EU Risk Management Plan for Avzivi® (bevacizumab)

RMP version to be assessed as part of this application:

RMP Version number: v.0.2

Data lock point for this RMP: 05 November 2019

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Rationale for submitting an updated RMP: Not applicable for an initial marketing authorization application submission

Summary of significant changes in this RMP: Not applicable for an initial marketing authorization application submission

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP: Not applicable

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Bevacizumab
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates (ATC code: L01F G01)
Marketing Authorisation Applicant	Bio-Thera Solutions
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Avzivi 25 mg/mL concentrate for solution for infusion (Avzivi)
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class: recombinant humanized monoclonal antibody
	Summary of mode of action: Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the biological activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth.
	Important information about its composition: Bevacizumab is a recombinant humanized monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells.
Hyperlink to the Product Information	Product information for Avzivi
Indication(s) in the EEA	**Current:** Metastatic carcinoma of the colon or rectum Avzivi in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. Metastatic breast cancer Avzivi in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1 of the

	summary of product characteristics (SmPC). Avzivi in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avzivi in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1 of the SmPC. Non-small cell lung cancer Avzivi, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology. Avzivi, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1 of the SmPC). Advanced and/or metastatic renal cell cancer Avzivi in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer. Epithelial ovarian, fallopian tube, or primary peritoneal cancer Avzivi, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (see section 5.1 of the SmPC). Avzivi, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. Avzivi 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 (see section 5.1 of the SmPC). Cervical cancer Avzivi, in combination with paclitaxel and cisplatin or,

	alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1 of the SmPC).
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: Metastatic carcinoma of the colon or rectum The recommended dose of Avzivi, administered as an intravenous 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 The recommended dose of Avzivi 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 treatment be continued until progression of the underlying disease or until unacceptable toxicity. Non-small cell lung cancer *First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy* Avzivi is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Avzivi as a single agent until disease progression. The recommended dose of Avzivi is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses (see section 5.1 of the SmPC). It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

	First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib EGFR mutation testing should be performed prior to initiation of treatment with the combination of Avzivi and erlotinib. It is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations. The recommended dose of Avzivi when used in addition to erlotinib is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that the treatment with Avzivi in addition to erlotinib is continued until disease progression. For the posology and method of administration of erlotinib, please refer to the full erlotinib prescribing information. <u>Advanced and/or metastatic renal cell cancer</u> The recommended dose of Avzivi is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity. <u>Epithelial ovarian, fallopian tube and primary peritoneal cancer</u> *Front-line treatment* Avzivi is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avzivi as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of Avzivi is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. *Treatment of platinum-sensitive recurrent disease* Avzivi is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Avzivi as single agent until disease progression. The recommended dose of Avzivi is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

	Treatment of platinum-resistant recurrent disease Avzivi is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Avzivi is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Avzivi is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Avzivi is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity (see section 5.1 of the SmPC, study MO22224). <u>Cervical cancer</u> Avzivi is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan. The recommended dose of Avzivi is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity (see section 5.1 of the SmPC).
	Proposed (if applicable): not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Avzivi is supplied in 100 mg and 400 mg preservative-free, single-use vials containing 4 mL or 16 mL Avzivi. Each 4 mL vial contains 100 mg of bevacizumab. Each 16 mL vial contains 400 mg of bevacizumab.
	Proposed (if applicable): not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indications:

Avzivi in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Avzivi in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1 of the SmPC.

Avzivi in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avzivi in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1 of the SmPC.

Avzivi, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Avzivi, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with EGFR activating mutations (see section 5.1 of the SmPC).

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

Avzivi, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (see section 5.1 of the SmPC).

Avzivi, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Avzivi 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 (see section 5.1 of the SmPC).

Avzivi, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1 of the SmPC).

BAT1706 is a similar biological product of the bevacizumab injection (Bevacizumab injection, brand name Avastin® [hereafter referred to as "Avastin"]). Avastin is administered as an intravenous infusion and it is an antitumor angiogenesis drug that has a proven clinical efficacy in extending the overall survival (OS) and progression-free survival (PFS) and overall response rate (ORR) in patients with cancer (Avastin Product Information 2015).

SI.1 Metastatic carcinoma of the colon or rectum

Incidence and prevalence:

According to data published by the International Agency for Research on Cancer (IARC), colorectal cancer (ICD10: C18-21) was the second most frequently occurring new cancer in Europe (WHO region) in 2018, with an estimated 530,611 cases and an age standardized rate of 28.4 cases per 100,000 per year for both sexes (International Agency for Research on Cancer [IARC] 2018).

The 5-year prevalence (all ages) of cancer of the colon and rectum in Europe was estimated at 896,825 and 546,339, respectively (Globocan 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

In the US, the median age at diagnosis is 67 years (Surveillance, Epidemiology, and End Results (SEER) Program data 2010-2016, 2020a). The age-standardized incidence rates are lower for women than for men; in 2018 the rates in Europe (WHO Europe region) were 35.6 for males and 22.8 for females (Globocan 2020).

Data from the US show that for males the rate of new cases is highest for Black males (51.3 new cases per 100,000 - age adjusted rate), followed by White (43.0 per 100,000), American Indian/Alaska Native (40.4 per 100,000), and Asian/Pacific Islander (37.9 per 100,000) males. The rate of new cases is highest in Black females (38.2 per 100,000), followed by American Indian/Alaska native (37.9 per 100,000), White (33.3 per 100,000), and Asian/Pacific Islander (26.8 per 100,000) females (SEER - data 2010-2016, 2020a).

Other risk factors for colorectal cancer besides increasing age include family history of colorectal cancer, personal history of colorectal adenomas or ovarian cancer, certain hereditary conditions, history of ulcerative colitis or Crohn's disease, excessive alcohol use, cigarette smoking, and obesity (PDQ [Physician Data Query] NCI [National Cancer Institute] 2020a). There is strong

evidence that diets high in processed or red meat increase risk of colorectal cancer, whereas consumption of foods containing dietary fiber and consumption of dairy products, and taking calcium supplements decrease the risk of colorectal cancer (World Cancer Research Fund [WCRF] and the American Institute for Cancer Research [AICR] 2018). An increased risk for colon cancer was observed with high intake of red and processed meat, but this was not observed with rectal cancer (Magalhães et al 2012). Physical activity appears protective, particularly for colon cancer (WCRF/AICR 2018). Other factors with some evidence for increasing risk for colorectal cancer include low consumption of non-starchy vegetables, low consumption of fruit, and consumption of foods containing iron (WCRF/AICR 2018).

Approximately 20-25% of colorectal cancer patients present with metastatic disease at the time of initial diagnosis (Elferink et al 2015), and approximately 50% eventually develop metastatic disease, most commonly to the liver and thorax, followed by peritoneum, bone, and nervous system (Keramida et al 2019).

The most common site of metastases for colon or rectal cancer is the liver. Approximately 50% of colon cancers patients develop hepatic metastases (PDQ NCI 2020a). Colorectal cancer may also metastasize to the lungs, bones, brain, or spinal cord (Cancer Treatment Centers of America, 2020). Treatment options vary depending on where the cancer has spread, but options include surgery, radiation therapy, chemotherapy, targeted therapy, and/or immunotherapy (e.g., checkpoint inhibitors) (PDQ NCI 2020a).

