributing to summary statistics.
DM11 04MAY2016:19:24:38                                                          (3 of 7)
```

Table 6   Age Group and Gender

expo_ageb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : COLORECTAL CANCER

	18-39 N = 82	40-64 N = 1078	>=65 N = 723	Missing N = 1
Female				
Mean	0.541	0.618	0.591	0.370
Median	0.485	0.553	0.482	0.370
Min-Max	0.01 - 1.20	0.02 - 2.27	0.04 - 2.13	0.37 - 0.37
Sum	25.43	276.96	162.44	0.37
n	47	448	275	1
Male				
Mean	0.677	0.655	0.611	-
Median	0.567	0.597	0.522	-
Min-Max	0.14 - 1.56	0.02 - 2.11	0.01 - 2.02	-
Sum	23.69	412.65	273.62	-
n	35	630	448	0
Total				
Mean	0.599	0.640	0.603	0.370
Median	0.509	0.579	0.501	0.370
Min-Max	0.01 - 1.56	0.02 - 2.27	0.01 - 2.13	0.37 - 0.37
Sum	49.11	689.61	436.07	0.37
n	82	1078	723	1

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33

Table 7   Dose

expo_doseb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : COLORECTAL CANCER

	2.5 MG/KG/WEEK N = 1331	5 MG/KG/WEEK N = 553	Total N = 1884
Total			
Mean	0.698	0.444	0.624
Median	0.632	0.348	0.546
Min-Max	0.01 - 2.13	0.01 - 2.27	0.01 - 2.27
Sum	929.50	245.66	1175.16
n	1331	553	1884

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:18:37:12

Table 8   Ethnic or Racial Origin

exp_raceb_rm07 DRAFT – Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin, Gender and Indication [Years] – Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population – Bevacizumab Patients only
Study Indication – High Level Term : COLORECTAL CANCER

	ASIAN N = 70	BLACK N = 139	CAUCASIAN N = 1593	OTHER N = 67	MISSING N = 15
Female					
Mean	0.756	0.636	0.594	0.598	0.348
Median	0.709	0.619	0.507	0.485	0.175
Min-Max	0.03 – 1.92	0.01 – 1.75	0.02 – 2.27	0.10 – 1.53	0.13 – 0.71
Sum	24.18	46.44	376.70	16.14	1.74
n	32	73	634	27	5
Male					
Mean	0.623	0.622	0.641	0.626	0.562
Median	0.542	0.504	0.578	0.493	0.253
Min-Max	0.16 – 1.23	0.04 – 1.85	0.01 – 2.11	0.02 – 2.02	0.14 – 1.62
Sum	23.66	41.08	614.56	25.04	5.62
n	38	66	959	40	10
Total					
Mean	0.683	0.630	0.622	0.615	0.490
Median	0.620	0.537	0.548	0.485	0.227
Min-Max	0.03 – 1.92	0.01 – 1.85	0.01 – 2.27	0.02 – 2.02	0.13 – 1.62
Sum	47.84	87.53	991.26	41.18	7.35
n	70	139	1593	67	15

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design.DM11 02MAY2016:15:34:03

3. METASTATIC BREAST CANCER

Table 9 Duration of Exposure

```
expo_durb_rm07  Summary of Clinical Exposure (21d Safety Follow-up) by Duration and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS      Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : BREAST CANCER
```

	<= 6 months N = 1073	>6 - 12 months N = 1056	>12 - 24 months N = 623	>24 - 36 months N = 56	>36 months N = 9
Total					
Mean	0.285	0.726	1.321	2.295	3.705
Median	0.290	0.712	1.259	2.193	3.603
Min-Max	0.01 - 0.50	0.51 - 1.00	1.00 - 1.98	2.01 - 2.97	3.05 - 4.50
Sum	305.84	766.37	822.87	128.53	33.34
n	1073	1056	623	56	9

```
n represents number of patients contributing to summary statistics.
DM11 04MAY2016:19:24:38
If at five
```

Table 10   Age Group and Gender

```
expo_ageb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS       Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : BREAST CANCER
```

	18-39 N = 230	40-64 N = 2018	>=65 N = 569
Female			
Mean	0.714	0.747	0.675
Median	0.578	0.654	0.575
Min-Max	0.06 - 3.75	0.01 - 4.21	0.02 - 4.50
Sum	163.53	1504.42	381.11
n	229	2013	565
Male			
Mean	0.925	1.234	0.342
Median	0.925	1.454	0.166
Min-Max	0.93 - 0.93	0.18 - 2.07	0.06 - 0.98
Sum	0.93	3.70	1.37
n	1	3	4
Total			
Mean	0.715	0.748	0.672
Median	0.578	0.654	0.569
Min-Max	0.06 - 3.75	0.01 - 4.21	0.02 - 4.50
Sum	164.45	1510.02	382.48
n	230	2018	569

```
n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33
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Table 11   Dose

expo_doseb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : BREAST CANCER

	2.5 MG/KG/WEEK N = 250	5 MG/KG/WEEK N = 2567	Total N = 2817
Total			
Mean	0.649	0.738	0.730
Median	0.654	0.635	0.635
Min-Max	0.06 - 1.56	0.01 - 4.50	0.01 - 4.50
Sum	162.36	1894.59	2056.95
n	250	2567	2817

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:18:37:12

Table 12   Ethnic or Racial Origin

exp_raceb_rm07   DRAFT - Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
             AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
             BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : BREAST CANCER

