Clinical Study Protocol

Protocol Title:	**A Multicenter, Randomized, Double-blind, Phase III Study of BAT1706 versus EU-Avastin® plus Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer**
Protocol Number:	**BAT1706-003-CR**
Date of Protocol:	**Version 5.0, 20 June 2019**
Amendment Number:	**4**
Replaced Version of Protocol:	**Version 4.0, 08 February 2019**
Product:	**BAT1706 (bevacizumab)**
Study Phase:	**Phase III**
IND Number	**To be determined**
EudraCT Number	**2017-001286-25**
Sponsor:	**Bio-Thera Solutions, Ltd. Building A6-5 floor, 11 Kai-Yuan Boulevard, Science City, Guangzhou, 510530, China**
Medical Monitor:	**Yana Pautova, MD, PhD IQVIA Frunze 80–612, Novosibirsk, Russia +7 9139164867**
Leading Principal Investigator:	**Prof. Li Zhang, MD, PhD Sun Yat-sen University Cancer Center**

Sponsor Signatory:

PROTOCOL TITLE: A Multicenter, Randomized, Double-blind, Phase III Study of BAT1706 versus EU-Avastin® plus Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer

PROTOCOL NO: BAT1706-003-CR

I have read this protocol in its entirety and agree to conduct the study accordingly:

Li Zhang ----------  ---------- 21June2019 ----------

Li Zhang **Signature** **Date**

Chief Medical Officer

Synopsis

Name of Sponsor/Company:	Bio-Thera Solutions, Ltd.
Name of Finished Product:	BAT1706
Name of Active Ingredient:	Bevacizumab
Title of Study:	A Multicenter, Randomized, Double-blind, Phase III Study of BAT1706 versus EU-Avastin® plus Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer
Protocol No:	BAT1706-003-CR
Investigators:	Prof. Li Zhang, leading Principal Investigator
Study centers:	Multicenter study conducted in approximately 100 study centers

Study duration:

The duration of participation for each patient is expected to be about 12 months. There will be a 21-day Screening period, followed by the administration of study drugs over a maximum of 12 months. A Safety Follow-up Visit (SFUV)/End of Treatment (EoT) Visit will take place 28 days ±2 days after the last dose during the study with a maximum at Week 53. Patients who are still benefiting of bevacizumab after 12 months of treatment will have the option to continue treatment with BAT1706 (regardless of the arm they were assigned to at randomization) in a Long-term extension (LTE) study until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for a maximum of 12 additional months (ie, for up to 24 months from initial randomization).

The end of study is set at 24 months after the Last Patient In (LPI).

Phase:

III

Objectives:

Primary:

- To compare the efficacy of BAT1706 and European Union (EU)-Avastin® given with chemotherapy as first line treatment using the ratio or the difference in overall response rate (ORR) to show clinical equivalence.

Secondary:

- To further evaluate the efficacy of BAT1706 and EU-Avastin® given with chemotherapy using ORR at different time points, duration of response (DoR), progression-free survival (PFS) and overall survival (OS) (time, and rate at 12 months).
- To evaluate the safety and immunogenicity of BAT1706 and EU-Avastin®.
- To characterize bevacizumab exposure after administration of BAT1706 and EU-Avastin®.

Exploratory:

- To explore population pharmacokinetics (popPK).

Methodology:

This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm study to compare the efficacy, and to evaluate the safety and immunogenicity of BAT1706 to EU-Avastin® in patients with previously untreated advanced non-squamous non-small cell lung cancer (nsNSCLC) to demonstrate clinical equivalence of BAT1706 and EU-Avastin®.

After stratification for disease stage, gender and ethnicity (Asian vs non-Asian), eligible patients will be randomized in a 1:1 ratio to receive BAT1706 plus paclitaxel and carboplatin (Arm A) or EU-Avastin® plus

paclitaxel and carboplatin (Arm B). Patients will be assessed for histology and randomization will occur after central imaging review (CIR) to confirm the presence of at least one measurable target lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Combination treatment will be administered every 3 weeks up to 6 cycles, followed for those with non-progressive disease with maintenance monotherapy with BAT1706 or EU-Avastin® until a maximum of total study treatment of 12 months (17 cycles). [redacted]

A data safety monitoring board (DSMB) will review all safety data after the first 20 patients have been treated for 6 weeks in each arm; then after, if no unexpected safety signal was identified, the study will continue and the safety data will be reviewed at regular intervals after approximately every 200 patients are evaluated after they received the first 4 cycles.

Patients will undergo tumor assessment at Weeks 6, 12 and 18, regardless of the number of cycles actually completed (with a visit window of 1 week maximum during the first 18 weeks), then after every 3 cycles (approximately every 9 weeks) and at SFUV/EoT. During the trial, tumor response will be assessed by local radiologist/Investigator for immediate therapeutic decision. To comply with the different statistical approaches of each regulatory agency, the main efficacy analyses (difference and ratio of ORR) will be based upon tumor response at different time points as determined by CIR according to RECIST 1.1. After Week 18, patients with responding or stabilized disease will remain in the study until a total study treatment duration of 12 months is reached to provide further comparative safety/immunogenicity data as well as other efficacy parameters (such as DoR, PFS and OS rates at 12 months for both BAT1706 and EU-Avastin®). All patients will remain in the study until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, study termination by the Sponsor, or for a maximum of 12 months of treatment, whichever occurs first. [redacted]

Survival Follow-up will occur every 3 months until 24 months after randomization. A complete clinical study report will be submitted to the China Food and Drug Administration (CFDA), United States (US) Food and Drug Administration (FDA), and the European Medicines Agency (EMA) when primary efficacy data are available in all patients. At the end of the LTE, a complementary study report will be released. The study will be conducted according to the national and international ethical standards, the Good Clinical Practice guidelines, and the protocol will be approved by the Institutional Review Boards/Independent Ethics Committees of the participating sites.

Planned number of patients:	Approximately 632 patients will be enrolled including a subgroup of 200 patients for pharmacokinetics (PK) and population PK (popPK).
Diagnosis and main criteria for inclusion:	Patients ≥ 18 years old, with advanced nsNSCLC (either previously untreated Stage IV or recurrent disease that is no longer amenable to curative surgery or local therapy), without activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) receptor alteration, with at least one measurable target lesion according to RECIST 1.1, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and life expectancy >3 months based on Investigator's judgment.
Test product, dose schedule and mode of administration:	BAT1706 will be supplied as 100 mg/4 mL. Dose: 15 mg/kg Mode of administration: BAT1706 must be administered prior to paclitaxel/carboplatin. Initial dose for the first infusion should be delivered over 90 minutes; if well tolerated, the second and subsequent infusion may be administered over 60 minutes.

