FULL PRESCRIBING INFORMATION

MVASI®

Bevacizumab

1. DESCRIPTION

MVASI is a biosimilar medicine to the reference product AVASTIN® (bevacizumab). The evidence for comparability supports the use of MVASI for the listed indications.

1.1 Therapeutic/Pharmacologic Class of Drug

Anti-neoplastic agent
ATC Code: L01F G01

1.2 Type of Dosage Form

Concentrate for solution for infusion.

1.3 Route of Administration

Clear to slightly opalescent, colourless to slightly yellow, sterile liquid for intravenous (i.v.) infusion. MVASI is not formulated for intravitreal use (*see 2.4.1 Warnings and Precautions, General*).

1.4 Sterile/Radioactive Statement

Sterile

1.5 Qualitative and Quantitative Composition

Active ingredient: Bevacizumab (humanised anti-VEGF monoclonal antibody).
MVASI is supplied in 100 mg preservative-free, single-use vials to deliver 4 ml of MVASI (25 mg/ml).
MVASI is supplied in 400 mg preservative-free, single-use vials to deliver 16 ml of MVASI (25 mg/ml).
For excipients, see section 4.1 “List of Excipients”.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indications

Metastatic Colorectal Cancer (mCRC)

MVASI (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Metastatic Breast Cancer (mBC)

MVASI in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

MVASI, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer (mRCC)

MVASI in combination with interferon-alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

Glioblastoma

MVASI is indicated for the treatment of glioblastoma with progressive disease following prior therapy as single agent.

The effectiveness of MVASI in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with MVASI.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

MVASI, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO* stages III B, III C, and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

MVASI, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF*-targeted angiogenesis inhibitors.

MVASI 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.
*FIGO: International Federation of Gynaecology and Obstetrics
*VEGF: Vascular Endothelial Growth Factor

Cervical Cancer

MVASI in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

2.2 Dosage and Administration

General

MVASI should be prepared by a healthcare professional using aseptic technique (*see section 4.3 Pharmaceutical Particulars, Special Instructions for Use, Handling and Disposal*).
The initial MVASI dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Dose reduction of MVASI for adverse events is not recommended. If indicated, MVASI should either be permanently discontinued or temporarily suspended as described in *section 2.4.1 Warnings and Precautions, General*.
MVASI is not formulated for intravitreal use (*see section 2.4.1 Warnings and Precautions, General*).

Metastatic Colorectal Cancer (mCRC)

The recommended dose of MVASI, administered as an 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.
It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Metastatic Breast Cancer (mBC)

The recommended dose of MVASI 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 intravenous infusion.
It is recommended that MVASI treatment be continued until progression of the underlying disease.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

MVASI is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by MVASI as a single agent until disease progression.
The recommended dose of MVASI when used in addition to cisplatin-based chemotherapy is 7.5 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
The recommended dose of MVASI when used in addition to carboplatin-based chemotherapy is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Advanced and/or metastatic Renal Cell Cancer (mRCC)

The recommended dose of MVASI is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion.
It is recommended that MVASI treatment be continued until progression of the underlying disease.

Glioblastoma

The recommended dose of MVASI, administered as an infusion is 10 mg/kg of body weight given once every 2 weeks.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

The recommended dose of MVASI administered as an intravenous infusion is as follows.

Front-line treatment:	15 mg/kg of body weight given once every 3 weeks when administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued use of MVASI as single agent for 15 months or until disease progression, whichever occurs earlier.

Treatment of recurrent disease:

Platinum-sensitive:	15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and paclitaxel for

	6 cycles and up to 8 cycles followed by continued use of MVASI as a single agent until disease progression. Alternatively, 15 mg/kg every 3 weeks when administrated in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of MVASI as single agent until disease progression.
Platinum-resistant:	10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin *(see section 3.1.2 Pharmacodynamic Properties, study MO22224 for chemotherapy regimens).* Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks *(see section 3.1.2 Pharmacodynamic Properties, study MO22224 for chemotherapy regimen).* It is recommended that treatment be continued until disease progression.

Cervical Cancer

MVASI is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan (*see section 3.1.2 Pharmacodynamic Properties, study GOG-0240 for further details on the chemotherapy regimens*).

The recommended dose of MVASI is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that MVASI treatment be continued until progression of the underlying disease.

2.2.1 Special Dosage Instructions

Pediatric use: The safety and efficacy of MVASI in children and adolescents (< 18 years) have not been established (*see section 2.5.4 Pediatric Use*).

Geriatric use: No dose adjustment is required in patients ≥ 65 years of age.

Renal impairment: The safety and efficacy of MVASI have not been studied in patients with renal impairment.

Hepatic impairment: The safety and efficacy of MVASI have not been studied in patients with hepatic impairment.

2.3 Contraindications

MVASI is contraindicated in patients with known hypersensitivity to:

- Any components of the product
- Chinese hamster ovary cell products or other recombinant human or humanised antibodies.

2.4 Warnings and Precautions

2.4.1 General

MVASI is a biosimilar product of AVASTIN.
In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Gastrointestinal Perforations and Fistulae

Patients may be at increased risk for the development of gastrointestinal perforation *(see section 2.6.1 Undesirable Effects, Clinical Trials)* and gallbladder perforation *(see section 2.6.2 Undesirable Effects, Postmarketing Experience)* when treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae) *(see section 2.6.1 Undesirable Effects, Gastrointestinal Perforations and Fistulae).*

Non-GI Fistulae (see section 2.6.1 Undesirable Effects, Clinical Trials)

Patients may be at increased risk for the development of fistulae when treated with bevacizumab *(see section 2.6.1 Undesirable Effects, Clinical Trials).*

Permanently discontinue bevacizumab in patients with TE (tracheoesophageal) fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Haemorrhage (see also section 2.6.1 Undesirable Effects, Clinical Trials)

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage *(see section 2.6.1 Undesirable Effects, Haemorrhage).*

Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patient has not been prospectively evaluated in randomised clinical studies *(see section 2.6.1 Undesirable Effects, Haemorrhage).* Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in cases of intracranial bleeding.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and bevacizumab concomitantly.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use (see section 2.6.2 Undesirable Effects, Postmarketing Experience)

Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous

administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Pulmonary Haemorrhage/Haemoptysis (see section 2.6 Undesirable Effects)

Patients with non-small cell lung cancer treated with bevacizumab may be at risk for serious and in some cases fatal, pulmonary haemorrhage/haemoptysis (*see section 2.6.1 Undesirable Effects, Haemorrhage*). Patients with recent pulmonary haemorrhage/haemoptysis (> 1/2 teaspoon red blood) should not be treated with bevacizumab.

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Monitoring of blood pressure is recommended during bevacizumab therapy *(see also section 2.6.1 Undesirable Effects, Clinical Trials)*. In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patients. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy *(see also sections 2.6.1 Undesirable Effects, Clinical Trials and 2.6.2 Undesirable Effects, Postmarketing Experience)*

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known *(see also sections 2.6.1 Undesirable Effects, Clinical Trials and 2.6.2 Undesirable Effects, Postmarketing Experience).*

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents, transient ischemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who receive chemotherapy alone.

Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.

Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetic or age greater than 65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating such patients with bevacizumab.

Venous Thromboembolism (see section 2.6 Undesirable Effects)

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of venous thromboembolic events *(see section 2.6.1 Undesirable Effects, Venous Thromboembolism).*

Bevacizumab should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events ≤ Grade 3 need to be closely monitored.