	ASIAN N = 240	BLACK N = 156	CAUCASIAN N = 2252	OTHER N = 112	MISSING N = 57
Female					
Mean	0.718	0.644	0.737	0.708	0.781
Median	0.693	0.433	0.635	0.591	0.731
Min-Max	0.06 - 1.90	0.04 - 2.90	0.01 - 4.50	0.06 - 2.41	0.16 - 2.03
Sum	171.49	98.50	1655.99	79.32	43.76
n	239	153	2247	112	56
Male					
Mean	0.214	1.234	0.520	-	-
Median	0.214	1.454	0.522	-	-
Min-Max	0.21 - 0.21	0.18 - 2.07	0.06 - 0.98	-	-
Sum	0.21	3.70	2.08	-	-
n	1	3	4	0	0
Total					
Mean	0.715	0.655	0.737	0.708	0.785
Median	0.693	0.438	0.635	0.591	0.734
Min-Max	0.06 - 1.90	0.04 - 2.90	0.01 - 4.50	0.06 - 2.41	0.16 - 2.03
Sum	171.70	102.20	1659.01	79.32	44.72
n	240	156	2252	112	57

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design.DM11 02MAY2016:15:34:03

4.   ADVANCED, METASTATIC OR RECURRENT NON–SMALL CELL LUNG CANCER

Table 13   Duration of Exposure

expo_durb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Duration and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
         AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
         BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : NSCLC

	<= 6 months N = 633	>6 - 12 months N = 382	>12 - 24 months N = 183	>24 - 36 months N = 30
Total				
Mean	0.266	0.691	1.286	2.397
Median	0.264	0.683	1.210	2.329
Min-Max	0.00 - 0.50	0.51 - 1.00	1.01 - 1.98	2.01 - 2.97
Sum	168.17	263.85	235.36	71.92
n	632	382	183	30

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:19:24:38

Table 14 Age Group and Gender

expo_ageb_rm07 Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : NSCLC

	18-39 N = 36	40-64 N = 758	>=65 N = 434
Female			
Mean	0.646	0.627	0.667
Median	0.476	0.520	0.537
Min-Max	0.12 - 1.84	0.03 - 2.97	0.02 - 2.95
Sum	11.62	203.65	119.45
n	18	325	179
Male			
Mean	0.435	0.576	0.580
Median	0.505	0.463	0.463
Min-Max	0.02 - 0.81	0.00 - 2.97	0.04 - 2.73
Sum	7.83	248.79	147.96
n	18	432	255
Total			
Mean	0.540	0.598	0.616
Median	0.505	0.482	0.483
Min-Max	0.02 - 1.84	0.00 - 2.97	0.02 - 2.95
Sum	19.45	452.44	267.41
n	36	757	434

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33

Table 15   Dose

expo_doseb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : NSCLC

	2.5 MG/KG/WEEK N = 363	5 MG/KG/WEEK N = 865	Total N = 1228
Total			
Mean	0.571	0.616	0.603
Median	0.479	0.482	0.482
Min-Max	0.02 - 2.43	0.00 - 2.97	0.00 - 2.97
Sum	207.29	532.02	739.30
n	363	864	1227

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:18:37:12

Table 16 Ethnic or Racial Origin

exp_raceb_rm07 DRAFT - Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
       AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
       BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : NSCLC

	ASIAN N = 152	BLACK N = 33	CAUCASIAN N = 995	OTHER N = 18	MISSING N = 30
Female					
Mean	0.959	0.671	0.573	0.586	0.621
Median	0.775	0.583	0.472	0.424	0.512
Min-Max	0.06 - 2.97	0.12 - 1.59	0.02 - 2.85	0.06 - 1.33	0.06 - 2.28
Sum	81.51	14.08	226.89	2.93	9.31
n	85	21	396	5	15
Male					
Mean	1.072	0.626	0.524	0.430	0.424
Median	0.947	0.560	0.441	0.402	0.345
Min-Max	0.06 - 2.97	0.05 - 1.34	0.00 - 2.50	0.12 - 1.10	0.06 - 1.57
Sum	71.80	7.52	313.31	5.60	6.35
n	67	12	598	13	15
Total					
Mean	1.009	0.655	0.543	0.474	0.522
Median	0.823	0.583	0.460	0.413	0.379
Min-Max	0.06 - 2.97	0.05 - 1.59	0.00 - 2.85	0.06 - 1.33	0.06 - 2.28
Sum	153.31	21.60	540.20	8.53	15.67
n	152	33	994	18	30

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design.DM11 02MAY2016:15:34:03

5. ADVANCED AND/OR METASTATIC RENAL CANCER

Table 17 Duration of Exposure

expo_ageb_rm07 Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : RENAL CANCER

	18-39 N = 11	40-64 N = 203	>=65 N = 123
Female			
Mean	0.549	0.966	0.715
Median	0.549	0.903	0.474
Min-Max	0.21 - 0.89	0.05 - 3.62	0.07 - 2.57
Sum	1.10	63.75	28.58
n	2	66	40
Male			
Mean	0.736	0.966	0.797
Median	0.671	0.999	0.663
Min-Max	0.17 - 1.98	0.08 - 3.13	0.06 - 3.60
Sum	6.62	132.31	66.12
n	9	137	83
Total			
Mean	0.702	0.966	0.770
Median	0.671	0.980	0.556
Min-Max	0.17 - 1.98	0.05 - 3.62	0.06 - 3.60
Sum	7.72	196.06	94.71
n	11	203	123

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33

Table 18 Age Group and Gender

expo_ageb_rm07 Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : RENAL CANCER

	18-39 N = 11	40-64 N = 203	>=65 N = 123
Female			
Mean	0.549	0.966	0.715
Median	0.549	0.903	0.474
Min-Max	0.21 - 0.89	0.05 - 3.62	0.07 - 2.57
Sum	1.10	63.75	28.58
n	2	66	40
Male			
Mean	0.736	0.966	0.797
Median	0.671	0.999	0.663
Min-Max	0.17 - 1.98	0.08 - 3.13	0.06 - 3.60
Sum	6.62	132.31	66.12
n	9	137	83
Total			
Mean	0.702	0.966	0.770
Median	0.671	0.980	0.556
Min-Max	0.17 - 1.98	0.05 - 3.62	0.06 - 3.60
Sum	7.72	196.06	94.71
n	11	203	123