	No dose modifications are allowed. The schedule is every 3 weeks. No more than 6-week delay (between the end of prior cycle and the start of next cycle) is allowed (maximum of 9 weeks between 2 administrations).
Reference therapy, dose, and mode of administration:	EU-Avastin® will be supplied as 100 mg/4 mL. Dose: 15 mg/kg Mode of administration: Same as that of BAT1706 as specified above.
Concomitant drugs, dose, schedule and mode of administration:	Paclitaxel/carboplatin regimen: *Dose*: Paclitaxel 200 mg/m² followed by carboplatin (target area under the curve [AUC] 6 mg/mL•minute). However, for Chinese patients (according to local label), paclitaxel will be given at a dose of 175 mg/m² For all patients in case of anticipated excessive toxicity (eg, elderly patients, prior toxicity during chemo-radiotherapy), the Investigator may start the first course of chemotherapy using paclitaxel at a dose of 175 mg/m² (or use a paclitaxel dose of 200 mg/m² after prophylactic administration of granulocyte-colony stimulating factor [G-CSF]), and/or carboplatin AUC 5 mg/mL•minute. *Mode of administration*: paclitaxel is administered intravenously over 3 hours or according to local standard practice or package insert after adequate premedication before carboplatin is administered. Carboplatin is administered intravenously according to local standard practice or package insert. The schedule is every 3 weeks (21 days) for up to 6 cycles of combination therapy. The drug sequence is as follows: Only BAT1706 or EU-Avastin® are administered on Day 1 of Cycle 1, and paclitaxel and carboplatin are given on Day 2. As of Cycle 2, BAT1706 or EU-Avastin® is given first, then paclitaxel followed by carboplatin on the same day. During the combination treatment period, any chemotherapy delay mandates a BAT1706/Avastin® administration delay and vice-versa.

Criteria for evaluation:

Primary Endpoint

Efficacy:

- Overall response rate based on tumor response at Week 18 (ORR_{18}) as assessed by CIR. The response is evaluated according to RECIST 1.1 but does not need to be confirmed.

Secondary Endpoints

Efficacy:

- Progression-free survival rate at 12 months, defined as the proportion of patients being alive without documented progression 12 months after randomization using Kaplan-Meier method.
- Progression-free survival time defined as the time from the date of randomization to the date of documented clinical or radiological progression or death due to any cause using Kaplan-Meier method.
- Overall survival rate at 12 months, defined as the probability of being alive 12 months after randomization using Kaplan-Meier method.
- Overall survival time defined as the time from randomization to death of any cause using Kaplan-Meier method.
- ORR at Week 6 (ORR_6) and at Week 12 (ORR_{12}), based on tumor response as assessed by CIR, and best ORR of confirmed responses at end of study assessed by local radiologist/Investigator if after Week 18 according to RECIST 1.1.
- Duration of response defined as the time from first documentation of a response (CR or PR) and the first documentation of progression (assessed by local radiologist/Investigator if after Week 18) according to RECIST 1.1.

Safety:

- The safety profile of the study drugs as measured by the incidence and severity of adverse events, clinical laboratory assessments, vital signs, physical examination, and electrocardiogram parameters.

Pharmacokinetics:

- Bevacizumab serum exposure following treatments of BAT1706 or EU-Avastin®.

Immunogenicity:

- Serum level of anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) correlated with bevacizumab serum level.

Exploratory Endpoint

Population PK (popPK):

- Bevacizumab serum exposure following treatment with BAT1706.

Statistical methods:

To demonstrate equivalence between BAT1706 and EU-Avastin® arms, the ratio of, as well as the difference between ORR_{18} will be analyzed. Equivalence will be declared if the 90% confidence interval (CI) of the ratio of ORR_{18} (BAT1706:EU-Avastin®) is entirely contained within the equivalence margin of (0.75, 1.33) to comply with CFDA requirements, and within the equivalence margin of (0.73, 1.36) to comply with US FDA requirements. The difference in ORR_{18} will be calculated, and equivalence will be declared if the 95% CI of the difference in the ORR_{18} between treatments is entirely contained within the asymmetrical equivalence margin of (-0.12, 0.15) to comply with EMA requirements.

Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using number, mean, standard deviation, median, minimum and maximum values. Time to event endpoints will be analyzed using Cox proportional hazards models stratified

according to the randomization stratification factors. Hazard ratios for the comparison of the two treatment arms and corresponding 95% CIs will be reported.

Pharmacokinetic analyses:

The PK analysis will be performed on the PK population. The PK and popPK analysis will be explored in a subgroup of 200 patients, from samples collected only at designated sites in China, Turkey, and Ukraine.

Serum bevacizumab concentrations will be listed and summarized by treatment using appropriate descriptive statistics. Graphical presentations of concentration-time data by treatment will be provided, as appropriate. Additional popPK modeling and/or correlation between bevacizumab exposure and response (safety, immunogenicity and/or efficacy) data may be evaluated separately, as appropriate. If performed, a separate analysis plan will be prepared and results will be reported separately from the clinical study report.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-t}	Area under the concentration-time curve from 0 hour to time t
BPD	biosimilar biological product development
CFDA	China Food and Drug Administration
CI	Confidence interval
CIR	Central imaging review
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency

EoT	End of Treatment
EU	European Union
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
G-CSF	Granulocyte-colony stimulating factor
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HUVEC	Human umbilical vein endothelial cells
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
LPI	Last Patient In
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LTE	Long-Term Extension
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NADA	Neutralizing anti-drug antibody
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
nsNSCLC	Non-squamous non-small cell lung cancer
ORR	Overall response rate

ORR_6	Overall response rate at Week 6
ORR_{12}	Overall response rate at Week 12
ORR_{18}	Overall response rate at Week 18
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PP	Per-protocol
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Prothrombin time
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SFUV	Safety Follow-up Visit
SOP	Standard operating procedures
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

2.0 INTRODUCTION

2.1 Background Information

2.1.1 Overview

Cancer is associated with a high morbidity and mortality rate worldwide. The incidence and mortality of lung cancer is rapidly increasing. Chemotherapy for non-small cell lung cancer (NSCLC) is a widely used treatment modality. However, patients undergoing chemotherapy often develop chemo-resistance, leading to disease progression; this demonstrates the need for more effective treatment.