Congestive Heart Failure (see section 2.6 Undesirable Effects)

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with bevacizumab.

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, were present.

Neutropenia

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

Wound Healing

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for elective surgery *(see also section 2.6.1 Undesirable Effects, Clinical Trials).*

Necrotising fasciitis including fatal cases, has been reported rarely in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated *(see also section 2.6.2 Undesirable Effects, Postmarketing Experience).*

Proteinuria (see section 2.6 Undesirable Effects)

In clinical trials, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. In the event of nephrotic syndrome bevacizumab treatment should be permanently discontinued.

Hypersensitivity Reactions, Anaphylactic Reactions (including Anaphylactic Shock), Infusion-related Reactions (see section 2.6 Undesirable Effects, Clinical Trials and Postmarketing Experience)

Patients may be at risk of developing hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock) and infusion-related reactions. Close observation of the patient during and following the administration of bevacizumab is recommended. If an

anaphylactic reaction occurs, the infusion should be permanently discontinued and appropriate medical therapies should be administered.
If an infusion-related reactions occurs, treatment should be temporarily interrupted until resolution of symptoms. Permanently discontinue Mvasi for severe (Grade ≥3) infusion related-reaction. A systemic premedication is not warranted.

Ovarian Failure/Fertility (see section 2.5.1 Use in Special Populations, Females and Males of Reproductive Potential and 2.6.1 Undesirable Effects, Clinical Trials)
Bevacizumab may impair female fertility. Therefore, fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with bevacizumab.

2.4.2 Drug Abuse and Dependence

Not applicable

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machine have been performed. However, there is no evidence that bevacizumab treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility
MVASI may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with MVASI (*see section 2.4.1 Warnings and Precautions, General* and *section 2.6.1 Undesirable Effects, Clinical Trials)*. Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (*see section 3.3.3 Impairment of Fertility*). A substudy with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on the fertility are unknown.

Contraception

In women with child-bearing potential, appropriate contraceptive measures should be used during MVASI therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of MVASI.

2.5.2 Pregnancy

Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy.

There are no adequate and well-controlled studies in pregnant women (*see section 3.3.4 Reproductive Toxicity*). IgGs are known to cross the placental barrier, and bevacizumab may inhibit angiogenesis in the foetus. In the postmarketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed *(see section 2.6.2 Undesirable Effects, Postmarketing Experience).*

Therefore, bevacizumab should not be used during pregnancy.

Labour and Delivery

Not applicable

2.5.3 Lactation

It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development, women should be advised to discontinue nursing during bevacizumab therapy and not to breast feed for at least 6 months following the last dose of bevacizumab.

2.5.4 Pediatric Use

Bevacizumab is not approved for use in patients under the age of 18 years. The safety and efficacy of bevacizumab in this population have not been established. Addition of bevacizumab to standard of care did not demonstrate clinical benefit in pediatric patients in two phase II clinical trials: one in pediatric high grade glioma and one in pediatric metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma.

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab (*see sections 2.6.2 Postmarketing Experience and 3.3.5 Other (Physeal Development)*).

2.5.5 Geriatric Use

Refer to *section 2.4.1* under the sub-heading *Arterial Thromboembolism*.

2.5.6 Renal Impairment

The safety and efficacy of bevacizumab have not been studied in patients with renal impairment.

2.5.7 Hepatic Impairment

The safety and efficacy of bevacizumab have not been studied in patients with hepatic impairment.

2.6 Undesirable Effects

2.6.1 Clinical Trials for AVASTIN

Summary of safety profile

Clinical trials have been conducted in patients with various malignancies treated with bevacizumab, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5, 500 patients is presented in this section. For postmarketing experience see *section 2.6.2 Undesirable Effects, Postmarketing Experience* below. See *section 3.1.2 Pharmacodynamic Properties, Clinical/Efficacy Studies* for details of major studies, including study designs and major efficacy results.

The most serious adverse events were:

- Gastrointestinal perforations (*see section 2.4.1 Warnings and Precautions, General*)
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (*see section 2.4.1 Warnings and Precautions, General*)
- Arterial thromboembolism (*see section 2.4.1 Warnings and Precautions, General*)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose-dependent.

The most frequently observed adverse drug reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Tabulated summary of adverse drug reactions from clinical trials

Table 1 lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC [common toxicity criteria] Grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials. Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy, however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.

Table 1 Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	**NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)**		**All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)**
	Very Common	**Common**	**Very Common**
Infections and infestations		Sepsis Abscess Cellulitis Infection	

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)
	Very Common	**Common**	**Very Common**
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia Lymphopenia	
Immune system disorders		Hypersensitivity, anaphylactic, infusion-related reactions	
Metabolism and nutrition disorders		Dehydration Hyponatraemia	Anorexia Hypomagnesaemia Hyponatraemia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
		Pulmonary embolism	Dyspnoea

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)
	Very Common	**Common**	**Very Common**
Respiratory, thoracic and mediastinal disorders		Dyspnoea Hypoxia Epistaxis	Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal Perforation Ileus Intestinal obstruction Recto-vaginal fistulae** Gastrointestinal disorder Stomatitis Proctalgia	Constipation Stomatitis Rectal haemorrhage Diarrhoea
Endocrine disorders			Ovarian failure*
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia Back pain	Arthralgia
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria
General disorders and	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)
	Very Common	**Common**	**Very Common**
administration site conditions			Mucosal inflammation
Reproductive System and Breast		Pelvic pain	
Investigations			Weight decreased

* Based on a substudy from AVF3077s (NSABP C-08) with 295 patients.

** Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Description of selected adverse drug reactions from clinical trials

The following adverse drug reactions, reported using NCI-CTC for assessment of toxicity have been observed in patients treated with bevacizumab.

Gastrointestinal perforation and Fistulae (see section 2.4.1 Warnings and Precautions, General)

Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2% in patients with metastatic renal cell cancer, or in patients with ovarian cancer receiving front-line treatment, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapses glioblastoma.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations, (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation. The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis,

diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2% - 1% of all bevacizumab-treated patients.

In bevacizumab clinical trials, gastrointestinal fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistulae (see section 2.4.1 Warnings and Precautions, General)

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon (≥ 0.1% to < 1%) reports of other types of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural, biliary fistulae) were observed across various indications.

Fistulae have also been reported in postmarketing experience.

Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in bevacizumab-treated patients, compared to 0 to 4.5% of patients in the chemotherapy control group. The haemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

Tumour-associated haemorrhage

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.
In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9.3% when treated with bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with < 1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome (*see section 2.4.1 Warnings and Precautions, General*).
Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal patients, and have been assessed as tumour-associated haemorrhages.
Tumour-associated haemorrhages were also seen rarely in other tumour types and locations and included cases of central nervous system (CNS) bleeding in patients with CNS metastases and in patients with glioblastoma. The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised in clinical studies. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported.
Intracranial haemorrhage can occur in patients with relapsed glioblastoma. In study AVF3708g, CNS haemorrhage was reported in 2.4% (2/84) of patients in the bevacizumab alone arm (Grade 1); and in 3.8% (3/79) of patients treated with bevacizumab and irinotecan (Grades 1, 2 and 4).