The main existing treatment options: Treatment of Stage IV and recurrent colon cancer includes surgery and chemotherapy and targeted therapy. The therapeutic approach for metastatic colorectal cancer is primarily based on the use of combination cytotoxic therapy (Keramida et al 2019). Medications used to treat metastatic colorectal cancer (either alone or in combination) include 5-fluoruracil, fluoropyrimidine (capecitabine), leucovorin, irinotecan, oxaliplatin, anti-vascular endothelial growth factor (VEGF) antibody (e.g., aflibercept, bevacizumab, regorafenib, ramucirumab), anti-epidermal growth factor receptor (EGFR) antibody (e.g., cetuximab, panitumumab), TAS-102 (combination of a thymidine-based nucleic acid analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride), and pembrolizumab (a programmed cell death protein, PD-1, antibody) (PDQ NCI 2020a).

Combination cytotoxic chemotherapy regimens that are generally accepted as first-line therapies for metastatic colorectal cancer include fluorouracil and leucovorin, 5-fluorouracil/ leucovorin/ oxaliplatin (FOLFOX), 5-fluorouracil/ leucovorin/ irinotecan (FOLFIRI), and capecitabine/oxaliplatin (Li & Saif 2009).

Aside from cancer treatment, comprehensive palliative care, including medications for cancer pain (opioids and non-opioids), antidepressant and anti-anxiety medications, anti-convulsant medications, and steroids, is important in advanced cancer. Anti-inflammatories including nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to treat pain in patients with advanced cancer. Radiation therapy and radiofrequency ablation are often used to relieve cancer pain (German Guideline Program in Oncology [GGPO]) 2015; Dixon & Stamos 2004). Patients with advanced cancer are also often on anticoagulants such as warfarin or enoxaparin due to cancer-associated venous thromboembolism (Johnstone & Rich 2018).

Natural history of the indicated condition in the population, including mortality and morbidity:

The acute complications of colorectal cancer include bleeding, obstruction, and perforation (Yang & Pan 2014). Bowel obstruction is a common complication of colorectal cancer. Cancer-associated venous thromboembolism is a common complication and is associated with a high morbidity and

mortality; pancreatic, gastric, and lung cancer are especially highly associated with cancer-associated venous thromboembolism (Kim et al 2019). Complications of metastatic colorectal cancer depend on the site(s) of metastases and the cancer treatment(s). Complications related to colorectal cancer surgery include pneumonia, urinary tract infections, myocardial infarction, wound infections, and abscess drainage (Hendren et al 2010). Perioperative cardiovascular complications include acute myocardial infarction, heart failure, and cardiovascular death, which increase with increasing age (Keramida et al 2019). Chemotherapies and targeted therapies for metastatic colorectal cancer are associated with adverse events, including gastrointestinal events (nausea/vomiting, diarrhea, stomatitis, constipation), hematologic events (anemia, neutropenia, thrombocytopenia), cardiovascular events (arrhythmias, congestive heart failure, hypertension), central nervous system (decreased appetite, asthenia/fatigue, pain/myalgia, headache, peripheral neuropathy), and other events (erythema, skin rash, hypokalemia, hypomagnesemia, hyponatremia, gastrointestinal hemorrhage, increased transaminases, dyspnea, and upper respiratory infection) (Latremouille-Viau et al 2017). Cardiotoxic effects specifically associated with 5-fluorouracil include angina, dyspnea, arrhythmias, hypotension, myocarditis, pericarditis, myocardial infarction, apical ballooning syndrome, heart failure, cardiogenic shock, and death. Cardiotoxic effects specifically associated with fluoropyrimidines (i.e., capecitabine) include angina, arrhythmias, acute coronary syndrome, heart failure, and sudden cardiac death (Keramida et al 2019).

Important co-morbidities: In a study of 2,755 patients with colorectal cancer (primary tumor site), the most prevalent comorbidities were hypertension (41.4%), diabetes (15.6%), previous solid tumor (14.3%), angina (12.1%), respiratory disease (11.7%), myocardial infarct (8.0%), congestive heart failure (5.4%), stroke (5.3%), stomach/intestinal disease (4.7%), and psychiatric disease (4.1%) (Piccirillo et al 2008).

SI.2 Metastatic breast cancer

Incidence and prevalence:

IARC data shows that breast cancer (ICD10: C50) was the most frequently occurring new cancer in Europe (WHO region), with an estimated 562,990 new cases (12.3% of all new cancers) occurring in Europe in 2018 (an age standardized rate of 69.5 cases per 100,000 females per year) (IARC 2018).

The 5-year prevalence (all ages) for 2018 in Europe was 2,182,328 (Globocan 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin - and risk factors for the disease:

The risk of breast cancer increases with age – it is more than 4 times higher for women at age ≥65 vs <65 years old (European Network of Cancer Registries [ENCR] 2014a). Breast cancer occurs almost exclusively in women; less than 1% of total breast cancer cases worldwide are in men (Anderson et al 2010). Ethnicity data are available for the US. In the US, breast cancer is most commonly diagnosed in White women (age standardized rate of 131.3 cases per 100,000 per year), followed by Black women (124.8), Asian/Pacific Islander (102.9), and American Indian/Alaska Native women (79.5) (SEER data - 2013-2017 2020b). Identified risk factors for breast cancer are family history, exposure to estrogen (early menarche, late menopause, not having children), hormone replacement therapy, genetic predisposition, breast conditions (dense breast tissue, benign breast proliferative lesions, non-invasive lobular carcinoma), obesity, tobacco use, alcohol consumption. Other risk factors are radiation (including high-dose radiation therapy to

the chest such as for Hodgkin lymphoma), and occupational exposures (ethylene oxide) (ENCR 2014a).

The main existing treatment options:

In locally-advanced breast cancer, a combination of systemic therapy, surgery, and radiotherapy is used in most cases. The type of therapy depends on the type of cancer: for hormone receptor (HR) positive breast cancer, endocrine therapy or anthracycline – and taxane-based chemotherapy is recommended, for HER2 positive breast cancer, anthracycline-based chemotherapy sequentially with taxanes and anti-HER2 therapy, and for triple-negative breast cancer, anthracycline and taxane-based chemotherapy are recommended. Patients may also receive radiotherapy as a neoadjuvant treatment (European Society for Medical Oncology [ESMO] guidelines – Cardoso et al 2018).

With metastatic breast cancer, the aim is to prolong life and maximize the quality of life. Chemotherapy (usually capecitabine, vinorelbine, or eribulin) is the standard treatment for triple-negative breast cancer and for estrogen receptor (ER)-positive, HER2-negative patients who have stopped responding to endocrine therapy. ER-positive patients may also receive chemotherapy if their cancer is particularly aggressive. Taxanes or anthracyclines may be used again if they have been given before as neoadjuvant or adjuvant therapy (Cardoso et al 2018). A platinum-containing chemotherapy such as carboplatin or cisplatin might also be used in patients with triple-negative disease who have previously been treated with anthracyclines.