Vascular endothelial growth factor (VEGF), binds with VEGF receptors (VEGFR), to promote vascular endothelial cell proliferation, migration, lumen formation, and angiogenesis with alterations of microvascular permeability. Bevacizumab developed by Genentech is a genetically engineered humanized monoclonal antibody directed against human VEGF. The antibody selectively binds with high affinity to VEGF A and neutralizes VEGF biologic activity through a steric blockade of the binding of VEGF to its receptors on the surface of endothelial cells. Based on proven clinical efficacy bevacizumab in combination with chemotherapy has been approved for several tumor types such as colon, lung, breast and ovarian cancer.

Use in lung cancer

Lung cancer is the most common cause of cancer-related death worldwide.[1] Less than 15% of all lung cancer patients are alive 5 years after diagnosis. At the time of diagnosis, the disease is often incurable and when indicated and tolerated, various chemotherapy regimens have yield survival of 8-10 months. Recent advances in the characterization of alterations in the epidermal growth factor receptor (EGFR) and the anaplastic lymphoma kinase (ALK) gene have allowed identifying a subgroup of lung cancer patients who can benefit more of oral targeted agents such tyrosine kinase inhibitors than of chemotherapy. This type of gene alteration is present in about 15-20% of non-Asian patients and up to 40% in Asian patients. Today, patients with no known mutations or with a mutation but no access to the targeted agent are offered a platinum based chemotherapy.[2,3] Patients with nonsquamous histology, and no risk of major bleeding, are offered the addition of bevacizumab, which prolongs survival to about 12-13 months and is considered standard of care. In October 2006, the United States (US) Food and Drug Administration (FDA) approved the use of chemotherapy protocols combining bevacizumab with paclitaxel and carboplatin as a first-line treatment for late-stage NSCLC. In 2015, the China FDA (CFDA) approved the use of bevacizumab with paclitaxel and carboplatin as a

first-line treatment for late-stage NSCLC. Bevacizumab has now been granted approval in over 120 countries and regions worldwide, including Europe and North America.[4,5]

Based on the results of Sandler's study[6] showing that the addition of bevacizumab significantly increased overall response rate (ORR), progression-free survival (PFS) and overall survival (OS), the Eastern Cooperative Oncology Group (ECOG; refer to Appendix 13.3) recommends bevacizumab in combination with paclitaxel and carboplatin for treatment of selected patients with advanced non-squamous NSCLC (nsNSCLC). Sandler's regimen is proposed for this study aimed at demonstrating the biosimilarity between BAT1706 and Avastin®. The optimal number of cycles of chemotherapy combined with bevacizumab is of 4 cycles but up to 6 cycles have been commonly administered. In studies comparing 4 or 6 cycles of chemotherapy, no survival benefit was shown with the administration of more than 4 cycles, and most responses are observed after 4 cycles.[7] The American Society of Clinical Oncology panel of experts recommends not to administer more than 4 cycles in non-responding patients who are then given maintenance monotherapy with bevacizumab until progression or intolerance.[8]

2.1.2 Summary of Nonclinical Findings

Bio-Thera has completed a suite of nonclinical studies using BAT1706. BAT1706 has been compared against US-Avastin® and European Union (EU)-Avastin® in a comprehensive comparative analytical and nonclinical study program, which provides evidence of the structural and functional similarity of BAT1706 to Avastin® as summarized in the Investigator's Brochure (IB).[9]

The results of comparative in vitro pharmacodynamic research showed that BAT1706 and Avastin® both exhibited specific binding with VEGF-A_{121} and VEGF-A_{165}, which was consistent with literature reports. The biological activity of BAT1706 was measured using human umbilical vein endothelial cells (HUVEC) proliferation inhibition testing. The results demonstrated that BAT1706 exhibited a similar dose-dependent relationship with the growth of HUVEC to Avastin®, with both agents exhibiting potent neutralizing efficacy against VEGF. The biological activity of BAT1706 was found to be comparable to that of Avastin® within the predetermined range of $(1.0 \pm 0.2) \times 10^{4}$ U/mg.

The antitumor effect of BAT1706 and Avastin® in several models of human cancer (NSCLC, ovarian cancer, and rhabdomyosarcoma) was also investigated. These results showed that treatment with BAT1706 and Avastin® at high doses (5 mg/kg in NSCLC and rhabdomyosarcoma and 10 mg/kg in ovarian cancer) was effective in all 3 tumor models, and none were effective at lower doses (0.5 mg/kg in NSCLC and rhabdomyosarcoma and 1 mg/kg in ovarian cancer). Except for the 0.5 mg/kg dose in the rhabdomyosarcoma model, the pharmacodynamic effects of BAT1706 and Avastin® were similar, and the tumor growth

curves showed a high degree of coincidence. Results from the 2 repeated tests were also consistent.

The results of a pharmacokinetic (PK) study suggested equivalence in in-vivo metabolism of BAT1706 and Avastin®. The concentration of the drug in blood plasma revealed extremely slow elimination, consistent with literature reports. Toxicokinetic parameters showed no significant gender-based difference in the drug exposure; the plasma drug concentration, mean area under the plasma concentration-time curve from 0 hours to time t (AUC_{0-t}), and maximum concentration (C_{max}) were dose-related. The values of AUC_{0-t}, elimination half-life, clearance, and C_{max} for the same dose (4 mg/kg) of BAT1706 and Avastin® were not notably different.

Results of the nonclinical toxicology studies demonstrated that BAT1706 has good local tolerance for intravenous (IV) administration, and no impact on the central nervous system (CNS), cardiovascular or respiratory systems, and no specific binding to non-target tissues in the body and no increase in immunogenicity or immunotoxicity when compared with Avastin®. A study conducted to observe the irritant effects of BAT1706 on the administration site as well as the surrounding tissues did not reveal any irritation reactions at the vascular injection site during or after drug administration.[9]

2.1.3 Summary of Clinical Findings

[redacted]

2.2 Rationale

To date, more than a million patients globally have undergone treatment with bevacizumab, the world's first anti-VEGF antibody that has been proven to extend the OS and PFS in multiple types of cancer. In the US, China, and Europe, bevacizumab's patent protection will be expired in July 2019, January 2020, and July 2019, respectively.