Across all bevacizumab clinical trials, ***mucocutaneous haemorrhage*** were seen in up to 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any change in the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent. There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Hypertension (see section 2.4.1 Warnings and Precautions, General)

An increased incidence of hypertension (all grades) of up to 42.1% has been observed in patients treated with bevacizumab compared with up to 14% in all the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab compared to up to 0.2% patients treated with the same chemotherapy alone. Hypertension was generally adequately controlled with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of bevacizumab treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (*see also section 2.4.1 Warnings and Precautions, General*). The risk of bevacizumab associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (see section 2.4.1 Warnings and Precautions, General)

Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Thromboembolism

Arterial thromboembolism

An increased incidence of arterial thromboembolic events was observed in patients treated with bevacizumab across indications including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab containing arms compared up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.7% of bevacizumab-treated patients versus 0.5% of patients in the control group: myocardial infarction was reported in 1.4% of bevacizumab-treated versus 0.7% of patients in the observed control group.
In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of bevacizumab patients compared to 5.8% (6/104) in the chemotherapy control group. In an uncontrolled clinical trial, AVF3708g, in patients with relapsed glioblastoma, arterial thromboembolic events were observed in 6.3% (5/79) of patients who received bevacizumab in combination with irinotecan compared to 4.8% (4/84) of patients who received bevacizumab alone.

Venous thromboembolism (see section 2.4.1 Warnings and Precautions, General)

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the bevacizumab containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.
Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive bevacizumab in combination with chemotherapy versus chemotherapy alone.
From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), Grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

Congestive heart failure

In clinical trials with bevacizumab, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In phase III studies (AVF2119g and E2100) in patients with metastatic breast cancer

an increase of CHF Grade 3 or more with bevacizumab was seen. CHF was reported in up to 3.5% of patients treated with bevacizumab compared with up to 0.9% in the control arms. Most of these patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.
In most clinical trials of bevacizumab, patients with pre-existing CHF of NYHA II – IV were excluded, therefore, no information is available on the risk of CHF in this population.
Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF (*see section 2.4.1 Warnings and Precautions, General*).
An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m^2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus bevacizumab arm.

Wound healing (see section 2.4.1 Warnings and Precautions, General)
As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting bevacizumab treatment were excluded from participation in phase III trials.
Across mCRC clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications occurring within 60 days of major surgery was observed if the patient was being treated with bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).
Cases of serious wound healing complications have been reported during bevacizumab use, some of which had a fatal outcome (*see section 2.4.1 Warnings and Precautions, General*).
In locally recurrent and metastatic breast cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving bevacizumab compared with up to 0.9% of patients in the control arms.
In a study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (including craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent bevacizumab and

1.3% in patients treated with bevacizumab plus irinotecan. In clinical trials of ovarian cancer, Grade 3-5 wound healing complications were observed in up to 1.2% of patients in the bevacizumab arm versus 0.1% in the control arm.

Proteinuria (see section 2.4.1 Warnings and Precautions, General)

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients.

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical studies urine protein levels of $\geq$ 2g/24 hrs led to the holding of bevacizumab until recovery to < 2g/24 hrs.

Hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), infusion-related reactions (see section 2.4.1 Warnings and Precautions, General and section 2.6.2 Undesirable Effects, Postmarketing Experience)

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab-treated patients).

Ovarian Failure/Fertility (see section 2.4.1 Warnings and Precautions, General and section 2.5.1 Use in Special Populations, Females and Males of Reproductive Potential)

The incidence of new cases of ovarian failure, defined as amenorrhea lasting 3 or more months, FSH level $\geq$ 30 mIU/ml and a negative serum β-HCG pregnancy test has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in majority of women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Elderly patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient

ischemic attacks and myocardial infarction as compared to those aged ≤ 65 years when treated with bevacizumab (*see sections 2.4.1 Warnings and Precautions, General and 2.6.1 Undesirable Effects, Clinical Trials, Thromboembolism*). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia, thrombocytopenia; and all Grade neutropenia, diarrhoea, nausea, headache and fatigue.
From a clinical trial in patients with metastatic colorectal cancer (study AVF2107), no increase in the incidence of other reactions, including gastrointestinal perforation, wound healing complications, congestive heart failure and haemorrhage, was observed in elderly patients (> 65 years) receiving bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

Laboratory Abnormalities

Decreased neutrophil count, decreased white blood count and presence of urine protein may be associated with bevacizumab treatment.
Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥ 2%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased PT (prothrombin time), normalised ratio.
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 bevacizumab. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with bevacizumab (Table 2) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2 Adverse Drug Reactions from Postmarketing Experience

Adverse reactions	**Frequency Category**
Infections and Infestations	
Necrotising fasciitis[1,2]	Rare
Nervous system disorders	
Hypertensive encephalopathy[2,3]	Very rare
Posterior Reversible Encephalopathy Syndrome (PRES)[2]	Rare
Vascular disorders	
Renal thrombotic microangiopathy, clinically manifested as proteinuria[2,3]	Unknown
Aneurysms and artery dissections	Unknown
Respiratory, thoracic and mediastinal disorders	
Nasal septum perforation	Unknown
Pulmonary hypertension	Unknown
Dysphonia	Common
Gastrointestinal disorders	
Gastrointestinal ulcer	Unknown
Hepatobiliary disorders	
Gallbladder perforation	Unknown
Musculoskeletal and connective tissue disorders	
Osteonecrosis of the Jaw (ONJ)[4]	Unknown
Osteonecrosis at sites other than the jaw[5,6]	Unknown
Congenital, familial and genetic disorders	
Foetal abnormalities[7]	Unknown

[1] Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.

[2] See *section 2.4.1 Warnings and Precautions, General*.

[3] See *section 2.6.1 Undesirable Effects, Clinical Trials.*

[4] Cases of (ONJ) observed in bevacizumab-treated patients mainly in association with prior or concomitant use of bisphosphonates.

[5] Cases observed in bevacizumab-treated pediatric patients. See *section 2.5.4 Use in*

special populations, Pediatric use.

[6] Osteonecrosis observed in pediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.

[7] Cases have been observed in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics. See *section 2.5.2 Use in Special Populations, Pregnancy*.

Description of selected adverse drug reactions from postmarketing experience

Eye disorders (reported from unapproved intravitreal use)

Infectious endophthalmitis (frequency not known; some cases leading to permanent blindness; one case reported extraocular extension of infection resulting in meningoencephalitis); Intraocular inflammation (some cases leading to permanent blindness; including a cluster of serious eye inflammation leading to blindness after compounding an anticancer chemotherapy product for intravenous administration) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage (frequency not known); Conjunctival haemorrhage (frequency not known). Following variable and non-validated methods in compounding, storage, and handling of bevacizumab, serious ocular adverse events (including infectious endophthalmitis and other ocular inflammatory conditions) affecting multiple patients have been reported.

Systemic Events (reported from unapproved intravitreal use)

Increased risk for haemorrhagic stroke; Increased risk for overall mortality. Increased risk of serious systemic adverse events for bevacizumab, most of which resulted in hospitalisation (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%).

2.7 Overdose

The highest dose tested in humans (20 mg/kg of body weight every 2 weeks, intravenous) was associated with severe migraine in several patients.

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on bevacizumab pharmacokinetics has been observed based on the results of a population PK analysis.