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33

Table 19 Dose

expo_doseb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : RENAL CANCER

	5 MG/KG/WEEK N = 337	Total N = 337
Total		
Mean	0.886	0.886
Median	0.827	0.827
Min-Max	0.05 - 3.62	0.05 - 3.62
Sum	298.49	298.49
n	337	337

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:18:37:12

Table 20 Ethnic or Racial Origin

exp_raceb_rm07 DRAFT - Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
        AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
        BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : RENAL CANCER

	BLACK N = 2	CAUCASIAN N = 324	MISSING N = 11
Female			
Mean	–	0.877	0.625
Median	–	0.715	0.468
Min-Max	–	0.05 - 3.62	0.11 - 1.32
Sum	–	90.31	3.12
n	0	103	5
Male			
Mean	0.557	0.904	0.690
Median	0.557	0.879	0.457
Min-Max	0.19 - 0.93	0.06 - 3.60	0.27 - 1.33
Sum	1.11	199.80	4.14
n	2	221	6
Total			
Mean	0.557	0.895	0.661
Median	0.557	0.867	0.468
Min-Max	0.19 - 0.93	0.05 - 3.62	0.11 - 1.33
Sum	1.11	290.11	7.27
n	2	324	11

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design. DM11 02MAY2016:15:34:03

6.   EPITHELIAL OVARIAN CANCER

Table 21   Duration of Exposure

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expo_durb_rm07  Summary of Clinical Exposure (21d Safety Follow-up) by Duration and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
             AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
             BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS      Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : OVARIAN CANCER
```

	<= 6 months N = 660	>6 - 12 months N = 872	>12 - 24 months N = 1113	>24 - 36 months N = 47	>36 months N = 20
Total					
Mean	0.331	0.753	1.192	2.402	4.149
Median	0.353	0.750	1.112	2.346	3.912
Min-Max	0.06 - 0.50	0.51 - 1.00	1.00 - 2.00	2.02 - 2.97	3.01 - 6.46
Sum	218.72	656.23	1326.76	112.90	82.99
n	660	872	1113	47	20