Bio-Thera has developed a recombinant humanized anti-VEGF monoclonal antibody injection, BAT1706, which is a proposed biosimilar of Avastin® to meet the need for alternatives to

high-priced biologic agents. The proposed clinical development is in accordance with published guidelines from regulatory authorities for the development of biosimilar monoclonal antibodies. The similarity between the biosimilar and the originator compound, will first be demonstrated in a Phase I PK study in healthy volunteers. After sufficient evidence is available to show PK similarity, and provided no safety signal was reported, the Phase III study can be launched to compare the clinical efficacy and demonstrate similarity for safety and immunogenicity in a homogenous population of lung cancer patients.

In this pivotal Phase III clinical study, patients with nsNSCLC will be randomly assigned to receive either BAT1706 or EU-Avastin®, plus a selected chemotherapy regimen according to standard of care (see Section 4.1).

Since targeted agents have become standard of care for patients with tumors expressing activating mutations in EGFR or alterations in ALK receptor, these patients will not be enrolled if the corresponding tyrosine kinase inhibitor is available. Patients with unknown mutation status or with activating mutation in EGFR or ALK receptor alteration may be included only provided chemotherapy is the study center standard of care and the patient has signed the informed consent form stating the superiority of targeted therapy. This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements. The protocol will be approved by the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the participating sites.

2.3 Hypothesis

The null hypothesis is that either (1) BAT1706 is inferior to EU-Avastin® or (2) BAT1706 is superior to EU-Avastin® based on a pre-specified equivalence margin.

To satisfy the different methods used by the regulatory agencies, different endpoints and methods of calculations will be used in this global study.

To satisfy the CFDA and US FDA statistical approaches, the null hypothesis will be rejected if the 90% confidence interval (CI) for the ratio of ORR_{18} (BAT1706: EU-Avastin®) falls completely within the predefined equivalence margin of (0.75, 1.33) to comply with CFDA requirements and within the predefined equivalence margin of (0.73, 1.36) to comply with FDA requirements. To satisfy the European Medicines Agency (EMA) statistical approach, the null hypothesis will be rejected if the 95% CI of the difference in the ORR_{18} between treatments (BAT1706 and EU-Avastin®) is entirely contained within the predefined equivalence margin of (-0.12, 0.15).

The alternative hypothesis is that BAT1706 is equivalent to EU-Avastin®, which can be demonstrated by showing that the true treatment ratio/difference is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. The equivalence margins have been calculated based on a meta-analysis including the 5 randomized studies[6,10-13] demonstrating the benefit of the addition of bevacizumab over chemotherapy alone in the same population as that enrolled in this study.

2.4 Risk Assessment

Patient risk is considered equivalent as that when receiving Avastin® as described in package insert in the US[5] and in the summary of product characteristics in the EU.[4] Conservative eligibility criteria, regular and long-term safety monitoring, including immunogenicity testing will ensure that no abnormal safety signal is observed. The potential for drug-induced liver injury requires constant surveillance. To ensure patients' safety, clinical evaluation and follow-up of selected liver laboratory parameters are implemented. The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study. The Sponsor will also notify the Principal Investigator of any new information that could potentially impact patient safety or management during the study.

Gastrointestinal Perforation and Fistulae

Patients treated with Avastin® have an increased risk of gastrointestinal perforation. The incidence of gastrointestinal perforation ranges from 0.3% to 3.2% across clinical studies.[9] The majority of cases occurred within the first 50 days of initiation of Avastin®. The Investigator is required to monitor the patients at regular intervals throughout the study for any new or worsening symptoms or signs that may be suggestive of gastrointestinal perforation.

Surgery and Wound Healing

Serious and sometimes fatal fistula formation may occur within the first 6 months of Avastin® therapy. An increased risk of wound healing complications has been observed in patients who underwent surgery during the course of Avastin®. Bevacizumab must be discontinued in patients with wound dehiscence. Bevacizumab must be discontinued at least 28 days prior to elective surgery and cannot be initiated for at least 28 days after surgery and until the surgical wound is fully healed. Restrictions for surgery are detailed in the exclusion criteria.

Hemorrhage

Treatment with Avastin® is associated with an increased risk of hemorrhage (including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal

bleeding) and arterial thromboembolic events (including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina). Patients with prior episodes of hemoptysis, thrombotic or hemorrhagic event within 6 months prior to Screening are not eligible. No anticoagulation therapy is allowed within 10 days of the first dose of study drug or during the study except for venous access or daily aspirin up to 325 mg. Avastin® must be discontinued in patients with clinically significant hemorrhage.

Arterial and Venous Thromboembolic Events

The incidence is < 5% and depends on the associated chemotherapy, a history of arterial thromboembolism, diabetes, or age greater than 65 years. Avastin® must be discontinued in patients presenting a severe event, or in case of pulmonary embolism.

Posterior Reversible Encephalopathy

The use of Avastin® has been shown to be associated with an increased risk of Posterior Reversible Encephalopathy Syndrome (PRES). The incidence is < 0.5%. The Investigator is required to monitor the patients at regular intervals throughout the study for any new or worsening neurological symptoms or signs that may be suggestive of PRES (typical symptoms are diverse and include headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances). If a patient develops new or worsening neurological signs or symptoms, he/she will be evaluated for PRES. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES. Any patient who is suspected of developing PRES will be discontinued from the study and the adverse event (AE) will be followed closely (see Section 6.2.1.1). Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae.

Hypertension

The incidence of severe hypertension in patients receiving Avastin® is 5-18%. Patients with systolic/diastolic blood pressure > 150/100 mmHg (in the presence or absence of a stable regimen of antihypertensive therapy) are excluded from this study. Blood pressure will be monitored every 3 weeks during the study. Patients who develop hypertension should be treated with appropriate antihypertensive therapy at the Investigator's discretion and should continue to have their blood pressure regularly monitored. If the hypertension remains uncontrolled, the patient is withdrawn from study.

Proteinuria

The incidence and severity of proteinuria is increased in patients receiving Avastin® as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin®.

Suspend Avastin® administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 grams/24 hours. Discontinue Avastin® in patients with nephrotic syndrome.

Infusion reaction

Infusion reactions with the first dose of Avastin® are uncommon (< 3%) and severe reactions occurred in 0.2% of patients. Refer to Section 5.6.1 for premedication and management.

Due consideration has been given to previous experience with Avastin® in NSCLC patients and toxicity management guidance (eg, for hypersensitivity reactions) is provided in this protocol. Females of reproductive potential must be informed of the potential of the risk of ovarian failure prior to starting treatment with Avastin®. [redacted] For details of blinding, please refer to Section 5.7.