There was neither statistical significance nor clinically relevant difference in clearance of bevacizumab in patients receiving bevacizumab monotherapy compared to patients receiving bevacizumab in combination with interferon-alfa-2a or other chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon-alfa-2a, or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate

In two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate (see Hypertension, Proteinuria, PRES in *section 2.4.1 Warnings and Precautions, General*).

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

MVASI (bevacizumab) is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

3.1.2 Clinical/Efficacy Studies

All studies performed in every single indication as approved are referring to the studies conducted by AVASTIN.

Efficacy data for MVASI

Comparative Study between MVASI and AVASTIN (Study 20120265):

Clinical equivalence was demonstrated between MVASI and AVASTIN in Study 20120265. The data below (Table 3) reflect exposure to MVASI in 324 patients with non-squamous NSCLC treated at the doses and schedules described below for a median of 6 doses of MVASI and 6 doses of AVASTIN, respectively.

Subjects in Study 20120265 were randomised in a 1:1 ratio to treatment consisting of:

Arm 1: MVASI at a dose of 15 mg/kg administered as an IV infusion every 3 weeks for 6 cycles, plus carboplatin and paclitaxel chemotherapy every 3 weeks for at least 4 and not more than 6 cycles, or;

Arm 2: AVASTIN at a dose of 15 mg/kg administered as an IV infusion every 3 weeks for 6 cycles, plus carboplatin and paclitaxel chemotherapy every 3 weeks for at least 4 and not

more than 6 cycles.

Subjects remained in the treatment phase until 21 days after the last dose of investigational product or study-specified chemotherapy. After completing the end-of-treatment (EOT) visit, subjects were followed for disease progression and overall survival (OS) every 9 weeks until the clinical study ended, consent was withdrawn, or they were lost to follow-up, died, or received proscribed therapy (e.g. commercial bevacizumab, non-study anticancer treatment).

For MVASI and AVASTIN, the median age was 62 and 63 years, respectively, 40.2% and 40.1% were female, 5.8% and 7.6% had recurrent disease, and 92.4% and 89.5% had Stage IV disease.

The primary endpoint was the risk ratio (RR) of the ORR (partial response or complete response as defined by RECIST v1.1). Clinical similarity was demonstrated by comparing the two-sided 90% confidence interval of the ORR risk ratio between MVASI and AVASTIN.

There were no clinically meaningful differences in ORR between bevacizumab and MVASI in Study 20120265 as evidenced by the similar ORR observed for MVASI and AVASTIN (Table 3).

Table 3 Objective Response Rate in Study 20120265

Objective Response Rate	PBC[a] + MVASI (N = 328)	PBC + AVASTIN (N = 314)
n (percent)	128 (39%)	131 (41.7%)
Risk Ratio (90% CI)	0.93 (0.80, 1.09)	

[a] PBC: Platinum-Based Chemotherapy

Clinical similarity of MVASI and AVASTIN was further confirmed by duration of response (DOR) as well as PFS analysis in Study 20120265. DOR was defined as time from the first objective response (partial response or complete response) to disease progression. The estimated DOR for subjects in MVASI group was 5.8 months (95% CI: 4.9, 7.7) versus 5.6 months (95% CI: 5.1, 6.3) for subjects in AVASTIN group. Progression-free survival was defined as the time from the randomisation date to the date of disease progression or death. The estimated hazard ratio (MVASI relative to AVASTIN) was 1.03 (90% CI: 0.83, 1.29).

Immunogenicity

In Study 20120265 in patients with advanced non-small cell lung cancer, using an immunoassay, the incidence of antibodies to MVASI was found to be similar to AVASTIN.

The number of subjects developing binding antibodies during the study were four (1.4%) for those receiving MVASI versus seven (2.5%) for those receiving AVASTIN. Among these subjects, no subject in either treatment group tested positive for neutralising antibodies. The clinical significance of these anti-product antibody responses to MVASI is unknown.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to MVASI with the incidence of antibodies to other products may be misleading.

As with all therapeutic proteins, there is potential for immunogenicity. Differences in assay methodology for measuring immunogenicity prevent direct comparison of immunogenicity rates between MVASI and AVASTIN or other biologics in different studies. In 20120265, binding anti-drug antibodies (ADA) activity was determined using electrochemiluminescence (ECL)-based bridging immunoassay to detect antibodies capable of binding to MVASI and the neutralising ADA activity was determined using a non-cell-based target binding assay.

Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of the recommended dose of AVASTIN (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. AVASTIN was combined with two chemotherapy regimens:

- **AVF2107g:** A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6 week cycle.
- **AVF0780g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week cycle (Roswell Park regimen).
- **AVF2192g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Three additional studies with AVASTIN have been conducted in mCRC patients: first-line (NO16966), second-line with no previous AVASTIN treatment (E3200), and second-line with previous AVASTIN treatment following disease progression in first-line (ML18147). In these studies, AVASTIN was administered at the following dosing regimens, in combination

with FOLFOX-4 (5FU/LV/Oxaliplatin), XELOX (Capecitabine/Oxaliplatin) and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin:

- **NO16966:** AVASTIN 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or AVASTIN 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- **E3200:** AVASTIN 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in AVASTIN naive patients.
- **ML18147:** AVASTIN 5.0 mg/kg of body weight every 2 weeks or AVASTIN 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with AVASTIN. Use of irinotecan- or oxaliplatin- containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

AVF2107g:

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating AVASTIN in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + AVASTIN (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV + AVASTIN (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of AVASTIN with the IFL regimen was established and considered acceptable.

The primary efficacy parameter of the trial was overall survival. The addition of AVASTIN to IFL resulted in a statistically significant increase in overall survival, progression-free survival and overall response rate (see Table 4 for details). The clinical benefit of AVASTIN, as measured by survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease.

Table 4 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 IFL + Placebo	Arm 2 IFL + AVASTIN[a]
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Secondary endpoint: Progression-Free Survival		
Median (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.00001)	
Overall Response Rate	34.8%	44.8%
	(p-value = 0.0036)	

[a] 5 mg/kg every 2 weeks

[b] Relative to control arm

Among the 110 patients randomised to Arm 3 (5-FU/LV + AVASTIN) prior to discontinuation of this arm, the median overall survival was 18.3 months, and the median progression-free survival was 8.8 months.

AVF2192g

This was a phase II randomised, double-blind, active-controlled clinical trial investigating AVASTIN in combination with 5-FU/leucovorin as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. One hundred and five patients were randomised to 5-FU/LV + placebo arm and 104 patients randomised to 5-FU/LV AVASTIN (5 mg/kg every 2 weeks). All treatments were continued until disease progression.

The addition of AVASTIN 5 mg/kg every two weeks to 5-FU/LV resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as compared with 5-FU/LV chemotherapy alone.

NO16966

This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating AVASTIN 7.5 mg/kg in combination with oral capecitabine and i.v. oxaliplatin (XELOX), administered on a 3-weekly schedule; or AVASTIN 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusional, with i.v. oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The study contained two parts: an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 × 2 factorial 4-arm part (Part II) in which patients were randomised to four treatments groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + AVASTIN, FOLFOX-4 + AVASTIN). In Part II, treatment assignment was double-blind with respect to AVASTIN. Approximately 350 patients were randomised into each of the 4 study arms in the Part II of the trial.