```
n represents number of patients contributing to summary statistics.
DM11 04MAY2016:19:24:38
```

Table 22   Age Group and Gender

expo_ageb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
             AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
             BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : OVARIAN CANCER

	18-39 N = 92	40-64 N = 1797	>=65 N = 823
Female			
Mean	0.922	0.911	0.821
Median	1.036	0.942	0.789
Min-Max	0.06 - 2.55	0.06 - 6.46	0.06 - 5.12
Sum	84.78	1637.05	675.77
n	92	1797	823
Male			
Mean	-	-	-
Median	-	-	-
Min-Max	-	-	-
Sum	-	-	-
n	0	0	0
Total			
Mean	0.922	0.911	0.821
Median	1.036	0.942	0.789
Min-Max	0.06 - 2.55	0.06 - 6.46	0.06 - 5.12
Sum	84.78	1637.05	675.77
n	92	1797	823

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33

Table 23   Dose

expo_doseb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : OVARIAN CANCER

	2.5 MG/KG/WEEK N = 746	5 MG/KG/WEEK N = 1966	Total N = 2712
Total			
Mean	0.896	0.880	0.884
Median	1.038	0.797	0.884
Min-Max	0.06 - 1.35	0.06 - 6.46	0.06 - 6.46
Sum	668.20	1729.40	2397.60
n	746	1966	2712

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:18:37:12

Table 24   Ethnic or Racial Origin

exp_raceb_rm07   DRAFT - Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin, Gender and Indication [Years] - Pool
RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : OVARIAN CANCER

	ASIAN N = 149	BLACK N = 85	CAUCASIAN N = 2305	OTHER N = 18	MISSING N = 155
Female					
Mean	1.046	0.952	0.879	1.133	0.739
Median	0.999	0.884	0.901	1.039	0.635
Min-Max	0.12 - 4.14	0.17 - 5.83	0.06 - 6.46	0.37 - 3.01	0.06 - 2.69
Sum	155.91	80.90	2025.86	20.39	114.54
n	149	85	2305	18	155
Male					
Mean	-	-	-	-	-
Median	-	-	-	-	-
Min-Max	-	-	-	-	-
Sum	-	-	-	-	-
n	0	0	0	0	0
Total					
Mean	1.046	0.952	0.879	1.133	0.739
Median	0.999	0.884	0.901	1.039	0.635
Min-Max	0.12 - 4.14	0.17 - 5.83	0.06 - 6.46	0.37 - 3.01	0.06 - 2.69
Sum	155.91	80.90	2025.86	20.39	114.54
n	149	85	2305	18	155

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design. DM11 02MAY2016:15:34:03

7.   **CERVICAL CANCER**

Table 25   Duration of Exposure

expo_durb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Duration and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : CERVICAL CANCER

	<= 6 months N = 130	>6 - 12 months N = 70	>12 - 24 months N = 16	>24 - 36 months N = 2 and a
Total				
Mean	0.291	0.668	1.271	2.441
Median	0.304	0.628	1.146	2.441
Min-Max	0.02 - 0.50	0.51 - 0.99	1.01 - 1.86	2.26 - 2.62
Sum	37.78	46.79	20.33	4.88
n	130	70	16	2

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:19:24:38

Table 26   Age Group and Gender

expo_ageb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Age Group, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : CERVICAL CANCER

	18-39 N = 47	40-64 N = 152	>=65 N = 19
Female			
Mean	0.505	0.519	0.374
Median	0.408	0.471	0.329
Min-Max	0.07 - 1.86	0.02 - 2.62	0.06 - 1.12
Sum	23.75	78.93	7.10
n	47	152	19
Male			
Mean	-	-	-
Median	-	-	-
Min-Max	-	-	-
Sum	-	-	-
n	0	0	0
Total			
Mean	0.505	0.519	0.374
Median	0.408	0.471	0.329
Min-Max	0.07 - 1.86	0.02 - 2.62	0.06 - 1.12
Sum	23.75	78.93	7.10
n	47	152	19

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:17:53:33

Table 27   Dose

expo_doseb_rm07   Summary of Clinical Exposure (21d Safety Follow-up) by Dose Level and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
            AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
            BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : CERVICAL CANCER
                                                                              to

	5 MG/KG/WEEK N = 218	Total N = 218
Total		
Mean	0.504	0.504
Median	0.454	0.454
Min-Max	0.02 - 2.62	0.02 - 2.62
Sum	109.78	109.78
n	218	218

n represents number of patients contributing to summary statistics.
DM11 04MAY2016:18:37:12

Table 28   Ethnic or Racial Origin

exp_raceb_rm07   DRAFT - Summary of Clinical Exposure (21d Safety Follow-up) by Ethnic Origin, Gender and Indication [Years] - Pool RM07
Protocol(s): AV00757 AV00780 ML01187 ML01230 AV02100 AV02107 AV02119 AV02192 AV03200 AV03390
          AV03693 AV03694 AV03708 AV04095 AV04599 NO16966 BO17704 BO17705 BO17707 BO17708
          BO20231 BO21990 MO22224 JO25567 GO25632
Analysis: ALL PATIENTS   Center: ALL CENTERS
Safety Population - Bevacizumab Patients only
Study Indication - High Level Term : CERVICAL CANCER

	ASIAN N = 12	BLACK N = 35	CAUCASIAN N = 164	OTHER N = 2	MISSING N = 5
Female					
Mean	0.538	0.496	0.505	0.355	0.473
Median	0.545	0.405	0.442	0.355	0.479
Min-Max	0.07 - 0.98	0.06 - 2.62	0.02 - 2.26	0.35 - 0.36	0.12 - 0.88
Sum	6.45	17.36	82.89	0.71	2.37
n	12	35	164	2	5
Male					
Mean	-	-	-	-	-
Median	-	-	-	-	-
Min-Max	-	-	-	-	-
Sum	-	-	-	-	-
n	0	0	0	0	0
Total					
Mean	0.538	0.496	0.505	0.355	0.473
Median	0.545	0.405	0.442	0.355	0.479
Min-Max	0.07 - 0.98	0.06 - 2.62	0.02 - 2.26	0.35 - 0.36	0.12 - 0.88
Sum	6.45	17.36	82.89	0.71	2.37
n	12	35	164	2	5

n represents number of patients contributing to summary statistics.
More than 100 missing values for Race in MO22224 (Ovarian Cancer) due to data collection design.
DM11 02MAY2016:15:34:03

7.1 SPECIAL POPULATION EXPOSURE

Four Roche-sponsored interventional clinical trials are being (or have been) conducted in special populations where bevacizumab is an investigational drug. A total of 223 patients enrolled in Studies MO19286 and ML21868 (elderly population) and 134 patients in Studies BO20924 and BO25041 (pediatric population) received bevacizumab as an investigational drug.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 29   Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity: Hypersensitivity to the active substance, any of the excipients, Chinese Hamster Ovary cell products or other recombinant human or humanized antibodies	Avastin should not be given if the patient has a known hypersensitivity to the active substance, any excipients, Chinese Hamster Ovary cell products or other recombinant human or humanized antibodies.	No	Hypersensitivity is contraindicated in EU-Summary of Product Characteristics (SmPC).
Pregnancy	Women of childbearing potential must use effective contraception	No	Pregnancy is contraindicated in EU-SmPC.
Active Gastrointestinal(GI) perforation or fistula	Due to known risk of GI perforation with Avastin	No	Since, it's a known risk with Avastin, caution should be exercised that any wound including GI perforation, be fully healed prior to initiating Avastin. This has been adequately described in the EU SmPC. The safety profile for GI perforation and fistula has been well characterized and presented within the SmPC. The SmPC adequately describes the known risk factors, including treatment with Avastin, that may predispose patients to developing either GI perforation or fistula and recommends that caution should be exercised when treating patients with any known risk factors for GI perforation or fistula.
Corticosteroids: Chronic daily treatment with corticosteroids (dose > 10 mg/day methylprednisolone equivalent),	Avastin delayed reepithelialisation in rabbits, which was dose dependent and the doses administered were	No	The potential risk of wound healing complication increases when corticosteroids are used concomitantly with Avastin but the benefit of the combined use of these