Based on extensive preclinical, analytical, functional and toxicological testing carried out prior to initiation of this study, and the Phase I data described above, BAT1706, as a proposed biosimilar product, may be seen to provide similar efficacy, safety, immunogenicity and PK to EU-Avastin® in patients with advanced nsNSCLC. For more preclinical information please refer to the most current IB[9] and to Avastin® label for full prescribing information, and extensive information on AEs incidence and management.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to compare the efficacy of BAT1706 and EU-Avastin® given with chemotherapy as first line treatment using the ratio or the difference in ORR to show clinical equivalence.

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To further evaluate the efficacy of BAT1706 and EU-Avastin® given with chemotherapy using ORR at different time points, duration of response (DoR), PFS, and OS (time and rate) at 12 months.
- To evaluate the safety and immunogenicity of BAT1706 and EU-Avastin®.
- To characterize bevacizumab exposure after administration of BAT1706 and EU-Avastin®.

3.3 Exploratory Objective

- To explore population pharmacokinetics (popPK).

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm study to compare BAT1706 plus paclitaxel and carboplatin (Arm A) versus EU-Avastin® plus paclitaxel and carboplatin (Arm B). To start the screening procedures and to be enrolled, all patients will sign the informed consent form (ICF) and have their target lesion confirmed measurable by independent central imaging review (CIR) performed by the imaging vendor. After stratification for disease stage, gender, and ethnicity (Asian vs non-Asian), eligible patients with previously untreated metastatic, or recurrent nsNSCLC, will be randomized in a 1:1 ratio to Arm A or Arm B.

After up to 6 cycles of combination therapy are given, all patients with complete response (CR), partial response (PR) or stable disease (SD) will receive maintenance monotherapy with BAT1706 or EU-Avastin® until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, study termination by the Sponsor, or for a maximum of 12 months (17 cycles) of treatment, whichever occurs first. [redacted]

A DSMB will review all safety data after the first 20 patients have been treated for 6 weeks in each arm; then after, if no unexpected safety signal was identified, the study will continue and the safety data will be reviewed at regular intervals after approximately every 200 patients are evaluated after they received the first 4 cycles (see Section 6.2.4).

During the conduct of the study, tumor response will be assessed by the local Investigator and/or radiologist according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; see Appendix 13.4) for immediate therapeutic decision. However, the primary efficacy analysis will be based upon the evaluation of tumor response as determined by CIR.

Patients will undergo tumor assessment at Weeks 6, 12 and 18, regardless of the number of cycles actually completed, then after every 3 cycles (approximately every 9 weeks) and at Safety Follow-up Visit (SFUV)/End of Treatment (EoT). Window for tumor assessment is 1 week at the maximum during the first 18 weeks. The main efficacy analyses (difference and ratio of ORR) will be based upon tumor response at Week 18 (ORR_{18}) as determined by CIR according to RECIST 1.1. Response at Week 6 and at Week 12 will also be evaluated by CIR to provide ORR_6 and ORR_{12} to show the pattern of response. After Week 18, patients with responding or stabilized disease will remain in the study up to 12 months to provide further

comparative safety/immunogenicity data as well as other efficacy parameters (such as DoR, PFS and OS rates at 12 months for both BAT1706 and EU-Avastin®).

A SFUV/EoT visit will take place 28 days ±2 days after the last dose during the study with a maximum at Week 53. Patients who are still benefiting of therapy after 12 months of treatment will have the option to continue treatment with BAT1706 as of Week 53 after SFUV (regardless of the arm they were assigned to at randomization) in a Long-term extension (LTE) study until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for an additional 12-month period (ie, for a maximum of 24 months from initial randomization).

The study will be conducted according to the national and international ethical standards, and the protocol will be approved by the IRBs/IECs of the participating sites.

Planned number of patients

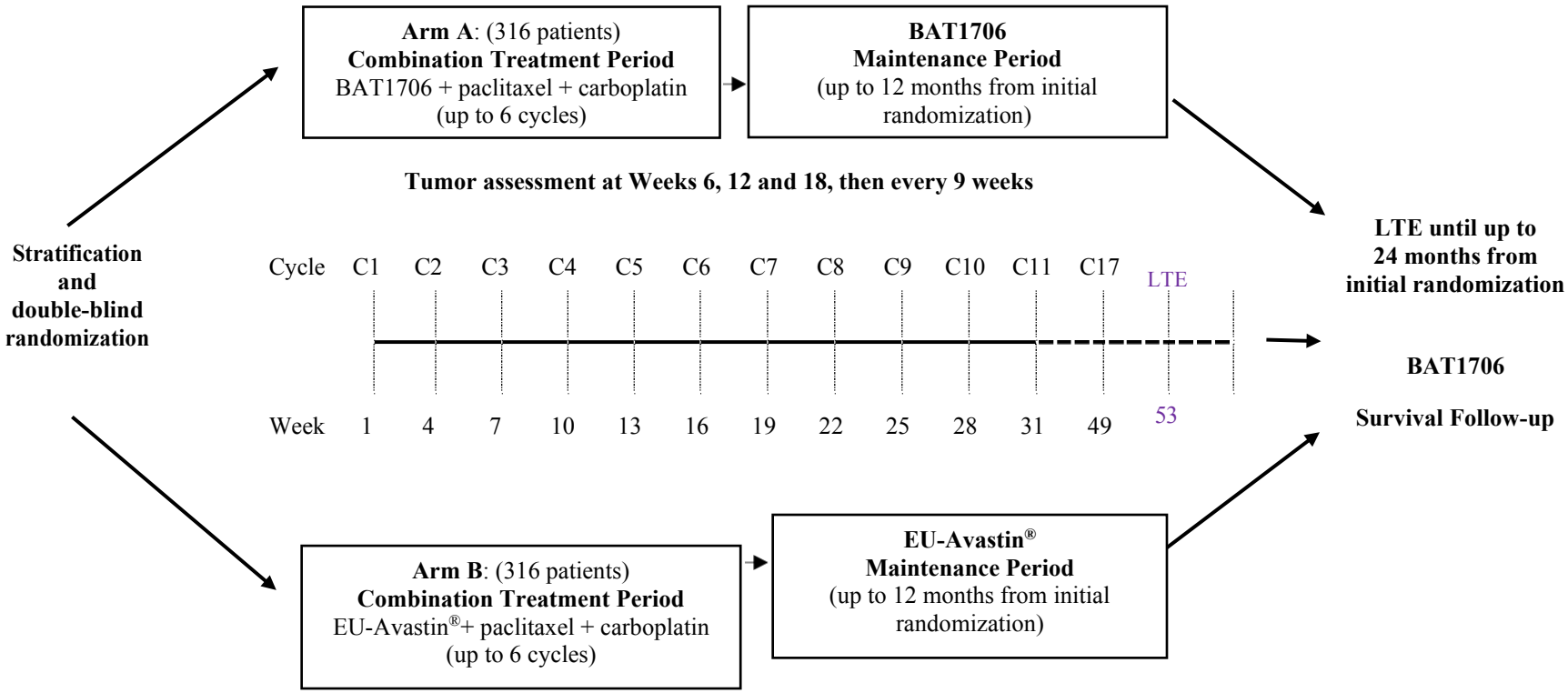
Approximately 632 patients will be enrolled including a subgroup of 200 patients for PK and popPK (from samples collected only at designated sites in China, Turkey, and Ukraine).