ER positive, HER2 negative advanced disease should almost always be initially treated with an aromatase inhibitor, tamoxifen, or fulvestrant (Cardoso et al 2018). In pre- and perimenopausal patients, ovarian function suppression or ablation is recommended in combination with endocrine therapy. Where available, endocrine therapy is usually combined with targeted therapies such as palbociclib, ribociclib, abemaciclib or everolimus to improve outcomes. Megestrol acetate and estradiol are options for further lines of treatment. Patients with ER positive, HER2 positive metastatic disease are usually treated with anti-HER2 therapy and chemotherapy as first-line treatment, which may be followed by endocrine therapy in combination with further anti-HER2 therapy as maintenance treatment after completing chemotherapy (Cardoso et al 2018).

The first-line treatment for HER2 positive advanced disease is likely to be trastuzumab and pertuzumab in combination with chemotherapy (usually docetaxel or paclitaxel) (Cardoso et al 2018). Second-line treatment in these patients is usually trastuzumab emtansine (T-DM1) or occasionally trastuzumab in combination with lapatinib. Further treatment lines may include combinations of trastuzumab with other chemotherapy drugs, or a combination of lapatinib and capecitabine.

CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) may be used for the treatment of ER positive advanced breast cancer in combination with an aromatase inhibitor or fulvestrant (Ibrance® SmPC, 2017; Kisqali® SmPC, 2017; Cardoso et al 2018). Everolimus in combination with exemestane, tamoxifen or fulvestrant is a treatment option for some postmenopausal patients with ER positive advanced breast cancer which has progressed after treatment with a non-steroidal aromatase inhibitor (Cardoso et al 2018). The new agents olaparib and talazoparib are PARP (poly adenosine diphosphate ribose polymerase) inhibitors that may be used as an alternative to chemotherapy in patients with BRCA1/2 mutations. Bevacizumab is an option in selected case settings (Cardoso et al 2018).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In Europe (WHO region) in 2018, an estimated 150,808 women died of breast cancer, with a cumulative risk of dying from breast cancer before the age of 75 years of 1.61% (Globocan 2020). Although it is considered treatable, with several new therapies approved in the past years, advanced/metastatic breast cancer remains a virtually incurable disease (Cardoso et al 2018).

Important co-morbidities:

In a study of 4,479 patients with breast cancer (primary tumor site), the most prevalent comorbidities were hypertension (34.5%), previous solid tumor (12.4%), diabetes (10.4%), respiratory disease (8.2%), psychiatric disease (5.8%), angina (4.2%), obesity (3.9%), myocardial infarct (3.1%), stroke (2.8%), and stomach/intestinal disease (2.4%) (Piccirillo et al 2008).

SI.3 Non-small cell lung cancer

Incidence:

IARC data shows that lung cancer (ICD10: C33-34) was the third most frequently occurring new cancer in Europe (WHO region), with an estimated 519,304 new cases (11.4% of all new cancers) occurring in Europe in 2018 (an age standardized rate of 29.4 cases per 100,000 per year) (IARC 2018).

Prevalence:

The 5-year prevalence (all ages) for 2018 in Europe was 544,309 (Globocan 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin - and risk factors for the disease:

In the US, the median age at diagnosis (lung and bronchus cancer) is 71 years (SEER data 2013-2017, 2020c).

The age-standardized incidence rates are lower for women than for men; in 2018 the rates in Europe (WHO Europe region) were 44.9 for males and 17.0 for females (Globocan 2020).

In US males, the rate of new cases is highest in Black males (71.2 new cases per 100,000 per year – age adjusted), followed by White (62.2), Asian/Pacific Islander (46.2), and American Indian/Alaska Native (43.5) males. In US females, the rate of new cases is highest in White females (51.5 new cases per 100,000 per year), followed by Black (43.8), American Indian/Alaska native (34.3), and Asian/Pacific Islander (28.6) females (SEER data 2013-2017, 2020c).

Smoking is the main risk factor and responsible for more than 80% of lung cancer. Other risk factors are environmental (living in an area with high air pollution, working with radioactive materials or asbestos), genetics, and a high fat diet also raise the risk of lung cancer (ENCR 2014b).

The main existing treatment options: Medications used to treat NSCLC are extensive and include afatinib dimaleate, alectinib, atezolizumab, bevacizumab, brigatinib, carboplatin, ceritinib, crizotinib, dabrafenib mesylate, dacomitinib, docetaxel, doxorubicin hydrochloride, durvalumab, entrectinib, erlotinib hydrochloride, everolimus, gefitinib, gemcitabine hydrochloride, lorlatinib, mechlorethamine hydrochloride, methotrexate, necitumumab, nivolumab, osimertinib mesylate,

paclitaxel, pembrolizumab, pemetrexed disodium, ramucirumab, trametinib, and vinorelbine tartrate.

Standard treatment options for newly diagnosed Stage IV relapsed and recurrent NSCLS include cytotoxic combination chemotherapy (e.g., platinum combinations [cisplatin or carboplatin] with vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan, protein-bound paclitaxel, and pemetrexed), combination chemotherapy with monoclonal antibodies (e.g., bevacizumab, cetuximab, or necituximab), maintenance therapy after first-line chemotherapy (for patients with stable or responding disease after four cycles of platinum-based combination chemotherapy), EGFR tyrosine kinase inhibitors and other targeted therapies, and immune checkpoint inhibitors (PDQ NCI 2020b).

Comprehensive palliative care, including medications for cancer pain (opioids and non-opioids), antidepressant and anti-anxiety medications, anti-convulsant medications, and steroids, is important in advanced cancer. Anti-inflammatories including nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to treat pain in patients with advanced cancer (GGPO 2015). Patients with advanced cancer are also often on anticoagulants such as warfarin or enoxaparin (Johnstone & Rich 2018). Radiation therapy and radiofrequency ablation are often used to relieve cancer pain.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In Europe (WHO region) in 2018, an estimated 434,749 persons died of lung cancer, with a cumulative risk of dying from lung before the age of 75 years of 2.97% (Globocan 2020). Unresectable advanced, metastatic or recurrent NSCLC cancer is not considered to be curable – the focus of treatment is to improve quality of life (ESMO guidelines - Planchard et al 2018).

Important co-morbidities:

Important co-morbidities: In a study of 3,793 lung cancer patients (primary tumor site), the most prevalent comorbidities were hypertension (37.7%), respiratory disease (28.5%), previous solid tumor (18.0%), angina (14.2%), diabetes (11.1%), myocardial infarct (9.9%), stroke (5.3%), congestive heart failure (5.1%), stomach/intestinal disease (5.0%), and psychiatric disease (4.8%) (Piccirillo et al 2008).

SI.4 Advanced and/or metastatic renal cell carcinoma

Incidence:

IARC data shows that there were an estimated 144,836 new cases of renal cancer (ICD10: C64-65) in Europe (3.2% of all new cancers) occurring in Europe (WHO region) in 2018 (an age standardized rate of 8.9 cases per 100,000 per year) (IARC 2018).

Prevalence:

The 5-year prevalence (all ages) for 2018 in Europe was 382,191 (Globocan 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin - and risk factors for the disease:

In the US, the median age at diagnosis is 64 years (SEER data 2013-2017, 2020d). Men are approximately twice as likely to develop kidney cancer as women. In 2018 in Europe (WHO region),

there were 12.3 new cases per 100,000 per year in males compared to 6.0 per 100,000 per year in females (Globocan 2020).