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
excluding inhaled steroids.	below clinical dose. Corticosteroid administration showed similar effects on wound healing.		medications has increased survival for these patients. Precaution should be exercised if a patient develops Wound-healing complications during therapy. Bevacizumab should be withheld until the wound is fully healed.
Urine protein-creatinine ratio (UPCR) ≥ 1.0. Proteinuria: at screening >1g/24 hrs; ≥0.5g/24hrs	Evidence from clinical trials suggested that proteinuria may be related to the dose of bevacizumab (dose dependent).	No	Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy and has been adequately described in EU SmPC.
Central Nervous System(CNS): Craniospinal metastases (in Gynaecologic Oncology Group (GOG)-0240)/ Untreated CNS metastases - Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack, or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.	Patients with CNS metastases may have been at greater risk of tumor-associated hemorrhage when treated with bevacizumab. Patients receiving Avastin plus chemotherapy with a history of ATE, diabetes, or age greater than 65 have an increased risk of developing ATE.	No	Caution should be taken when treating patients with a previous history of ATE with Avastin. The contraindication for untreated brain metastases was removed from the Avastin SmPC [variation EMEA/ H/C/582/II/ 025, Commission Decision received on 25 March 2009] based on data showing no increased CNS bleeding risk compared to the reported background rates.
Wound healing : Patients with or with anticipation of invasive procedure, including a major surgical procedure, open biopsy or	Wound healing complication is an identified risk for bevacizumab, detected in non-clinical studies.	No	Preclinical data showed the effects of wound healing to be reversible when bevacizumab was withheld until wound was fully healed. Caution should be exercised not to initiate

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
significant traumatic injury within 28 days prior to the first date of bevacizumab therapy; major surgical procedure anticipated during the course of the study; or core biopsy, within 7 days prior to randomization. - Surgery, significant traumatic injury within the last 3-4 weeks - Minor surgical procedures (fine needle aspiration, core biopsy, central venous access device placement) within 2-7 days of study start - Non-healing wound, ulcer or bone fracture, including history of abdominal fistula, GI perforation, or intra-abdominal abscess for which an interval of 3 to 6 months must have passed before study entry			Avastin at least 28 days following a major surgery or until surgical wound is fully healed or any wound that is considered a wound healing complication. This has been adequately described in the EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
- Active infection - Inadequate bone marrow function	Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.	No	Infections are very common in this patient population especially if given concomitantly with myelotoxic chemotherapy and bevacizumab. Infections are manageable with appropriate treatment measures. The benefit received from Avastin outweighs the risk in the development of infection.
Prior invasive malignancy (except non-melanoma skin cancer) within 5 years of study start	Patients with other malignancies were excluded to provide quality data for the specific malignancy under investigation.	No	The Marketing Authorization Holder (MAH) considers that this concern is specific to the conduct of clinical trials and does not justify restriction of the treatments that may be prescribed by oncologists.
- Patients with active bleeding or pathologic conditions that carried high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels. - Inadequate coagulation parameters. - Current or recent (within 10 days of study treatment) full dose oral or parenteral anti-coagulation therapy or anti-platelet therapy - Chronic daily use of aspirin >325 mg/day	In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischemic attacks and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Patients treated with bevacizumab have an increased risk of hemorrhage.	No	Patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Cardiovascular system: Clinically significant cardiovascular disease e.g. uncontrolled hypertension, unstable angina, CHF New York Heart Association class II or greater, serious cardiac arrhythmia requiring medication, or Common Terminology Criteria for Adverse Events (CTCAE) (version 3) Grade II or greater peripheral vascular disease, MI (usually 3-12 months prior to study start) - Left ventricular ejection fraction (LVEF) defined by MUGA (multiple-gated acquisition scan)/ECHO (echocardiogram) below the institutional lower limit of normal for patients to be treated with anthracyclines	CHF were reported in clinical trials and the symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy. Reactions consistent with congestive heart failure were reported in clinical trials involving bevacizumab.	No	Benefit from Avastin has been shown across studies in patients with pre-existing controlled hypertension. Monitoring of blood pressure is recommended during therapy. Permanently discontinue, if medically significant hypertension cannot be adequately controlled with antihypertensive therapy. Serious cardiac arrhythmias have not been seen with Avastin, the most common findings seen were supraventricular tachycardia. Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure.
History of bowel obstruction, including sub-occlusive disease, related to the underlying disease and history of abdominal fistula, GI perforation, or intra-abdominal abscess. Evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on Computerised tomography (CT) scan or clinical symptoms of bowel obstruction was seen.	In clinical trials, Avastin showed an increased risk of bowel obstruction, abscess and GI perforation.	No	Underlying carcinoma is usually the main cause of bowel obstruction. Caution should be exercised for any patients with a wound healing complication and should not initiate treatment with Avastin until wound is fully healed. This has adequately described in EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Pre-existing peripheral neuropathy ≥CTC grade 2	Increased risk of peripheral neuropathy	No	Peripheral sensory neuropathy has commonly been seen in chemotherapy treated patients (paclitaxel or oxaliplatin) and Avastin may possibly exacerbate these reactions when combined with chemotherapy but patients have tolerated this adverse effect due to the benefit received from the combined treatments.

CNS = central nervous system; CT = computerised tomography; CTCAE = Common Terminology Criteria for Adverse Events; CVA = cerebrovascular accidents; ECHO = echocardiogram; GI = gastrointestinal; GOG = Gynaecologic Oncology Group; LVEF = left ventricular ejection fraction; MAH = Marketing Authorization Holder; MUGA = multiple-gated acquisition scan; M = myocardial infarction; UPCR = urine protein-creatinine ratio