Study duration

After the patient has signed the ICF, there will be a 21-day Screening period to confirm eligibility. All patients will be treated in the study until progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for a maximum total duration of 12 months (up to 17 cycles), whichever occurs first. [redacted]

A schematic of the study design is presented in Figure 1. The Schedule of Events is presented in Table 1. The schedule of PK, anti-drug antibody (ADA), and neutralizing anti-drug antibody (NADA) blood sampling is presented in Table 2.

Figure 1 Schematic of the Study Design



Combination treatment period up to Week 18 (maximum 6 cycles), and maintenance period for a maximum of 12 months from initial randomization (up to a total of 17 cycles); then maintenance with BAT1706 in the LTE study up to 24 months from initial randomization.

Note: To be eligible, patients must meet all I/E criteria. Patients must have at least one measurable lesion per CIR according to RECIST 1.1. and no known EGFR mutation/ALK receptor alteration. If positive or unknown EGFR mutation/ALK receptor alteration, chemotherapy must be standard first line therapy in the institution.

Abbreviations: ALK = anaplastic lymphoma kinase; CIR = central imaging review; EGFR = epidermal growth factor receptor; EU = European Union; I/E = inclusion/exclusion; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; LTE = long-term extension.

Table 1 Schedule of Events

Assessments	**Screening**	**Treatment Period[a]**						**Maintenance Period[a]**	**SFUV[s]/ EoT Visit[b]**	**LTE Study[c] EoT Visit[b]**
Cycle	**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 17**	**28 days from last dose or Week 53 at the latest**	**Cycle 18 onward**
Week	**-3 to -1**	**1-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19 to 49**		**Week 53 up to 104**
Day	**-21 to -1**	**1-21**	**22-42**	**43-63**	**64-84**	**85-105**	**106-126**	**127 to 343**		
Written informed consent	X									
Eligibility assessment including central imaging review	X	X								
EGFR mutation and ALK receptor alteration status	X									
Demographics[d]	X									
Relevant medical/surgical history[e]	X									
LABORATORY/SAFETY ASSESSMENTS[f]										
Infection Screen[g]	X									
Hematology[h]	X	Day 1 and 8	Day 1 and 8	Day 1 and 8	Day 1 and 8	Day 1 and 8	Day 1 and 8	Day 1	X	Day 1
Chemistry, coagulation, and urine test [h]	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[i]	X								X	
Urine Pregnancy Test[j]				X		X		Day 1 Q6W		Day 1 Q6W
Vital Signs[k]	X	Day 1 and 8	X	X	X	X	X	Day 1	X	Day 1
Physical Examination[l]	X	Day 1 and 8	X	X	X	X	X	Day 1	X	Day 1
12-Lead ECG[m]	X	X	X	X	X	X	X		X	
AE/AESI and SAE Review[n]	X	Continuous assessment								
Previous/concomitant medications[o]	X	Continuous assessment								

Assessments	Screening	Treatment Period[a]						Maintenance Period[a]	SFUV[s]/ EoT Visit[b]	LTE Study[c] EoT Visit[b]
Cycle	**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 17**	**28 days from last dose or Week 53 at the latest**	**Cycle 18 onward**
Week	**-3 to -1**	**1-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19 to 49**		**Week 53 up to 104**
Day	**-21 to -1**	**1-21**	**22-42**	**43-63**	**64-84**	**85-105**	**106-126**	**127 to 343**		
DISEASE ASSESSMENTS										
Tumor Assessment (RECIST 1.1)[p]	X	Weeks 6, 12, 18						Weeks 27, 36, 45	X[q]	X[r]
ECOG performance status	X			X		X		Day 1 Q6W	X	
Survival[s]										Every 3 months
OTHER ASSESSMENTS										
Serum PK sampling[t]		X						Day 1 Q9W	(X)	
ADA/NADA[u] before therapy		X						Day 1 Q9W	(X)	(X)
STUDY TREATMENT										
Randomization[v]		X								
BAT1706 or EU-Avastin®[w]		X	X	X	X	X	X	Day 1		Day 1 (BAT1706 only)
Carboplatin/Paclitaxel after premedication and after BAT1706 or EU-Avastin®		X[x]	X	X	X[y]	(X[y])	(X[y])			

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; ALK = anaplastic lymphoma kinase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CIR = central imaging review; CT = computed tomography; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EGFR = epidermal growth factor receptor; EoT = End of Treatment; EU = European Union; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous(ly); LTE = long-term extension; MRI = magnetic resonance imaging; NADA = neutralizing anti-drug antibody; PET = positron emission tomography; PK = pharmacokinetic(s); popPK = population pharmacokinetics; PT = prothrombin time; Q6W = every 6 weeks; Q9W = every 9 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SFUV = Safety Follow-up Visit.

[a] Day 1 of each cycle should be planned on Day 22 ***after the previous cycle*** was given (ie, an interval of 21 days) with a maximum window of -1 up to +3 days. During the combination treatment period, efforts should be made to conduct study visits on the day scheduled with a maximum time window of -1 up to + 3 days for Day 1 of each cycle (except Cycle 1), and for Day 8 of each cycle. During the maintenance period, visits should occur as scheduled with a maximum window of -1 up to + 3 days for Day 1 of each cycle. Please refer Table 2 for time window for PK samplings.

[b] All patients who received at least one infusion of BAT1706 or EU-Avastin® will attend the SFUV/EoT visit while on main study 28 days ±2 days after last dose. For patients continuing in the LTE study after one-year therapy, an SFUV will be conducted at Week 53 before they start therapy in the LTE study. During the LTE study, the EoT Visit will take place 28 days ±2 days after last dose is administered and at the latest at Week 104.