In US males, the rate of new cases of kidney and renal pelvis cancer was highest in Black males (24.5 new cases per 100,000 per year – age adjusted), followed by White (23.0), American Indian/Alaska native (22.9), and Asian/Pacific Islander (12.5) males. In US females, the rate of new cases of kidney and renal pelvis cancer was highest in American Indian/Alaska Native females (13.7 new cases per 100,000 per year – age adjusted), followed by Black (12.2), White (11.4), and Asian/Pacific Islander (5.8) females (SEER data 2013-2017, 2020d).

Risk factors for kidney cancer are smoking, high protein and fat consumption, obesity, acquired cystic kidney disease, hypertension, kidney stones, and kidney infection. Renal cancer has also been associated with some hereditary syndromes such as von Hippel-Lindau syndrome, hereditary leiomyomatosis, and Birt-Hogg-Dubé syndrome (ENCR 2017).

The main existing treatment options: Nephron-sparing surgery and thermal ablation may be used for smaller tumors. Radical nephrectomy is a standard treatment for larger and central tumors.

Main treatment options in patients with metastatic renal cell carcinoma include 3 agents that target angiogenesis (sunitinib, bevacizumab, and pazopanib). In addition, tivozanib, has been shown to improve PFS and response rate, especially in good-risk patients. Temsirolimus has demonstrated efficacy in poor-risk patients. A combination of nivolumab and ipilimumab was superior to sunitinib in intermediate- and poor-risk patients, but not in good-risk patients and is now the standard of care in intermediate- and poor-risk patients. Some efficacy has been reported with sorafenib, high-dose interleukin-2 and low-dose IFN combined with bevacizumab, and such therapies should be considered as possible options when standard treatments are not available. Finally, cabozantinib appeared to be superior to sunitinib in intermediate- and poor-risk patients and is therefore an option in these patients (ESMO guidelines – Escudier et al 2019).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In Europe (WHO region) in 2018, an estimated 59,078 persons died of renal cancer, with a cumulative risk of dying from renal cancer before the age of 75 years of 0.34% (Globocan 2020). In the US, the 5-year survival relative survival rate was 70.4% for regional cancer and 13.0% for metastatic renal cancer (SEER data 2010-2016, 2020d).

Important co-morbidities:

Information on specific comorbidities in European patients was not identified. In a study of 1,992 US patients initiating treatment for metastatic renal cell carcinoma, the most common comorbidities (in >10% of patients) were diabetes (27%), chronic kidney disease (20%), liver disease (18%), and chronic obstructive pulmonary disease (12.6%) (Pal et al 2019).

SI.5 Epithelial Ovarian, fallopian tube, and primary peritoneal cancer

Incidence and prevalence:

Ovarian cancer

IARC data published in 2018 shows that there were an estimated 74,548 new cases of ovarian cancer (ICD10: C56) in Europe (1.6% of all new cancers) occurring in Europe in 2018 (an age standardized rate of 9.1 cases per 100,000 per year) (IARC 2018).

The 5-year prevalence (all ages) for 2018 in Europe was 206,144 (Globocan 2020).

Identified risk factors for ovarian cancer are age, menstrual-related factors, endometriosis, family history, BRCA mutations, Lynch syndrome, and lower socioeconomic status. Parity, higher age of childbirth, hormonal contraception, and breastfeeding/lactation appear to be protective (Momenimovahed et al 2019).

Fallopian tube cancer

Fallopian tube cancer is a rare malignant tumor thought to account for 0.1-1.8% of all gynecological tumors (reviewed in Goswami et al 2006). In Finland the age-adjusted incidence rate was 0.54/100,000 in 1993–97 (Riska et al 2003).

In Europe, fallopian tube cancer has an estimated prevalence of 1-9/100,000 (Orphanet 2020a).

Fallopian tube cancer occurs most often after the fourth decade of life, with an average age of 62 years (Bacalbaşa et al 2016).

The risk factors for fallopian tube cancer appear to be similar to those for ovarian cancer (PDQ Screening and Prevention Editorial Board 2002).

Primary peritoneal cancer

Primary peritoneal cancer is a rare malignant tumor of the peritoneal cavity of extra-ovarian origin of unknown incidence and prevalence (Orphanet 2020b).

The risk factors for primary peritoneal cancer appear to be similar to those for ovarian and fallopian tube cancer (PDQ Screening and Prevention Editorial Board 2002).

The main existing treatment options:

The standard treatment for locally advanced and metastatic epithelial ovarian cancer is a regimen of paclitaxel and carboplatin. If paclitaxel cannot be given, docetaxel or pegylated liposomal doxorubicin can be substituted and given with carboplatin instead (ESMO guidelines – Ledermann et al 2013). Bevacizumab is licensed in Europe in combination with paclitaxel and carboplatin for front-line treatment of women with Stage III B, III C or IV epithelial ovarian cancer.

Treatment options for recurrent epithelial ovarian cancer are sequential treatment with one chemotherapy drug at a time for patients with an early relapse, a carboplatin-based doublet chemotherapy regimen for those patients with a later relapse (over 6 months and especially over 12 months), or a range of potential and mostly platinum-based combination options if the cancer has kept its sensitivity to platinum-type drugs (such as carboplatin). Bevacizumab is also been licensed in Europe for treating women with relapsed epithelial ovarian cancer as per it approved indications and combinations (ESMO guidelines – Ledermann et al 2013). The PARP inhibitors niraparib, olaparib, and rucaparib have recently been recommended for maintenance treatment in

patients with recurrent platinum-sensitive high-grade ovarian cancer, irrespective of BRCA (EMSO Guidelines Committee 2020).

Standard guidelines regarding the optimal management of fallopian tube carcinoma and primary peritoneal cancer are not well defined. Management follows the same guidelines as ovarian cancer (Bacalbaşa et al 2016; Foundation for Women's Cancer 2020).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In Europe (WHO region) in 2018, an estimated 48,870 women died of ovarian cancer, with a cumulative risk of dying from ovarian cancer before the age of 75 years of 0.59% (Globocan 2020). As early-stage ovarian cancer is asymptomatic, most women who are diagnosed with ovarian cancer already have metastatic disease. In the US, the 5-year relative survival rate is 48.6% (SEER data 2010-2016, 2020e).

Patients with platinum-resistant or refractory disease generally have a poor prognosis with a short expected overall survival (usually <12 months). Treatment of these patients should be focused on quality of life and control of symptoms (ESMO guidelines – Ledermann et al 2013).

Important co-morbidities:

A cross-sectional study was carried out in France with patients over 18 years, diagnosed with advanced (stage IIIB–IV) or recurrent epithelial ovarian cancer (EOC) between 2009 and 2012. A total of 23 physicians (oncologists and gynecologists) participated, contributing 127 patients. A total of 73 comorbidities were reported in 44 patients (34.6%). The most common types of comorbidities were vascular disorders (10.2%), metabolic and nutrition disorders (7.1%), respiratory and thoracic disorders (5.5%), psychiatric disorders (5.5%), musculoskeletal disorders (4.7%), endocrine disorders (4.7%) (Le Saux et al 2015).