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by cumulative exposure.

Bevacizumab is routinely administered until disease progression or unacceptable toxicity in both clinical trials and the post-marketing setting. Bevacizumab is approved for the treatment of patients with advanced cancer, who are likely to have a shortened life expectancy. Thus, clinical trial development programme limitations due to prolonged exposure and long latency periods are not anticipated in this patient population.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 30 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical trial program.
Breastfeeding women	Not included in the clinical trial program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in the clinical trial program.
Patients with renal impairment	Not included in the clinical trial program.
Patients with cardiovascular impairment	Not included in the clinical trial program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical trial program.
Immuno-compromised patients	Not included in the clinical trial program.
Population with relevant different ethnic origin: There is no preclinical or clinical data to date suggesting differences in the angiogenic pathway and mode of action of VEGF in patients of different ethnic origin	Patients of all ethnic origins were included into the clinical trials.
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical trial program.
Other:	
Children	71 patients (aged ≥ 6 months to <18 years; Study: BO20924), 60 patients (aged ≥ 3 years to < 18 years: Study BO25041) and 18 patients (Study PBTC-022)
Elderly	2665 patients (> 65 years)

VEGF = vascular endothelial growth factor

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE
SV.1.1 Method used to calculate exposure
Cumulative Patient Exposure (excluding Japan)

The calculation of drug utilization by age ranges/sex per indication outside Japan is based on Ipsos Synovate Oncology Monitor (updated Q4 2018) for EU5 countries (Germany, France, Italy, Spain, and the United Kingdom) and Tracking Study Chart Audits performed by ZS Associates in the United States. Drug utilization by age ranges/sex per indication for Rest of World (ROW: ex-US, ex-EU5 countries, ex-Japan) is based on utilization assumptions for the five major European markets.

The calculation of drug utilization by age ranges/sex per indication in Japan is based on the MDV® database (Medical Data Vision Co. Ltd) and information about age and gender component ratio.

It should be noted that use of Ipsos Synovate data is the only consistent approach to reflect drug utilization by age ranges/sex by indication. The market research projects that track studies for bevacizumab do not cover all indications and therefore cannot be used as a basis to calculate drug utilization.

Until 2017, drug utilization by age ranges/sex was not possible to include in the cumulative patient exposure calculation for marketing areas outside Japan as the contract Roche has in place with Ipsos Synovate covers a rolling 5-year time period only. Therefore, a breakdown of data by demography and dose is not available to Roche for the years until 2017 and hence are presented as part of the 'Unknown' bucket in the cumulative exposure in Table 33.

The calculation of cumulative patient exposure includes exposure in indications for which bevacizumab is approved for marketing in parts of the world other than the European Union, such as glioblastoma.

Based on the total amount of kilograms sold (volume sales), the assumptions listed in Table 31 have been considered to calculate patient exposure to bevacizumab by indication worldwide (excluding Japan).

Table 31   Assumptions Considered to Calculate Worldwide Patients (Excluding Japan) Exposed to Bevacizumab by Indication Based on Total Kg Sold

Worldwide assumptions (ex-US, ex-Japan)	US assumptions
mCRC Patients	
The average patient has a body weight of 70 kg	75 kg
The average administration is 5 mg/kg every 2 weeks for 6.0 months	30 % on standard dose (high dose)
Every patient receives 2.00 doses per month	27 weeks
mBC Patients	
The average patient has a body weight of 65 kg	70.2 kg
80% of patients receives average administration of 15 mg/kg every 3 weeks for 6.5 months	38.3 % on standard dose (high dose)
20% of patients receives average administration of 7.5 mg/kg every 3 weeks for 6.5 months	24 weeks
Every patient receives 3.30 doses per month	N/A
mNSCLC Patients	
The average patient has a body weight of 70 kg	73 kg
25% of patients receives average administration of 15 mg/kg every 3 weeks for 4.5 months	68 % on standard dose (high dose)
75% of patients receives average administration of 7.5 mg/kg every 3 weeks for 4.5 months	20 weeks
Every patient receives 2.50 doses per month	N/A
mRCC Patients	
The average patient has a body weight of 70 kg	75 kg
The average administration is 10 mg/kg every 2 weeks for 5.5 months	50 % on standard dose (high dose)
Every patient receives 4.00 doses per month	16 weeks

mBC = metastatic breast cancer; mCRC = metastatic colorectal cancer; mNSCLC = metastatic nonsmall cell lung carcinoma, mRCC = metastatic real cell carcinoma

Table 31   Assumptions Considered to Calculate Worldwide Patients (Excluding Japan) Exposed to Bevacizumab by Indication Based on Total Kg Sold (cont.)

Worldwide assumptions (ex-US, ex-Japan)	US assumptions
OC Patients	
The average patient has a body weight of 65 kg	70 kg
70% of patients receives average administration of 15 mg/kg every 3 weeks for 6.7 months	78.5 % on standard dose (high dose)
30% of patients receives average administration of 7.5 mg/kg every 3 weeks for 6.7 months	19.4 weeks
Every patient receives 2.3 doses per month	N/A
Every patient receives 4.00 doses per month	18 weeks
CC Patients	
The average patient has a body weight of 65 kg	70 kg
80% of patients receives average administration of 15 mg/kg every 3 weeks for 5 months	70 % on standard dose (high dose)
20% of patients receives average administration of 7.5 mg/kg every 3 weeks for 5 months	15.5 weeks
Every patient receives 2.3 doses per month	N/A
Other non-Promoted Indications	
The average patient has a body weight of 70 kg	N/A
The average administration is 10 mg/kg every 2 weeks for 5.5 months	N/A
Every patient receives 4.00 doses per month	N/A
GBM Patients	
The average patient has a body weight of 70 kg	75 kg
The average administration is 10 mg/kg every 2 weeks for 5.5 months	77 % on standard dose (high dose)
Every patient receives 4.00 doses per month	18 weeks

CC = Cervical cancer; GBM = glioblastoma multiforme; OC = Ovarian cancer

Note: 70 (Patient's weight in KG) × 2 (times a month every 2 weeks) × 10 (mg/kg needed by administration)=1,400 mg per month

1,400 mg per month/400 mg (Avastin Vial)=4 doses per month

Methodology for Japan (Chugai)

The assumption and methodology used for the calculation of marketing exposure to bevacizumab in Japan are presented in Table 32.

Table 32 Assumptions Considered to Calculate Japan Patients Exposed to Bevacizumab by Indication Based on Total Kg Sold

The period from approval acquisition in each indication	Calculation method