Table 5 Treatment Regimens in Study NO16966 (mCRC)

	Treatment	**Starting Dose**	**Schedule**
FOLFOX-4 or FOLFOX-4 + AVASTIN	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/m^2 IV 22 h	Oxaliplatin on Day 1 Leucovorin on Days 1 and 2 5-flurouracil IV bolus/infusion, each on Days 1 and 2
	Placebo or AVASTIN	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX Or XELOX + AVASTIN	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bid	Oxaliplatin on Day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)

	Treatment	Starting Dose	Schedule
	Placebo or AVASTIN	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q 3 weeks
5-Fluorouracil:	IV bolus injection immediately after leucovorin		

The primary efficacy parameter of the trial was the duration of progression-free survival. In this study, there were two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and to show that AVASTIN in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. Both co-primary objectives were met:

i) Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4 containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per-protocol population.

ii) Superiority of the AVASTIN-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 6).

Secondary PFS analyses, based on Independent Review Committee (IRC)- and 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with AVASTIN (subgroup analyses shown in Table 6), consistent with the statistically significant benefit observed in the pooled analysis.

Table 6 Key efficacy results for the superiority analysis (ITT population, Study NO16966)

Endpoint (months)	**FOLFOX-4 or XELOX + Placebo (n = 701)**	**FOLXFOX-4 or XELOX + AVASTIN (n = 699)**	**p-value**
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[a]	0.83 (0.72-0.95)		
Secondary endpoint			
Median PFS (on treatment)**	7.9	10.4	< 0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		

Endpoint (months)	FOLFOX-4 or XELOX + Placebo (n = 701)	FOLXFOX-4 or XELOX + AVASTIN (n = 699)	p-value
Median PFS (Indep. review)**	8.5	11.0	< 0.0001
Hazard ratio (97.5% CI)	0.70 (0.58-0.83)		
Overall response rate (Invest. Assessment)**	49.2%	46.5%	
Overall response rate (Indep. Review)**	37.5%	37.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76-1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007

** Primary analysis at clinical cut-off 31 January 2006

[a] relative to control arm

ECOG E3200

This was a phase III randomised, active-controlled, open-label study investigating AVASTIN 10 mg/kg in combination with leucovorin 5-fluorouracil bolus and then 5-fluorouracil infusional, with iv oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 5 for Study NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 bevacizumab + FOLFOX-4 and 244 AVASTIN monotherapy). The addition of AVASTIN to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 7).

Table 7 Efficacy Results for Study E3200

	E3200	
	FOLFOX-4	FOLFOX-4 + AVASTIN[a]
Number of Patients	292	293
Overall Survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b]	0.751 (p-value = 0.0012)	
Progression-Free Survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
Objective Response Rate		
Rate	8.6%	22.2%
	(p-value < 0.0001)	

[a] 10 mg/kg every 2 weeks

[b] Relative to control arm

No significant difference was observed in the duration of overall survival between patients who received AVASTIN monotherapy compared to patients treated with FOLFOX-4. Progression-free survival and objective response rate were inferior in the AVASTIN monotherapy arm compared to the FOLFOX-4 arm.

ML18147

This was a Phase III randomised, controlled, open-label trial investigating AVASTIN 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with metastatic colorectal cancer who have progressed on a first-line AVASTIN-containing regimen.

Patients with histologically confirmed mCRC and disease progression were randomised 1:1 within 3 months after discontinuation of AVASTIN first-line therapy to receive fluoropyrimidine/oxaliplatin or fluoropyrimidine/irinotecan-based chemotherapy

(chemotherapy switched depending on first-line chemotherapy) with or without AVASTIN. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival (OS) defined as the time from randomisation until death from any cause.

A total of 820 patients were randomised. The addition of AVASTIN to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with metastatic colorectal cancer who have progressed on a first-line AVASTIN-containing regimen (ITT = 819) (see Table 8).

Table 8 Efficacy Results for Study ML18147

	ML18147	
	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy + AVASTIN[a]
Number of Patients	410	409
Overall Survival		
Median (months)	9.8	11.2
95% confidence interval	9-11	10-12
Hazard ratio	0.81 (p-value = 0.0062)	
Progression-Free Survival		
Median (months)	4.1	5.7
Hazard ratio	0.68 (p-value < 0.0001)	
Objective Response Rate (ORR)		
Rate	3.9%	5.4%
	(p-value = 0.3113)	

[a] 2.5 mg/kg/week

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and did not meet statistical significance.

Adjuvant Colon Cancer (aCC)

BO17920

This was a phase III randomised open-label, 3-arm study evaluating the efficacy and safety of AVASTIN administered at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule in combination with FOLFOX-4, or on a 3-weekly schedule in combination with XELOX versus FOLFOX-4 alone as adjuvant chemotherapy in 3451 patients with high-risk stage II and stage III colon carcinoma.

More relapses and deaths due to disease progression were observed in both AVASTIN arms compared to the control arm. The primary objective of prolonging disease free survival (DFS) in patients with stage III colon cancer (n = 2867) by adding AVASTIN to either chemotherapy regimen was not met. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX-4 + AVASTIN arm and 1.07 (95% CI: 0.91-1.28) for the XELOX + AVASTIN arm.

Metastatic Breast Cancer (mBC)

ECOG E2100

E2100 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating AVASTIN in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry. Patients were randomised to paclitaxel alone (90 mg/m^2 IV over 1 hour once weekly for three out of four weeks) or in combination with AVASTIN (10 mg/kg IV infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In cases where patients discontinued chemotherapy prematurely, treatment with AVASTIN as a single agent was continued until disease progression. The primary endpoint was progression-free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or

positive (2%). Patients who were HER-2 positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.
The results of this study are presented in Table 9.

Table 9 Study E2100 Efficacy Results: Eligible Patients

Progression-free survival				
	Investigator Assessment*		IRF Assessment	
	Paclitaxel (n = 354)	Paclitaxel/AVASTIN (n = 368)	Paclitaxel (n = 354)	Paclitaxel/AVASTIN (n = 368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-value	< 0.0001		< 0.0001	
Response rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n = 273)	Paclitaxel/AVASTIN (n = 252)	Paclitaxel (n = 243)	Paclitaxel/AVASTIN (n = 229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	

*** primary analysis**

Overall Survival		
	Paclitaxel (n = 354)	Paclitaxel/AVASTIN (n = 368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722; 1.046)	
p-value	0.1374	

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of AVASTIN in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to platinum-based chemotherapy in studies E4599 and BO17704.

E4599

E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating AVASTIN as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 every 3-week cycle for up to 6 cycles or PC in combination with AVASTIN at a dose of 15 mg/kg IV infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the AVASTIN + carboplatin-paclitaxel arm continued to receive AVASTIN as a single agent every 3 weeks until disease progression. 878 patients were randomised to the two arms. During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of AVASTIN and 21.1% (89/422) of patients received 13 or more administrations of AVASTIN. The primary endpoint was duration of survival. Results are presented in Table 10.