SI.6 Cervical cancer

Incidence:

IARC data shows that there was an estimated 69,114 new cases of cervical cancer (ICD10: C53) in Europe (1.5% of all new cancers) in 2018 (an age-standardized rate of 10.5 cases per 100,000 per year) (IARC 2018).

Prevalence:

The 5-year prevalence (all ages) for 2018 in Europe was 213,417 (Globocan 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin - and risk factors for the disease:

In the US, the median age at diagnosis is 50 years. Incidence by ethnicity is available for the US. The rate of new cases is higher in Hispanic and Black women (9.2 and 8.7 per 100,000 women per year, respectively) and lowest in Asian/Pacific Islander women (6.5 per 100,000 women per year) (SEER data 2013-2017, 2020f).

Human papillomavirus (HPV) infection is the main cause of nearly all cases of cervical cancer. Other identified risk factors include smoking, oral contraceptives, hormone replacement therapy,

and starting sexual activity early, however, these may be a proxy for risk of HPV infection (ENCR 2016).

The main existing treatment options: Chemoradiotherapy is the standard primary treatment for patients with locally advanced cervical cancer, with cisplatin-based chemoradiotherapy the most commonly used regimen. Neoadjuvant chemotherapy may be given to certain patients with locally advanced disease to reduce the size of the tumor before subsequent surgical removal (EMSO guidelines – Marth et al 2017).

Metastatic cervical cancer is not considered to be curable. Palliative chemotherapy is typically given to patients who are able to tolerate treatment. The chemotherapy drugs paclitaxel and cisplatin are often used as first-line therapy for metastatic disease in combination with bevacizumab. Other chemotherapy drugs that might be used include carboplatin and topotecan. Radiotherapy is sometimes used to treat patients with recurrent disease or certain lymph node metastases. It may also be used to treat the symptoms arising from metastases and to manage slow-growing lung metastases (EMSO guidelines – Marth et al 2017).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In Europe (WHO region) in 2018, an estimated 30,204 women died of cervical cancer, with a cumulative risk of dying from cervical cancer before the age of 75 years of 0.41% (Globocan 2020). Metastatic cervical cancer is not considered to be curable, but treatable with focus on relieving symptoms and improving quality of life (EMSO clinical practice guidelines – Marth et al 2017).

Important co-morbidities:

No information on comorbidity in Europe was found. A study of 275,246 patients with cervical cancer in the US found the most frequent comorbidities to be chronic pulmonary disease (in 25.8% of patients), connective tissue disease (15.4%), diabetes (14.3%), cerebrovascular disease (4.2%), hemiplegia (4.1%), myocardial infraction (3.8%), moderate/severe liver disease (3.3%), congestive heart failure (2.0%), peripheral vascular disease (2.0%), mild liver disease (1.8%), renal disease (1.3%), ulcer disease (1.2%), and lymphoma (0.5%) (Shah et al 2020).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings	Relevance to human usage
In studies of up to 26 weeks duration in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.	Physeal dysplasia: Angiogenesis, in general, and Vascular Endothelial Growth Factor (VEGF) are critically implicated in embryogenesis and growth. It should be noted that physeal dysplasia only occurred in actively growing animals with open growth plates. Wound healing: Angiogenesis, in general, and VEGF are implicated in wound healing. The inhibition of angiogenesis following administration of bevacizumab could adversely affect wound healing in humans. Wound healing complications have been observed in clinical trials with bevacizumab.
Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased incidence of specific gross and skeletal fetal malformations. Adverse fetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks.	Angiogenesis is critically important to fetal development. The inhibition of angiogenesis following administration of bevacizumab could results in an adverse pregnancy outcome. Cases of fetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed post-marketing. Information on fetal malformations observed in the post-marketing setting are provided in section 4.6 Fertility, Pregnancy and Lactation and 4.8 Undesirable Effects of the SmPC.
No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.	Angiogenesis, in general, and VEGF are implicated in ovarian function. Cases of ovarian failure have been observed in patients treated with bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of women; however, the long-term effects of treatment with bevacizumab on fertility are unknown.

Key safety findings	Relevance to human usage
Studies to evaluate the mutagenic and carcinogenic potential of bevacizumab have not been performed.	The omission of genotoxicity and carcinogenicity studies is considered acceptable for this type of compound.
No significant effect on the nervous system was observed or obvious effects on cardiovascular parameters or on the respiratory system were observed.	None.

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

Part II: Module SIII - Clinical trial exposure

BAT1706 has been developed as a biosimilar to Avastin (bevacizumab), a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A).

Clinical safety data obtained by the Applicant to support the marketing authorization application are from the single-dose Phase I studies BAT1706-001-CR and BAT1706-002-CR and the Phase III study BAT1706-003-CR (Table SIII.1). The clinical safety database included a total of 854 subjects who received at least one dose of study drug: 205 healthy male subjects (79, 84, and 42 patients who received BAT1706, EU-Avastin and US-Avastin, respectively) from studies BAT1706-001-CR and BAT1706-002-CR and 649 patients with advanced non-squamous NSCLC (325 and 324 patients who received BAT1706 and EU-Avastin, respectively) from study BAT1706-003-CR.

Table SIII.1 Summary of Clinical Development

Study **No. study centers** **Location**	**Study status** **Study period**	**Design**	**Objectives**	**Treatment regimen**	**Main inclusion criteria**	**Enrolled / completed**	**Sex** **Mean age (range)** **Ethnicity**
BAT1706-001-CR 1 New Zealand	Completed 15Mar2016-14Nov2016	Phase I, randomized, double-blind, single-dose, 3-arm parallel design study	PK, safety, tolerability and immunogenicity	1 mg/kg as a single 90-minute infusion: • BAT1706 • EU-Avastin • US-Avastin	Healthy adult male volunteers	128 / 122	128 Male 24.6 (18-48) years 103 W, 15 missing, 8 A, 2 NH
BAT1706-002-CR 1 China	Completed First subject enrolled: 17Aug2016 Last subject completed: 06Feb2017	Phase I randomized, double-blind, single-dose, 2 parallel group study	PK, safety, tolerability and immunogenicity	1 mg/kg as a single 90-minute infusion: • BAT1706 • EU-Avastin	Healthy adult male volunteers	82 / 79	82 Male 32.4 (18-45) years 82 A
BAT1706-003-CR 86 China, Turkey, Ukraine, South Africa, and Mexico	Completed First subject enrolled: 11Dec2017 Primary data cut [(a)]: 05Nov2019	Phase III, randomized, double blind, multicenter, active comparator, parallel 2-arm study	Efficacy, safety, immunogenicity, PK	15 mg/kg as a 60 or 90-minute infusion: • BAT1706 + C/P • EU-Avastin + C/P Dosing was every 3 weeks for up to 6 cycles of combination therapy, followed by maintenance therapy every 3 weeks with test drug up to 12 months.	Patients with previously untreated advanced nsNSCLC	651 / 218	457 Male / 194 Female 60 (26-88) years 343 W, 281 A, 24 AI-AN, 2 B, 1 NH, 1 O

A = Asian; AI-AN = American Indian or Alaska Native; B = Black or African American; C/P = carboplatin and paclitaxel; EU = European Union; NH = Native Hawaiian or other Pacific Islander; nsNSCLC = non-squamous non-small cell lung cancer; O = other; PK = pharmacokinetic(s); US = United States; W = white.