The first and second year from approval acquisition	1. Calculate <u>the ratio of the total dose for each indication</u> from sales assumption data for each year. 2. Calculate <u>the total dose for each indication</u> by multiplying the ratio of the total dose for each indication (previously calculated in "1".) by shipment volume for each year. 3. Calculate <u>the dose for each patient in each indication</u> from sales assumption data for each year. 4. Calculate <u>the estimated number of patients in each indication</u> by dividing the total dose for each indication (previously calculated in "2".) by the dose for each patient in each indication (previously calculated in "3".).

From the third year on	1. Calculate <u>the ratio of the total dose for each indication</u> from sales assumption data for each year.
	2. Calculate <u>the total dose for each indication</u> by multiplying the ratio of the total dose for each indication (previously calculated in "1".) by shipment volume for each year.
	3. Define <u>the dose for each patient in each indication</u> as follows:
	 o CRC: 3,300 mg
	 o NSCLC: 3,700 mg
	 o BC: 4,500 mg
	  o MG (Malignant Glioma): 3,900 mg
	  o OC: 5,800 mg
	  o CC:4,000mg
	4. Calculate <u>the estimated number of patients in each indication</u> by dividing the total dose for each indication (previously calculated in "2".) by the dose for each patient in each indication (previously calculated in "3".).

SV.1.2 Exposure

Since the IBD, an estimated cumulative total of 3,500,759 patients have received bevacizumab from marketing experience (see Table 33).

Table 33 Cumulative Exposure from Marketing Experience

Indicatio n	Sex			Age (years)				Region		
	M	F	Unknown[a]	2 to ≤ 16	> 16 to <=65	> 65	Unknown[a]	Worldwid e (ex-US, ex-Japan)	U.S	Japan
CRC	393,864	273,157	1,382,138	52[c]	299,200	367,770	1,382,136	1,251,099		
NSCLC	148,487	84,497	397,189	18[c]	115,595	117,371	397,188	191,874		
BC	112[b]	93,937	231,105	-	67,172	26,875	231,106	173,000		
GBM	16,757	9,526	71,445	189[c]	17,773	8,404	71,362	14,416		
OC	-	114,062	180,605	1	69,248	39,828	185,590	172,787		
CC	-	19,073	12,322	-	15,460	2,737	13,198	15,507		
RCC	2,260	1,679	39,308	-	2,487	1,452	39,308	15,454		
Others	1,306	2,133	25,798	-	1,411	2,029	25,798	12,804		
Total	562,786	598,064	2,339,910	260	588,346	566,466	2,345,686	1,846,941		

BC = breast cancer; CC = cervical cancer; CRC = colorectal cancer; F = female; GBM = glioblastoma multiforme; M = male; NSCLC = non-small cell lung cancer; OC = ovarian cancer; RCC = renal cell carcinoma

Note: Rounding errors may be introduced in the total figure. This table is derived from PBRER 1092163.

a   There is no sex and age split for Worldwide & US, until 2017; these patients were grouped into Unknown
b   Japan region: The number of male patients of breast cancer were actual numbers extracted from AE database etc.
c   Japan region: The number of pediatric patients were actual numbers extracted from AE database etc.
d   Japan region: Avastin is approved for malignant glioma (MG) not for GBM.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of hemoglobin levels. There is no evidence that bevacizumab is associated with psychostimulatory effects or dependency. Therefore, the potential for bevacizumab to be misused for illegal purposes is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

As this is an updated EU RMP rather than an initial submission, this section is not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

As this is an updated EU RMP rather than an initial submission, this section is not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since this module of the RMP was last submitted.

Long-term effects of bevacizumab when used in the pediatric population, which was previously presented as missing information in the EU RMP, has now been removed from the list of safety concerns.

Reasons for removal from the list of safety concerns

The clinical trial BO20924 (BERNIE), which evaluated bevacizumab for the treatment of rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma to provide long-term follow up information in the pediatric population, is completed. Safety data indicate that the addition of bevacizumab to chemotherapy appears to be tolerable in this patient population.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Information on important identified risks

There are no important identified risks for bevacizumab.

Information on important potential risks

There are no important potential risks for bevacizumab.

SVII.3.2. Presentation of the Missing Information

There is no missing information for bevacizumab.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 34   Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There were no ongoing routine pharmacovigilance activities beyond adverse reactions reporting and signal detection for bevacizumab.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 35 On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorizations under exceptional circumstances				
There are no imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
There are no required additional pharmacovigilance activities				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no post authorization efficacy studies planned for bevacizumab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURE

Since there are no safety concerns identified in Module SVIII "Summary of the Safety Concerns," no summary of routine minimization measures is applicable in Part V.1.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk-minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Since there are no safety concerns identified in Module SVIII, no summary of routine risk minimization measures is applicable.

BIBLIOGRAPHY

American_Cancer_Society. Global Cancer Facts & Figures 2007. Atlanta: American Cancer Society, 2007. [10985]

American_Cancer_Society. Breast Cancer Facts & Figures 2007-2008. Atlanta, 2008. [10986]

American_Cancer_Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society, 2010a. [10987].

Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research. Sep 15 2012;18(18):4910-4918. [11145]

Beasley MB and Milton DT. ASCO provisional clinical opinion: epidermal growth factor receptor mutation testing in practice. J Oncol Pract. 2011;7(3):202-204. [11033]

Bray, F., Loos, A. H., Tognazzo, S., and La Vecchia, C. Ovarian cancer in Europe: Cross-sectional trends in incidence and mortality in 28 countries, 1953-2000. Int J Cancer, 113: 977-90, 2005. [10045]

Bray, F., J. S. Ren, E. Masuyer and J. Ferlay (2013). "Global estimates of cancer prevalence for 27 sites in the adult population in 2008." Int J Cancer 132(5): 1133-1145. [10878]

Cardoso, F., A. Costa, L. Norton, E. et al. "ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)dagger." Ann Oncol, 2014 25(10): 1871-1888. [11137]

Chia VM, O'Malley CD, Danese MD, et al. Prevalence and incidence of comorbidities in elderly women with ovarian cancer. Gynecol Oncol. 2013;129 (2):346-352. [10720]

Coleman, M. P., G. Gatta, A. Verdecchia, J. Esteve, M. Sant, H. Storm, C. Allemani, L. Ciccolallo, M. Santaquilani, F. Berrino and E. W. Group (2003). "EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century." Ann Oncol 14 Suppl 5: v128-149. [10563]