Table 10 Efficacy results for Study E4599

	Arm 1 **Carboplatin/Paclitaxel**	**Arm 2** **Carboplatin/Paclitaxel + AVASTIN** **15 mg/kg q 3 weeks**
Number of Patients	444	434
Overall Survival		
Median (months)	10.3	12.3
Hazard ratio		0.80 (p = 0.003) 95% CI (0.69, 0.93)

	Arm 1 Carboplatin/Paclitaxel	Arm 2 Carboplatin/Paclitaxel + AVASTIN 15 mg/kg q 3 weeks
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio		0.65 ($p < 0.0001$) 95% CI (0.56, 0.76)
Overall Response Rate		
Rate (percent)	12.9	29.0 ($p < 0.0001$)

BO17704

Study BO17704 was a randomised, double-blind phase III study of AVASTIN in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression-free survival, secondary endpoints for the study included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 i.v. infusion on day 1 and gemcitabine 1250 mg/m^2 i.v. infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with AVASTIN at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the AVASTIN-containing arms, patients could receive AVASTIN as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Study results show that 94% (277/296) of eligible patients went on to receive single agent AVASTIN at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 11.

Table 11 Efficacy results for study BO17704

	Cisplatin/Gemcitabine + placebo	**Cisplatin/Gemcitabine + AVASTIN 7.5 mg/kg q 3 weeks**	**Cisplatin/Gemcitabine + AVASTIN 15 mg/kg q 3 weeks**
Number of Patients	347	345	351
Progression-Free Survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62; 0.91]	0.82 [0.68; 0.98]
Best Overall Response Rate[a]	20.1%	34.1% (p < 0.0001)	30.4% (p = 0.0023)

[a] patients with measurable disease at baseline

Overall Survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86, 1.23]

Advanced and/or metastatic Renal Cell Cancer (mRCC)

BO17705

Study BO17705 was a multicenter randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of AVASTIN in combination with interferon (IFN)-alfa-2a (Roferon®) versus IFN-alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. IFN-alfa-2a (x3/week at a recommended dose of 9 MIU) plus AVASTIN (10 mg/kg q2w) or placebo was given until disease progression. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression-free survival. The addition of AVASTIN to IFN-alfa-2a significantly increased

PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR = 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% bevacizumab/IFN) received a variety of non-specified, post-protocol anti-cancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.
The efficacy results are presented in Table 12.

Table 12 Efficacy Results for Study BO17705

	BO17705	
	IFN + Placebo	IFN + AVASTIN
Number of Patients	322	327
Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio [95% CI]	0.63 [0.52; 0.75] (p-value < 0.0001)	
Objective Response Rate (%) in Patients with Measurable Disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value < 0.0001)	
Overall survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10] (p-value 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated, that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to study entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63; 0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the AVASTIN + IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety seven (97) patients in the IFN alfa-2a arm and 131 patients in the AVASTIN arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU, three times a week as pre-specified in the protocol. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of AVASTIN and IFN alfa-2a, based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the AVASTIN + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months, PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving AVASTIN + IFN alfa-2a.

AVF2938

This was a randomised, double-blind, phase II clinical study investigating AVASTIN 10 mg/kg in a 2 weekly schedule with the same dose of AVASTIN in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this study, 53 to AVASTIN 10 mg/kg q2w plus placebo and 51 to AVASTIN 10 mg/kg q2w plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the AVASTIN + PI arm and the AVASTIN + Erl arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response.

Glioblastoma

AVF3708g

The efficacy and safety of AVASTIN as treatment for patients with glioblastoma was studied in an open-label, multicenter, randomised, non-comparative study (study AVF3708g). Glioblastoma patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving AVASTIN) and temozolomide, were randomised (1:1) to receive AVASTIN (10 mg/kg IV infusion every 2 weeks) or AVASTIN plus irinotecan (125 mg/m^2 IV or 340 mg/m^2 IV for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility (IRF). Other outcome measures were duration of PFS, duration of response and overall survival.

Results of the study are summarised in Table 13.

Table 13 Efficacy Results from Study AVF3708g

	AVASTIN		**AVASTIN + Irinotecan**	
Number of patients	85		82	
	Inv	IRF	Inv	IRF
Primary endpoints				
6-month progression-free survival 95% CI (Inv) 97.5% CI (IRF)	43.6% (33.0, 54.3) -	42.6% - (29.6, 55.5)	57.9% (46.6, 69.2) -	50.3% - (36.8, 63.9)
Objective Response Rate 95% CI (Inv) 97.5% CI (IRF)	41.2% (30.6, 52.3) -	28.2% - (18.5, 40.3)	51.2% (39.9, 62.4) -	37.8% - (26.5, 50.8)
Secondary endpoints				
Progression-free survival (months) Median (95% CI)	4.2 (3.0, 6.9)	4.2 (2.9, 5.8)	6.8 (5.0, 8.2)	5.6 (4.4, 6.2)
Duration of objective response (months) Median (95% CI)	8.1 (5.5, *)	5.6 (3.0, 5.8)	8.3 (5.5, *)	4.3 (4.2, *)
Overall survival (months) Median (95% CI)	9.3 (8.2, *)		8.8 (7.8, *)	

ORR was determined using modified McDonald criteria; Inv = Investigator's assessment; IRF = Independent Review Facility

* Upper limit of the confidence interval could not be obtained

In study AVF3708g, six-month PFS based on IRF assessments was significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 42.6% in the AVASTIN arm and 50.3% in the AVASTIN plus irinotecan arm (investigator assessment: 43.6% in the AVASTIN arm and 57.9% in the AVASTIN plus irinotecan arm). Objective response rates were also significantly higher ($p < 0.0001$) compared with historical controls

for both treatment arms: 28.2% in the AVASTIN arm and 37.8% in the AVASTIN plus irinotecan arm (investigator assessment: 41.2% in the AVASTIN arm and 51.2% in the AVASTIN plus irinotecan arm).
The majority of patients who were receiving steroids at baseline, including responders and non-responders, were able to reduce their steroid utilisation over time while receiving AVASTIN treatment. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive functions while on study treatment compared to baseline. The majority of patients that remained in the study were progression-free at 24 weeks, had a Karnofsky performance status (KPS) that remained stable.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Front-line Ovarian Cancer

The safety and efficacy of AVASTIN in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that compared the effect of the addition of AVASTIN to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218

The GOG-0218 study was a phase III multicenter, randomised, double-blind, placebo-controlled, three arm study evaluating the effect of adding AVASTIN to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked Stage III or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.
A total of 1873 patients were randomised in equal proportions to the following three arms:

- CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of AVASTIN (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (AVASTIN commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of AVASTIN (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (AVASTIN commenced

at cycle 2 of chemotherapy) followed by continued use of AVASTIN (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The primary endpoint was Progression-Free Survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 14.

Table 14 Efficacy Results from Study GOG-0218

Progression-free survival						
	Investigator Assessment[1]			IRC Assessment		
	CPP (n= 625)	CPB15 (n= 1248)[2]	CPB15+ (n= 1248)[2]	CPP (n= 625)	CPB15 (n= 1248)[2]	CPB15+ (n= 1248)[2]
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 [0.513, 0.773]
p-value[4]		0.0204[5]	< 0.0001[5]		0.2663	< 0.0001
Objective response Rate[6]						
	Investigator Assessment			IRC Assessment		
	CPP (n= 396)	CPB15 (n= 393)	CPB15+ (n= 403)	CPP (n= 474)	CPB15 (n= 460)	CPB15+ (n= 499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p-value[4]		0.2341	0.2041		0.0106	0.0012

Overall survival[7]			
	CPP (n= 625)	CPB15 (n= 625)[2]	CPB15+ (n= 623)[2]
Median OS (months)	40.6	38.8	43.8
Hazard Ratio (95% CI)[3]		1.065 (0.908, 1.249)	0.879 (0.745, 1.038)
p-value[4]		0.2197	0.0641

1 Primary PFS analysis
2 Events prior to Cycle 7 from the CPB15 and CPB15+ arms were pooled for the analyses
3 Relative to the control arm; stratified hazard ratio
4 One-sided log-rank p-value
5 Subject to a p-value boundary of 0.0116
6 Patients with measurable disease at baseline
7 Final overall survival analysis

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received front-line AVASTIN at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive AVASTIN alone, had a clinically meaningful and statistically significant improvement in PFS.