(a) Treatment ongoing at the time of the primary data cut. The data cut for the primary CSR in support of this submission = last patient enrolled evaluated at Week 18 and where there are safety and immunogenicity data for 1 year from enrollment for at least one-third of the study population enrolled.

Study BAT1706-001-CR

A total of 128 subjects were randomized: 42 subjects to the BAT1706 group, 43 subjects to the EU-Avastin group and 43 subjects to the US-Avastin group administered at a dose of 1 mg/kg as a single 90-minute infusion.

Out of the 128 randomized subjects, a total of 125 subjects received a single dose of study drug.

Demographics were similar between the 3 treatment groups. All subjects enrolled in the study were male. The mean age of study subjects was 24.6 years (range from 18 to 48 years). The majority of subjects (103 [80.5%]) were white, 7 (5.5%) subjects were Asian-other, 2 (1.6%) subjects were native Hawaiian or other Pacific Islander, and 1 (0.8%) subject was Asian-Chinese, and for 15 (11.7%) subjects the ethnicity data were missing.

Study BAT1706-002-CR

A total of 82 subjects were randomized: 41 subjects in the BAT1706 group and 41 subjects in the EU-Avastin group administered at a dose of 1 mg/kg as a single 90-minute infusion.

Out of the 82 randomized subjects, a total of 80 subjects received a single dose of study drug.

Demographics were similar between the BAT1706 and EU-Avastin groups. All subjects were male, and all subjects were of Asian extraction. Overall, the mean age was 32.4 (range: 18-45) years.

Study BAT1706-003-CR

A total of 651 patients were randomized, 325 patients in the BAT1706 group and 326 patients in the EU-Avastin group (Intent-To-Treat population); and 325 and 324 patients, respectively, received treatment (Safety population) (Table SIII.2). By the data cut-off date, a total of 431 (66.2%) patients had stopped treatment (209 [64.3%] in the BAT1706 group and 222 [68.1%] in the EU-Avastin group), and 218 (33.5%) patients were still receiving therapy (116 [35.7%] in the BAT1706 group and 102 [31.3%] in the EU-Avastin group), of whom 42 (6.5%) patients had entered the long-term extension (LTE) study (25 [7.7%] in the BAT1706 group and 17 [5.2%] in the EU-Avastin group).

The majority of patients in the BAT1706 group (201 [61.8%]) and EU-Avastin group (157 [48.2%]) completed 6 cycles of combination chemotherapy treatment (Table SIII.2).

Table SIII.2 Patient Disposition, Study BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel (Arm A)	EU-Avastin + Carboplatin + Paclitaxel (Arm B)	Total
Randomized Patients, n (%)	325 (100.0)	326 (100.0)	651 (100.0)
Received Treatment, n (%)	325 (100.0)	324 (99.4)	649 (99.7)
Treatment Ongoing, n (%)	116 (35.7)	102 (31.3)	218 (33.5)
Number of Patients who Stopped Treatment n (%)	209 (64.3)	222 (68.1)	431 (66.2)
Number of Patients who Received Combination Treatment during Study, n (%)	325 (100.0)	324 (99.4)	649 (99.7)
1 cycle	13 (4.0)	27 (8.3)	40 (6.1)
2 cycles	24 (7.4)	25 (7.7)	49 (7.5)
3 cycles	12 (3.7)	18 (5.5)	30 (4.6)
4 cycles	61 (18.8)	75 (23.0)	136 (20.9)
5 cycles	14 (4.3)	22 (6.7)	36 (5.5)
6 cycles	201 (61.8)	157 (48.2)	358 (55.0)
Number of Patients who Received Maintenance Treatment, n (%)	236 (72.6)	209 (64.1)	445 (68.4)
1-4 cycles	99 (30.5)	89 (27.3)	188 (28.9)
5-9 cycles	92 (28.3)	88 (27.0)	180 (27.6)
10-14 cycles	45 (13.8)	32 (9.8)	77 (11.8)
Number of Patients who Received BAT1706 in LTE, n (%)	25 (7.7)	17 (5.2)	42 (6.5)

Abbreviations: LTE = long-term extension.
Note: Percentage was based on randomized patients.
Source: CSR BAT1706-003-CR Table 14.1.1.1a.

Overall, the Safety population included 455 (70.1%) male patients and 194 (29.9%) female patients. The mean ± SD age of patients was 60 ± 9.3 years, and 210 (32.4%) patients were 65 years of age or older. The majority of patients were white (342 [52.7%]), followed by Asian race (280 [43.1%]), American Indian or Alaska Native (24 [3.7%]), black or African American (2 [0.3%]), Native Hawaiian or Other Pacific Islander (1 [0.2%]), and Other (1 [0.2%]) (Table SIII.3).

Table SIII.3 Patient Demographics, Safety population, Study BAT1706-003-CR

		BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325 (100%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=324 (100%)	Total N=649 (100%)
Gender, n (%)	Male	228 (70.2)	227 (70.1)	455 (70.1)
	Female	97 (29.8)	97 (29.9)	194 (29.9)
Race, n (%)	Asian	141 (43.4)	139 (42.9)	280 (43.1)
	American Indian or Alaska Native	11 (3.4)	13 (4.0)	24 (3.7)
	Black or African American	1 (0.3)	1 (0.3)	2 (0.3)
	Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (0.2)
	White	172 (52.9)	170 (52.5)	342 (52.7)
	Other	0	1 (0.3)	1 (0.2)
Age (Years)	Mean ±SD	59 ±9.7	61 ±8.8	60 ±9.3
	Median (Min, Max)	60 (27, 84)	61 (26, 88)	61 (26, 188)
Age Categories, n (%)	< 65 years	233 (71.7)	206 (63.6)	439 (67.6)
	≥ 65 years	92 (28.3)	118 (36.4)	210 (32.4)
	65 - < 75 years	79 (24.3)	105 (32.4)	184 (28.4)
	75 - < 85 years	13 (4.0)	12 (3.7)	25 (3.9)
	≥ 85 years	0	1 (0.3)	1 (0.2)

Patient 216001 had multiple races, including Asian, White.
Source: CSR BAT1706-003-CR Table 14.1.4.1.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria for the Study BAT1706-003-CR, in the indication advanced NSCLC, are discussed here.

1. Diagnosis of small cell carcinoma of the lung, mixed predominant (>50% of tumor cells) squamous cell carcinoma of the lung, or NSCLC not otherwise specified.

Reason for exclusion: Bevacizumab is indicated for non-squamous NSCLC only.

Is it considered to be included as missing information?: No.

Rationale: Other types of lung cancer fall outside of the indication.

2. Known receptor tyrosine kinase 1 (ROS-1) positive tumor or tumor positive for EGFR mutation or anaplastic lymphoma kinase (ALK) receptor alteration.

(Note, patients with a non-squamous NSCLC tumor positive for ROS-1 mutation was an exclusion criterion, whereas tumors without EGFR mutation or ALK receptor alteration was an inclusion criterion.)