[c] Patients who are still benefiting of therapy after 12 months of treatment will be transferred to a LTE study to receive BAT1706 treatment up to a total of 24 months as of randomization in initial study. The visit window for LTE visits is -1 to +7 days. All tests are to be performed as indicated until the patient starts another anticancer therapy.

[d] Demographics will include the collection of date of birth, gender, and ethnicity.

[e] Medical history will include lung cancer history and other past and current medical disease with clinical significance. Prior anticancer treatments, including adjuvant chemo and/or radiotherapy, should also be recorded in the eCRF.

[f] All clinical laboratory tests (hematology [complete blood cell count (CBC) including hemoglobin, hematocrit, platelets, lymphocytes, neutrophils with differential]; serum chemistry [creatinine, AST, ALT, ALP, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, glucose, total cholesterol, total protein, albumin, sodium, potassium, chloride, calcium], coagulation [INR and aPTT or PT], and urinalysis [protein, glucose, and blood]) will be performed at the local laboratory. Laboratory samples must be drawn prior to infusion of premedication and study treatment. In case therapeutic doses of anti-coagulants are started during the treatment period, coagulation tests will be repeated no more than 3 days prior to each cycle. Urine dipstick will be assessed 7 days prior to randomization and then every 6 weeks during the treatment period. In case proteinuria is observed, 24-hour urine test should be performed.

Written informed consent must be required for performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used for screening assessments rather than repeating such tests.

[g] Infection screen will include serum virology of Hepatitis B and C, HIV, syphilis and tuberculosis to be performed according to local practice and local regulatory guidance. Infection screen within -21 days of patient consent of screening is acceptable.

[h] At Screening, a first set of laboratory tests will take place as soon as a patient starts the screening procedures. In case CBC was done > 7 days prior to Day 1 of Cycle 1, CBC will be repeated to confirm eligibility. For subsequent cycles, all laboratory tests must be performed within a maximum of 3 days prior to Day 1 of each cycle (i.e., before BAT1706 or EU-Avastin® administration). The results must be available before each study drug infusion. Hematology test will be repeated on Day 8 of each cycle during combination therapy.

[i] For female of child-bearing potential, serum pregnancy test will be performed within 7 days prior to first dose at Screening, during the treatment period in case of positive urine test, and at EoT Visit. In case of suspected pregnancy, a serum pregnancy test must be performed.

[j] For female of child-bearing potential, urine pregnancy test will be performed every 6 weeks. Serum pregnancy test will be performed if a urine pregnancytest is positive.

[k] Assessments will include blood pressure (5 minutes rest before start of measurement), pulse rate, and body temperature.

[l] A comprehensive physical examination (including general appearance, abdomen, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, skin, thyroid/neck, lymph nodes, and neurological/psychiatric) will be performed at Screening and at the visits indicated. Height will be measured at screening only. Weight will be measured at Screening and then every cycle for body surface area adjustment of dose, if change is ≥10%.

[m] A computerized 12-lead ECG will be performed with the patient in a supine position after the patient has rested comfortably for at least 5 minutes (if paper format a copy must be available). Additional ECG will be performed if clinically indicated.

[n] For AEs, patients will be evaluated from the time of signing informed consent through 28 days after the last study treatment or up to Week 53 after randomization. However, SAEs assessed as related to study treatment or study procedures will be collected through the last day of study participation and followed until the events are resolved, return to baseline, stabilize, or the patient is lost to follow-up, whichever occurs first. During the LTE study, only AEs of special interest and SAE until 28 days after the subject's last dose will be collected (see Section 6.2.1.2) up to Week 104 after randomization.

[o] Concomitant medications will be recorded from the time of signing informed consent through 28 days after last study treatment.

[p] Tumor assessment for confirmation of the presence of a measurable target lesion must be performed at baseline by CIR before the patient can be randomized. Tumor assessment includes CT or MRI of at least the chest and abdomen (including the adrenals and the liver using the same method throughout the whole study). Brain CT or MRI scan, and bone scans or X-rays should be performed at Screening if clinically indicated and during the treatment period as clinically indicated. If the bone scan is positive at screening, it will be repeated at no less than 12-week intervals. Plain X-ray can be used at time of intercurrent regular tumor assessments as clinically indicated. PET scans are not accepted as sole method for assessment of efficacy but can be used to identify new lesions if a baseline PET scan was done. Tumor assessments will occur at Weeks 6, 12 and 18, regardless of the number of cycles actually received (with a visit window of 1 week maximum during the first 18 weeks), then after every 3 cycles (approximately every 9 weeks [assessed within Days 15-21 after the third cycle treatment is given]). The results must be available for treatment decision before the planned next cycle. If a patient is unable to undergo a contrast CT due to allergy or renal insufficiency during follow-up, a chest CT without contrast, combined with MRI images of the target lesions with gadolinium contrast, is preferred if tolerated by the patient.

Patients who discontinued study drug without disease progression will continue to undergo tumor assessments until disease progression.

Tumor imaging (CT or MRI scan) within 28 days before randomization is acceptable if the CT or MRI scan was performed with an imaging format that meets the CIR requirements. Bone scan within 3 months before randomization is acceptable if the bone scan was performed with an imaging format that meets the CIR requirements. If the patient has bone lesions identified by bone scan within 3 months before randomization he/she will have plain X-ray of bone lesions during the 21-day screening period. X-ray will be repeated at each tumor assessment (Weeks 6, 12, 18, etc.) and bone scan will be repeated at no less than 12-week intervals.

[q] Tumor assessment at the SFUV/EoT Visit is only necessary if more than 4 weeks have passed since the previous assessment.

[r] During LTE study period, tumor assessment will be performed at Investigator's discretion until disease progression, withdrawal of consent, Investigator's decision or up to 24 months after randomization, whichever occurs first.

[s] After SFUV/EoT visit, survival will be monitored via telephone call every 3 months up to 24 months after randomization.

[t] The PK and popPK analysis will be explored in a subgroup of 200 patients. Please refer to Table 2 for more details on the time points of PK blood samples.

[u] Please refer to Table 2 for the details on the time points of ADA/NADA blood samples.

[v] Patients will be randomized within 3 days before Day 1 of Cycle 1 (baseline).

[w] BAT1706/EU-Avastin® will be administered on Day 1 of each cycle (every 21 days) prior to administration of paclitaxel and carboplatin.