Although there was an improvement in PFS for patients who received front-line AVASTIN in combination with chemotherapy and did not continue to receive AVASTIN alone, the improvement was neither clinically meaningful nor statistically significant compared to patients who received chemotherapy alone.

BO17707 (ICON7)

BO17707 was a Phase III, two arm, multicenter, randomised, controlled, open-label study comparing the effects of adding AVASTIN to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear cell histology only), or FIGO Stage IIB – IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression.

A total of 1528 patients were randomised in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles plus AVASTIN (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was Progression-Free Survival (PFS) as assessed by the investigator. The results of this study are summarised in Table 15.

Table 15 Efficacy Results from Study BO17707 (ICON7)

Progression-free survival		
	CP (n = 764)	CPB7.5+ (n = 764)
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective Response Rate[1]		
	CP (n = 277)	CPB7.5+ (n = 272)
Response rate	41.9%	61.8%
	(p-value < 0.0001)	
Overall Survival[2]		
	CP (n = 764)	CPB7.5+ (n = 764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15]	

[1] in patients with measurable disease at baseline
[2] Final OS analysis when 46.7% of patients died

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received AVASTIN at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive AVASTIN for up to 18 cycles had a statistically significant improvement in PFS.

Recurrent Ovarian Cancer

GOG-0213

GOG-0213 was a phase III randomised controlled trial studying the safety and efficacy of Avastin in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting. There was no exclusion criterion for prior anti-angiogenic therapy. The study evaluated the effect of adding AVASTIN to carboplatin + paclitaxel and continuing Avastin as a single agent compared to carboplatin + paclitaxel alone.

A total of 673 patients were randomised in equal proportions to the following two treatment arms.

- CP arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 and up to 8 cycles.
- CPB arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 IV over 3 hours) and concurrent AVASTIN (15 mg/kg) every 3 weeks for 6 and up to 8 cycles followed by AVASTIN (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Objective response rates (ORR) were also examined. Results are presented in Table 16.

Table 16 Efficacy results from study GOG-0213

Primary Endpoint		
Overall Survival (OS)	CP (n = 336)	CPB (n = 337)
Median OS (months)	37.3	42.6
Hazard Ratio [95% CI]	0.823 (CI: 0.680, 0.996)	
p-Value	0.0447	
Secondary Endpoints		
Progression-Free Survival (PFS)	CP (n = 336)	CPB (n = 337)
Median PFS (months)	10.2	13.8
Hazard Ratio [95% CI]	0.613 (CI: 0.521, 0.721)	
p-Value	< 0.0001	
Objection Response Rate	CP* (n = 286)	CPB* (n = 274)
No. (%) of patients with Objective Response (CR, PR)	159 (55.6%)	213 (77.7%)
p-Value	< 0.0001	

* Intent-to-treat population with measurable disease at baseline

Treatment with AVASTIN at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles then followed by AVASTIN as a single

agent resulted in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

AVF4095g

The safety and efficacy of AVASTIN in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting or prior AVASTIN treatment, was studied in a phase III trial randomised, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding AVASTIN to carboplatin and gemcitabine chemotherapy and continuing AVASTIN as a single agent to progression to carboplatin and gemcitabine alone.

A total of 484 patients with measurable disease were randomised in equal portions to either:

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity
- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent AVASTIN (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by AVASTIN (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 17.

Table 17 Efficacy Results from Study AVF4095g

Progression-free survival				
	Investigator Assessment*		IRC Assessment	
	Placebo + C/G (n = 242)	AVASTIN + C/G (n = 242)	Placebo + C/G (n = 242)	AVASTIN + C/G (n = 242)
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388, 0.605]		0.451 [0.351, 0.580]	
p-value	< 0.0001		< 0.0001	
Objective response rate				
	Investigator Assessment		IRC Assessment	
	Placebo + C/G (n = 242)	AVASTIN + C/G (n = 242)	Placebo + C/G (n = 242)	AVASTIN + C/G (n = 242)
% pts with objective response	57.4%	78.5%	53.7%	74.8%
p-value	< 0.0001		< 0.0001	
Overall survival**				
	Placebo + C/G (n = 242)		AVASTIN + C/G (n = 242)	
Median OS (months)	32.9		33.6	
Hazard Ratio (95% CI)	0.952 [0.771; 1.176]			
p-value	0.6479			

* Primary analysis

** Final overall survival analysis performed when approximately 73% of the patients had died

MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of AVASTIN in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an open-label, randomised, two-arm phase III evaluation of AVASTIN plus chemotherapy (CT+BV) versus chemotherapy alone (CT). A total of 361 patients were enrolled into this

study and administered either chemotherapy (paclitaxel, topotecan, or PLD) alone or in combination with AVASTIN:

- CT Arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1-5 every 3 weeks.
  - PLD 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 only every 4 weeks. After Cycle 1, the drug could be delivered as a 1-hour infusion.
- CT+BV Arm (chemotherapy plus AVASTIN):
  - The chosen chemotherapy was combined with AVASTIN 10 mg/kg IV every 2 weeks (or AVASTIN 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m^2 on Days 1-5 on a every 3 weeks schedule).

Eligible patients had ovarian cancer that progressed within 6 months of previous platinum therapy. If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent.

The primary endpoint was progression-free survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 18.

Table 18 Efficacy Results from Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (n = 182)	CT+BV (n = 179)
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	< 0.0001	

Secondary Endpoints		
Objective Response Rate*		
	CT (n = 144)	CT+BV (n = 142)
% pts with objective response	18 (12.5%)	40 (28.2%)
p-value	0.0007	
Overall Survival (final analysis)**		
	CT (n = 182)	CT+BV (n = 179)
Median OS (months)	13.3	16.6
Hazard Ratio (95% CI)	0.870 (0.678, 1.116)	
p-value	0.2711	

All analyses presented in this table are stratified analyses

* Randomised Patients with Measurable Disease at Baseline

** At the time of the final OS analysis (25 January 2013), 266 patients (73.7%) had died across the two treatment arms.

Cervical Cancer

GOG-0240

The efficacy and safety of AVASTIN in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomised, four-arm, multicentre phase III trial.

A total of 452 patients were randomised to receive either:

- Paclitaxel 135 mg/m^2 IV over 24 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 1 (q3w)
- Paclitaxel 135 mg/m^2 IV over 24 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 plus AVASTIN 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 plus AVASTIN 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 1 and AVASTIN 15 mg/kg IV on day 1 (q3w)

- Paclitaxel 175 mg/m^2 over 3 hours on Day 1 and topotecan 0.75 mg/m^2 over 30 minutes on Days 1-3 (q3w)
- Paclitaxel 175 mg/m^2 over 3 hours on Day 1 and topotecan 0.75 mg/m^2 over 30 minutes on Days 1-3 plus AVASTIN 15 mg/kg IV on Day 1 (q3w)

Eligible patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.
The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 19.