Reason for exclusion: Approximately 1-2% of patients with NSCLC have ROS-1 rearrangements. Patients with ROS-1 positive lung cancer tend to have a worse prognosis than patients with ROS-1 negative cancer. Targeted therapy has been well established and approved for NSCLC with driver mutations such as EGFR, ALK, and ROS-1 (for example, a tyrosine kinase inhibitor such as erlotinib for non-squamous NSCLC patients whose tumors harbor an EGFR mutation).

Is it considered to be included as missing information?: No.

Rationale: This was to avoid confounding factors affecting efficacy and safety assessments.

3. Tumor cavitation, tumor invading into large blood vessels or close to large vessels with an increased risk of bleeding, according to Investigator's judgment.

Reason for exclusion: Bevacizumab use is associated with an increased risk of bleeding.

Is it considered to be included as missing information?: No.

Rationale: The risk of bleeding has been well characterized and is described in the SmPC.

4. Prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or vascular endothelial growth factor receptor (VEGFR), including Avastin.

Reason for exclusion: To avoid confounding factors affecting efficacy assessments.

Is it considered to be included as missing information?: No.

Rationale: This exclusion criterion was for efficacy reasons, rather than safety.

5. Prior systemic therapy for metastatic disease.

Reason for exclusion: To avoid confounding factors affecting efficacy assessments.

Is it considered to be included as missing information?: No.

Rationale: This exclusion criterion was for efficacy reasons, rather than safety.

6. Prior systemic anticancer therapy, or radiotherapy for locally advanced non-squamous NSCLC if completed < 6 months prior to screening/the diagnosis of relapsing disease.

Reason for exclusion: To avoid confounding factors affecting efficacy assessments.

Is it considered to be included as missing information?: No.

Rationale: This exclusion criterion was for efficacy reasons, rather than safety.

7. Previous malignancy other than NSCLC in the last 5 years except for basal cell cancer of the skin or pre-invasive cancer of the cervix.

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information?: No.

Rationale: This exclusion criterion was to avoid confounding factors – the safety profile is not expected to differ in these patients.

8. Known brain metastasis or other central nervous system (CNS) metastasis that was either symptomatic or untreated. Metastases that had been treated by complete resection and/or radiotherapy demonstrating stability or improvement was not an exclusion criterion provided they were stable as shown by computed tomography (CT) or magnetic resonance imaging (MRI) scan for at least 4 weeks before Screening without evidence of cerebral edema. Patients on stable dose of corticosteroids or anticonvulsants are permitted.

Reason for exclusion: Uncontrolled CNS metastases were to be avoided to reduce confounding factors affecting efficacy and safety assessments. Bevacizumab use is associated with an increased risk of intracranial hemorrhage.

Is it considered to be included as missing information?: No.

Rationale: This exclusion criterion was to avoid confounding factors affecting safety and efficacy assessments. The risk of CNS bleeding has been characterized and is adequately described in the SmPC.

9. Any unresolved toxicity > Grade 1 (except alopecia) from previous anticancer therapy (including radiotherapy).

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information?: No.

Rationale: This broad exclusion criterion was to avoid confounding factors affecting safety and efficacy assessments. The decision to treat with bevacizumab is to be made by the healthcare provider, after consideration of the patient's medical history/present medical condition and the product information for bevacizumab.

10. History of hemoptysis (> 1/2 teaspoons per event over the past 6 months) or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding. Clinically non-significant minor bleeding was acceptable.

Reason for exclusion: Bevacizumab use is associated with an increased risk of bleeding.

Is it considered to be included as missing information?: No.

Rationale: The risk of bleeding has been well characterized and is adequately described in the SmPC.

11. A significant thrombotic or hemorrhagic event ≤ 6 months prior to screening (including hemoptysis [> 2.5 mL of red blood], gastrointestinal bleeding, hematemesis, CNS hemorrhage, severe epistaxis or vaginal bleeding, cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and uncontrolled coronary artery disease).

Reason for exclusion: Bevacizumab use is associated with an increased risk of bleeding.

Is it considered to be included as missing information?: No.

Rationale: The risk of bleeding has been well characterized and is adequately described in the SmPC.

12. Current or recent (within 10 days of first dose of study drugs) use of full dose oral or parenteral anticoagulants or other thrombolytic agents for therapeutic (as opposed to prophylactic) purposes, clinically serious non-healing wounds, or incompletely healed bone fracture.

Reason for exclusion: Bevacizumab use is associated with an increased risk of bleeding.

Is it considered to be included as missing information?: No.

Rationale: The risk of bleeding has been well characterized and is adequately described in the SmPC.

13. Known hypersensitivity to any of the study drugs or their excipients, or history of clinically significant atopic allergy (e.g., asthma including childhood asthma and urticarial).

Reason for exclusion: Bevacizumab should not be given to patients with hypersensitivity to the active substance or any of its excipients or hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanized antibodies.

Is it considered to be included as missing information?: No.

Rationale: Use in patients with hypersensitivity is contraindicated in the SmPC.

14. Live/attenuated vaccine within 12 weeks prior to the Screening Visit.

Reason for exclusion: Vaccines containing live organisms may cause severe infection in immunocompromised patients, due to extensive replication of the vaccine strain.

Is it considered to be included as missing information?: No.

Rationale: Severely immunocompromised persons are routinely excluded from vaccination with live/attenuated vaccines.

15. History of myocardial infarction (≤6 months prior to Screening), unstable angina, New York Heart Association Grade II or greater, congestive heart failure, or serious cardiac arrhythmia requiring medication.

Reason for exclusion: Bevacizumab has been associated with an increased risk of cardiac complications.

Is it considered to be included as missing information?: No.

Rationale: The risk of cardiac complications, including risk factors, has been well characterized and is described in the SmPC.

16. History of poorly controlled hypertension or resting blood pressure >150/100 mmHg in the presence of a stable regimen of antihypertensive therapy.

Reason for exclusion: An increased incidence of hypertension was observed in bevacizumab-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting Avzivi treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy.

Is it considered to be included as missing information?: No

Rationale: The risk of hypertension is adequately described in the SmPC.

Monitoring of blood pressure is generally recommended during therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avzivi 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.

17. Any major surgical procedure (risk of bleeding or wound healing complications) within 28 days prior to the first dose or anticipated elective surgery during the study and until 3 months after the last dose of study drug.

Reason for exclusion: Bevacizumab may adversely affect the wound healing process and is also associated with an increased risk of bleeding. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported.

Is it considered to be included as missing information?: No.

Rationale: The SmPC adequately states that therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

18. History of active gastroduodenal ulcer, abdominal fistula as well as non-gastrointestinal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to screening.

Reason for exclusion: Due to the known risk of gastro-intestinal perforation with bevacizumab.

Is it considered to be included as missing information?: No.

Rationale: The safety profile for gastrointestinal perforation and fistula has been well characterized and presented within the SmPC. The SmPC adequately describes known risk factors, including treatment with bevacizumab, that may predispose patients to developing either gastrointestinal perforation or fistula and recommends that caution should be exercised when treating patients with any known risk factors for gastrointestinal perforation or fistula. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

19. Clinically significant active infection requiring systemic therapy.

Reason for exclusion: Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

Is it considered to be included as missing information?: No.

Rationale: The risk of infection, including risk factors, are adequately described in the SmPC. The benefit received from bevacizumab outweighs the risk of infection.