Colombo, N., S. Carinelli, A. Colombo, C. Marini, et al (. "Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Ann Oncol, 2012, 23 Suppl 7: vii27-32. [10791]

D'Addario, G., M. Fruh, et al. (2010). "Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Ann Oncol 21 Suppl 5: v116-119. [10986]

D'Angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. May 20 2011;29(15):2066-2070. [11148]

Dong X, Zhao X, Hao Y, Wei Y, Yin Q, Du J. Response to first-line chemotherapy in patients with non-small-cell lung cancer according to epidermal growth factor receptor and K-RAS mutation status. Clinical lung cancer. Nov 2013; 14(6):680-687. [11150]

du Bois A, Luck HJ, Meier W, Adams HP, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003; 95 (17), 1320-1329. [8636]

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013; 49: 1374-1403. [10689]

Gahr S, Stoehr R, Geissinger E, et al. EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. British journal of cancer. Oct 1 2013;109(7):1821-1828. [11151]

Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011 47(17):2493-511. [10618]

Gutierrez, J. C., N. Housri, L. G. Koniaris, A. C. Fischer and J. E. Sola (2008). "Malignant breast cancer in children: a review of 75 patients." J Surg Res 147(2): 182-188. [10982]

Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. Semin Surg Oncol 2000; 19 (1), 3-10. [10151]

Huang YS, Yang JJ, Zhang XC, et al. Impact of smoking status and pathologic type on epidermal growth factor receptor mutations in lung cancer. Chinese medical journal. Aug 2011;124(16):2457-2460. [11226]

Hunn J, and Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. Clin Obstet Gynecol. 2012;55(1): 3-23. [10693]

Jaaback KS, Ludeman L, Clayton NL and Hirschowitz L. Primary peritoneal carcinoma in a UK cancer center: comparison with advanced ovarian carcinoma over a 5-year period. Int J Gynecol Cancer. 2006;16(1):123-128. [10719]

Karim-Kos H, de Vries E, Soerjomataram I, et al. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. European Journ of Cancer 2008; 44:1345-1389. [10886]

Kothari, A. S., N. Beechey-Newman, C. D'Arrigo, A. M. Hanby, K. Ryder, H. Hamed and I. S. Fentiman (2002). "Breast carcinoma in women age 25 years or less." Cancer 94(3): 606-614. [10983]

Kosary CL. Chapter 20: Cancer of the Fallopian Tube. In: Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner MJ (Eds.), SEER Survival Monographs: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, Bethesda 2007a. [10292]

Kwaan HC, Gordon LI. Thrombotic microangiopathy in the cancer patient. Acta Haematol 2001;106:52–56 [10592]

Lund, L., Jacobsen, J., Norgaard, M., McLaughlin, et al. "The prognostic impact of comorbidities on renal cancer, 1995 to 2006: a Danish population based study." J Urol, 2009, 182(1): 35-40; discussion 40. [11256]

Miller, K., Wang, M., Gralow, J., et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med, 357: 2666-76, 2007. [8112]

Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003; 21 (17), 3194-3200. [8635]

Parkin, D. M., Bray, F., Ferlay, J., and Pisani, P. Global cancer statistics, 2002. CA Cancer J Clin, 55: 74-108, 2005. [8808].

Piccirillo JF, Vlahiotis A, Barrett LB, et al. The changing prevalence of comorbidity across the age spectrum. Crit Rev Oncol Hematol 2008; 67(2):124-32. [10613].

Pruthi S, Gostout BS and Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. Mayo Clin Proc. 2010;85(12):1111-1120. [10718]

Reck, M., S. Popat, et al. (2014). "Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger." Ann Oncol 25 Suppl 3: iii27-iii39. [11007]

Riska A, Martinsen JI, Kjaerheim K, et al. Occupation and risk of primary fallopian tube carcinoma in Nordic countries. Int J Cancer. 2012;1;131(1):186-192. [10717]

Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. The New England journal of medicine. Sep 3 2009;361(10):958-967. [11158]

Salzberg M, Thurlimann B, Bonnefois H, et al. Current concepts of treatment strategies in advanced or recurrent ovarian cancer. Oncology. 2005;68:293-298. [10705]

Shaboodien R, Diamnatis N, Blagden S, et al. Feasibility of trials in ovarian cancer by line of therapy and platinum sensitivity. Int J Gynecol Cancer. 2013;23:481-487. [10708]

Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. Annals of surgical oncology. Mar 2010;17(3):889-897. [11159]

Van Cutsem, E., A. Cervantes, B. Nordlinger, D. et al. "Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Ann Oncol, 2014, 25 Supp 3: iii1-9. [11136]

Wang R, Hu H, Pan Y, et al. RET fusions define a unique molecular and
clinicopathologic subtype of non-small-cell lung cancer. Journal of clinical oncology:
official journal of the American Society of Clinical Oncology. Dec 10
2012;30(35):4352-4359. [11162]

Wethington SL, Herzog TJ, Seshan VE, et al. Improved survival for fallopian tube
cancer: a comparison of clinical characteristics and outcome for primary fallopian
tube and ovarian cancer. Cancer. 2008;113(12):3298-306. [10617]

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR AVASTIN (BEVACIZUMAB)

This is a summary of the risk management plan (RMP) for Avastin. The RMP details important risks of Avastin, how these risks can be minimized, and how more information will be obtained about Avastin risks and uncertainties (missing information).

Avastin summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Avastin should be used.

This summary of the RMP for Avastin should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns will be included in updates of Avastin RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Avastin is authorized for Metastatic Colorectal Cancer, Metastatic Breast Cancer, Advanced, metastatic or recurrent Non–Small Cell Lung Cancer, Advanced and/or metastatic Renal Cell Cancer, Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer, and Cervical Cancer (see summary of product characteristic [SmPC] for the full indications).

It contains bevacizumab as the active substance and it is given by intravenous route.

Further information about the evaluation of Avastin's benefits can be found in Avastin's EPARincluding in its plain-language summary, available on the European Medicines Agency's website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Avastin, together with measures to minimize such risks and the proposed studies for learning more about Avastin risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status—the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Avastin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Avastin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Since there are no safety concerns identified in summary of the safety concerns, no summary of routine risk minimization measures is applicable.

II.C POST-AUTHORISATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

All studies which were conditions of the marketing authorization have been completed.

II.C.2 Other studies in post-authorization development plan

All studies in post-authorization development plan have been completed.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Not Applicable