Table 19 Overall Efficacy by AVASTIN Treatment (ITT Population) from study GOG-0240

	Chemotherapy (n = 225)	Chemotherapy + BV (n = 227)
Primary Endpoint		
Overall Survival		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58; 0.94] (p-value[5] = 0.0132)	
Secondary Endpoints		
Progression-free survival		
Median PFS (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54; 0.81] (p-value[5] = < 0.0001)	
Best Overall Response		
Response rate[2]	76 (33.8%)	103 (45.4%)
95% CI for Response Rates[3]	[27.6; 40.4]	[38.8; 52.1]
Difference in Response Rates	11.60	
95% CI for Difference in Response Rates[4]	[2.4; 20.8]	
p-Value (Chi-squared Test)	0.0117	

[1] Kaplan-Meier estimates

[2] Patients with best overall response of confirmed CR or PR
[3] 95% CI for one sample binomial using Pearson-Clopper method
[4] Approximately 95% CI for difference of two rates using Hauck-Anderson method
[5] log-rank test (stratified)

3.1.3 Immunogenicity

No robust assessment of anti-drug antibodies has been done in Avastin clinical trials.
For MVASI , see section 3.1.2 Clinical/Efficacy Studies, Efficacy data for MVASI, Immunogenicity.

3.2 Pharmacokinetic Properties

The pharmacokinetics of MVASI is similar to AVASTIN.
The pharmacokinetics of bevacizumab were characterised in patients with various types of solid tumours. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.
As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (V_c), and a long elimination half-life. This enables target therapeutic bevacizumab serum levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).
In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 year with 5^{th} and 95^{th} percentiles of 37 and 76 year]).
Low albumin and high tumour burden are generally indicative of disease severity.
Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

3.2.1 Absorption

No text

3.2.2 Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male subjects respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (V_p) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is coadministered with anti-neoplastic agents. After correcting for body weight, male subjects had a larger Vc (+20%) than females.

3.2.3 Metabolism

Assessment of bevacizumab metabolism in rabbits following a single i.v. dose of ^{125}I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor result in protection from cellular metabolism and the long terminal half-life.

3.2.4 Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk. The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

3.2.5 Pharmacokinetics in Special Populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Pediatric population: The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years; 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and the volume of distribution of bevacizumab were comparable between pediatric and adult patients when

normalized by body-weight. Age was not associated with the pharmacokinetics of bevacizumab when body-weight was taken into account.

Renal impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.

Hepatic impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

Studies have not been performed to evaluate the carcinogenic potential of bevacizumab.

3.3.2 Genotoxicity

Studies have not been performed to evaluate the mutagenic potential of bevacizumab.

3.3.3 Impairment of Fertility

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. No adverse effect on male reproductive organs was observed in repeat dose toxicity studies in cynomolgus monkeys. 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 13 or 26 weeks. The doses associated with this effect were ≥ 4 times the human therapeutic dose or ≥ 2-fold above the expected human exposure based on average serum concentrations in female monkeys. In rabbits, administration of 50 mg/kg of bevacizumab resulted in a significant decrease in ovarian weight and number of corpora lutea. The results in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of bevacizumab is likely to result in an adverse effect on female fertility.

3.3.4 Reproductive Toxicity

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses of 10-100 mg/kg. Information on foetal malformations observed in the postmarketing setting are provided in *section 2.5.1 Use in Special Populations, Pregnancy and 2.6.2 Undesirable Effects, Postmarketing Experience*.

3.3.5 Other

Physeal development:

In studies of up to 26 weeks duration in cynomolgus monkeys, bevacizumab was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥ 0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

Wound healing:

In rabbits, the effects of bevacizumab on circular wound healing were studied. Wound re-epithelialisation was delayed in rabbits following five doses of bevacizumab, ranging from 2-50 mg/kg, over a 2-week period. A trend toward a dose-dependent relationship was observed. The magnitude of effect on wound healing was similar to that observed with corticosteroid administration. Upon treatment cessation with either 2 or 10 mg/kg bevacizumab, the wounds closed completely. The lower dose of 2 mg/kg was approximately equivalent to the proposed clinical dose. A more sensitive linear wound healing model was also studied in rabbits. Three doses of bevacizumab ranging from 0.5-2 mg/kg dose-dependently and significantly decreased the tensile strength of the wounds, consistently with delayed wound healing. The low dose of 0.5 mg/kg was 5-fold below the proposed clinical dose.

As effects on wound healing were observed in rabbits at doses below the proposed clinical dose, the capacity for bevacizumab to adversely impact wound healing in human should be considered.

In cynomolgus monkeys, the effects of bevacizumab on the healing of a linear incision were highly variable and no dose-response relationship was evident.

Renal function:

In normal cynomolgus monkeys, bevacizumab had no measurable effect on renal function treated once or twice weekly for up to 26 weeks, and did not accumulate in the kidney of rabbits following two doses up to 100 mg/kg (approximately 80-folds the proposed clinical dose).

Investigative toxicity studies in rabbits, using the models of renal dysfunction, showed that bevacizumab did not exacerbate renal glomerular injury induced by bovine serum albumin or renal tubular damage induced by cisplatin.

Albumin:

In male cynomolgus monkeys, bevacizumab administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks was associated with a statistically significant decrease in albumin and albumin to globulin ratio and increase in globulin. These effects were reversible upon cessation of exposure. As the parameters remained within the normal reference range of values for these endpoints, these changes were not considered as clinically significant.

Hypertension:

At doses up to 50 mg/kg twice weekly in cynomolgus monkeys, bevacizumab showed no effects on blood pressure.

Haemostasis:

Non-clinical toxicology studies of up to 26 weeks duration in cynomolgus monkeys did not find changes in haematology or coagulation parameters including platelet counts, prothrombin and activated partial thromboplastin time. A model of haemostasis in rabbits, used to investigate the effect of bevacizumab on thrombus formation, did not show alteration in the rate of clot formation or any other haematological parameters compared to treatment with bevacizumab vehicle.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Trehalose dihydrate, Sodium phosphate, Polysorbate, Water for injections.

4.2 Storage

MVASI should not be used after the expiry date (EXP) shown on the pack.

Store vials in a refrigerator at 2°C-8°C.

Keep vial in the outer carton in order to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

MVASI does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 35 days at 2°C to 8°C plus an additional 48 hours at temperatures not exceeding 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

4.3 Special Instructions for Use, Handling and Disposal

MVASI infusions should not be administered or mixed with dextrose or glucose solutions (see "Incompatibilities" below)

Do not administer as an intravenous push or bolus.

MVASI should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare MVASI. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4-16.5 mg/ml.

Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

MVASI is not formulated for intravitreal use.

Incompatibilities

No incompatibilities between MVASI and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of MVASI was observed when diluted with dextrose solutions (5%).

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

5. NATURE AND CONTENTS OF CONTAINER

4 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 100 mg of bevacizumab.

16 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 400 mg of bevacizumab.

Pack of 1 vial.

Not all presentations may be marketed.

Product Registration Holder:

Amgen Biopharmaceuticals Malaysia Sdn Bhd
Common Ground, 1 Powerhouse,
Horizon Penthouse, No. 1,
Persiaran Bandar Utama, Bandar Utama,
47800 Petaling Jaya, Selangor, Malaysia.

Date of Revision: Aug 2024

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