20. Active Hepatitis B infection (according to local site standards) or active Hepatitis C infection (Hepatitis C virus [HCV] antibody positive); the patient was able to be included in the study if he/she was HCV RNA negative (refer to the study protocol for details).

Reason for exclusion: Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

Is it considered to be included as missing information?: No.

Rationale: The risk of infection, including risk factors, are adequately described in the SmPC. The benefit received from bevacizumab outweighs the risk of infection.

21. Human immunodeficiency virus (HIV) infection, syphilis, or active tuberculosis infection. Screening for HIV, syphilis, and tuberculosis was performed according to local practice and local regulatory guidance.

Reason for exclusion: Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

Is it considered to be included as missing information?: No.

Rationale: The risk of infection, including risk factors, are adequately described in the SmPC. The benefit received from bevacizumab outweighs the risk of infection.

22. Patient considered unsuitable for inclusion by the Investigator (e.g., inability to understand and/or comply with study requirements or presence of any condition, which, in the opinion of the Investigator, would not allow safe participation in the study).

Reason for exclusion: This is a standard exclusion criterion to protect study subjects.

Is it considered to be included as missing information?: No.

Rationale: This is a standard exclusion criterion that is not linked to a particular safety concern. The decision to treat with bevacizumab is to be made by the healthcare provider, after consideration of the patient's medical history/present medical condition and the product information for bevacizumab.

23. Pregnant or lactating women.

Reason for exclusion: There are no clinical trial data on the use of bevacizumab in pregnant women. Studies in animals have shown reproductive toxicity including malformations. Maternal IgG is excreted in milk and bevacizumab could harm infant growth and development.

Is it considered to be included as missing information?: No.

Rationale: The SmPC states that bevacizumab is contraindicated in pregnant women. Women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of bevacizumab.

24. Poor oral hygiene that may require surgical intervention during the study or any planned dental interventions during the study until 1 month after last dose of study drug.

Reason for exclusion: Patients treated with bevacizumab have an increased risk of hemorrhage and poor wound healing.

Is it considered to be included as missing information?: No.

Rationale: The risks of hemorrhage and poor wound healing are adequately described in the SmPC.

25. Use of:

– Anti-infective drugs: within 5 days for drugs from the Western pharmacopeia, prior to the first administration of study drug. The patient was eligible provided the infection was under control.

For sites in China only:

– Anti-infective drugs: within 10 days for Chinese herbal medicines or Chinese patent medicines prior to the first administration of study drug. The patient was eligible provided the infection was under control.

– Anticancer or immune-stimulating agents from Chinese herbal medicines or Chinese patent medicines: within 10 days prior to the first administration of study drug. In case of relapsing disease, if the anticancer Chinese herbal medicines or Chinese patent medicines were given for documented new lesions diagnosed less than 6 months after prior chemotherapy for local disease, the patient was not eligible.

Reason for exclusion: Treatment with bevacizumab is associated with an increased risk of infection.

Is it considered to be included as missing information?: No.

Rationale: The risk of infection is adequately described in the SmPC.

26. Patients who required permanent oral anticoagulation (e.g., warfarin, rivaroxaban, dabigatran, acenocumarol, etc.) treatment.

Reason for exclusion: Bevacizumab is associated with an increased risk of bleeding, which may be potentiated with oral anticoagulation.

Is it considered to be included as missing information?: No.

Rationale: As stated in the SmPC caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly (NCI-CTCAE v.3).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

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

Bevacizumab is routinely administered until disease progression or unacceptable toxicity. Bevacizumab is indicated for advanced cancer and, as such, patients typically have a shortened life expectancy. Thus, clinical trial development program limitations due to prolonged exposure and long latency periods are not anticipated in this patient population.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Patients of all ethnic origins have been included in clinical trials for bevacizumab
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no evidence that bevacizumab is associated with psychostimulatory effects or dependency. The potential for bevacizumab to be misused for illegal purposes is low.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The clinical development program for Avzivi did not identified any additional risks of BAT1706 over the reference medicinal product, Avastin. As the RMP for Avastin (v.34; signed December 2020) does not include any important identified or potential risks for bevacizumab, all adverse reactions listed in the SmPC for Avzivi (see Table SVII.1) are considered to be non-important.

Table SVII.1 Adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis[a]		
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, Infusion reactions[a,b,d]		Anaphylactic shock		
Metabolism and nutrition disorders	Anorexia, Hypomagnes-aemia, Hypo-natraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalo-pathy syndrome[a,b,d]	Hypertensive encephalo-pathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorders		Congestive heart failure[b,d], Supra-ventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thrombo-embolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d], Deep vein thrombosis				Renal thrombotic microangio-pathy[a,b], Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Hypoxia, Dysphonia[a]				Pulmonary hypertension[a], Nasal septum perforation[a]
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d], Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal disorder, Proctalgia				Gastrointesti-nal ulcer[a]
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeleta l and connective tissue disorders	Arthralgia, Myalgia	Fistula[b,d], Muscular weakness, Back pain				Osteonecrosis of the jaw[a,b], Non-mandibular osteo-necrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and	Ovarian failure[b,c,d]	Pelvic pain				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
breast disorders						
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

Source: SmPC, Section 4.8, Table 1.
When events were noted as both all Grade and Grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.
[a] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting' in the Section 4.8 of the SmPC.
[b] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a substudy from NSABP C-08 with 295 patients.
[d] For additional information refer below within section "Description of selected serious adverse reactions."
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in paediatric population only.

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

The clinical development program for Avzivi has not identified any additional risks of BAT1706 over the reference medicinal product, Avastin. The RMP for Avastin (v.34; signed December 2020) does not include any safety concerns; therefore no safety concerns are included in this RMP for Avzivi.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable for an initial marketing authorization application.

SVII.3 Details of important identified risks, important potential risks, and missing information

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

There are no important identified risks or important potential risks for Avzivi.

SVII.3.2. Presentation of the missing information

There is no missing information for Avzivi.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

There are no ongoing routine pharmacovigilance activities beyond adverse reactions reporting and signal detection for Avzivi.

III.2 Additional pharmacovigilance activities

The marketing authorization holder (MAH) considers routine pharmacovigilance activities to be sufficient to obtain and analyze relevant post-marketing safety data.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

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

Part IV: Plans for post-authorisation efficacy studies

There are no post-authorization efficacy studies planned for Avzivi.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product (see Module SVII).

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for Avzivi (bevacizumab)

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

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

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

Important new concerns or changes to the current ones will be included in updates of Avzivi's RMP.

I. The medicine and what it is used for

Avzivi is authorised for Metastatic Colorectal Cancer, Metastatic Breast Cancer, Advanced, metastatic or recurrent Non-Small Cell Lung Cancer, Advanced and/or metastatic Renal Cancer, Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer, and Cervical Cancer (see the summary of product characteristics [SmPC] for the full indications). It contains bevacizumab as the active substance and it is given by the intravenous route.

Further information about the evaluation of Avzivi’s benefits can be found in Avzivi’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Avzivi, together with measures to minimise such risks and the proposed studies for learning more about Avzivi's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

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

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

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product. Since no safety concerns were identified in the summary of safety concerns, no summary of important risks is applicable.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Avzivi.

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

There are no studies required for Avzivi.