[x] The drug sequence is as follows: Only BAT1706 or EU-Avastin® are administered on Day 1 of Cycle 1, and paclitaxel and carboplatin are given on Day 2. As of Cycle 2, BAT1706 or EU-Avastin® is given first, then paclitaxel followed by carboplatin on the same day.

[y] Patients intolerant to chemotherapy after 2 dose reductions can start monotherapy with BAT1706 or EU-Avastin® or start another line of anti-cancer therapy after investigator's judgment.

Table 2 Pharmacokinetic[e], Anti-drug Antibody[f], and Neutralizing Anti-drug Antibody[f] Sampling Time Points

Date		**Allowed window period**	**Event**	**PK Sampling** (4 mL per sample)	**ADA/NADA Sampling** (6 mL per sample)
Cycle 1	Day 1	Up to -7 days	prior to infusion[a]	X	X
		+15 minutes	end of infusion[c]	X	
	Day 4	±1 day	at the time equivalent to the prior infusion approximate start time on Day 1[b]	X	
	Day 8	±1 day	at the time of blood sampling for laboratory tests	X	
	Day 15	±1 day	at the time equivalent to the prior infusion approximate start time on Day 1[b]	X	X
Cycle 2	Day 1	Up to -3 days	Prior to the start of the Cycle 2 infusion, at the time of blood sampling for laboratory tests	X	
Cycle 3	Day 1	Up to -3 days	Prior to the start of the Cycle 3 infusion, at the time of blood sampling for laboratory tests	X	X
Cycle 4	Day 1	Up to -3 days	Prior to the start of the Cycle 4 infusion, at the time of blood sampling for laboratory tests	X	
Cycle 5	Day 1	Up to -3 days	Prior to the start of the Cycle 5 infusion, at the time of blood sampling for laboratory tests	X	X
Cycle 6	Day 1	Up to -3 days	Prior to the start of the Cycle 6 infusion, at the time of blood sampling for laboratory tests	X	
		+15 minutes	end of infusion[c]	X	
	Day 4	±1 day	at the time equivalent to the prior infusion approximate start time on Day 1[b]	X	
	Day 8	±1 day	at the time equivalent to the prior infusion approximate start time on Day 1[b]	X	
	Day 15	±1 day	at the time equivalent to the prior infusion approximate start time on Day 1[b]	X	
Cycle 7	Day 1	Up to -3 days	Prior to the start of the Cycle 7 infusion, at the time of blood sampling for laboratory tests	X	X
After Cycle 7	Day 1	Up to -3 days	Prior to the start of the cycle infusion, at the time of blood sampling for laboratory tests	Every 9 weeks up to Week 53	Every 9 weeks up to Week 53
SFUV/EoT Visit	28 days from last dose	±2 days	at the time of blood sampling for laboratory tests	X[d]	X[d]

Abbreviations: ADA = anti-drug antibody; NADA = neutralizing anti-drug antibody; PK = pharmacokinetic(s); EoT = End of Treatment; SFUV = Safety Follow-up Visit.

a. Blood samplings at Day 1 of Cycle 1 before infusion can be made within 7 days prior to dosing at time of laboratory tests.
b. Efforts should be made to collect blood samples approximately at the same time as the time of prior infusion on Day 1 at Cycle 1 and on Day 1 at Cycle 6.
c. Blood sampling should be taken from the opposite arm of that used for the infusion.
d. In case a patient is tested positive for ADA/NADA at the EoT visit or at SFUV 12 months after the first dose, whichever comes first, ADA/NADA blood samples should continue to be collected every 9 weeks until 2 tests are negative (no later than 24 months after randomization). In case the first positive ADA/NADA result is found at the SFUV/EoT Visit, one PK sampling will be collected.
e. Blood samples will be collected only at designated sites in China, Turkey, and Ukraine.
f. Blood samplings for ADA/NADA will be collected in all patients.

4.2 Discussion of Study Design

This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm study to compare the efficacy, and to evaluate the safety and immunogenicity of BAT1706 to EU-Avastin® in patients with previously untreated advanced nsNSCLC to demonstrate clinical equivalence of BAT1706 with EU-Avastin®. The design of the study complies with US FDA, CFDA, and EMA guidelines for the demonstration of clinical equivalence of biologic products.

Eligible patients will be randomized in a 1:1 ratio to receive BAT1706 plus paclitaxel and carboplatin or EU-Avastin® plus paclitaxel and carboplatin. To ensure a high degree of compliance to eligibility criteria, a CIR is made before randomization to confirm the target lesion is measurable according to RECIST 1.1.

Paclitaxel + carboplatin + Avastin® is one of the standard first-line chemotherapy regimens for advanced nsNSCLC patients without known EGFR mutation or ALK receptor alteration. The sample size was calculated based on equivalence margins derived from reference studies as discussed in Section 9.1. Randomized patients will be assigned to receive either BAT1706 or EU-Avastin® throughout the study. No crossover is allowed. The randomization is used to ensure that the outcome is not affected by known and unknown differences in prognostic factors between treatment arms. Patients will remain in the study for a maximum duration of 12 months after which, patients who still tolerate and benefit of the treatment will have the option to continue treatment with BAT1706 as of Week 53 after SFUV (regardless of the arm they were assigned to at randomization) in a LTE open label study until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for a maximum of 12 additional months (ie, for up to 24 months from initial randomization).

The double-blind will be maintained throughout the study to avoid bias in the assessment of the primary endpoint of tumor measurement and minimize any other bias that could be introduced by knowledge of the treatment by either the Investigator or the patient. The blind can be broken any time for emergency safety reasons only.

4.3 Selection of Study Population

The ICF must be signed before starting any screening procedure. The measurability of the target lesion must be confirmed by the independent CIR before randomization can occur.

4.3.1 Inclusion Criteria

Patients will be randomized only if they meet all of the following criteria:

1. Age ≥ 18 years.

2. Stage IV nsNSCLC or recurrent disease (any stage at initial diagnosis) no longer amenable to curative surgery or local therapy (histologically or cytologically confirmed).

3. No prior systemic therapy for metastatic disease. Prior systemic therapy and/or radiotherapy for locally advanced disease is permitted if completed ≥ 6 months prior to the diagnosis of relapsing disease.

4. Tumors without EGFR mutation or ALK receptor alteration. Patients with unknown mutation status or known EGFR mutation or ALK receptor alteration may be included provided the corresponding targeted agent is not available and chemotherapy is the standard of care of the study center.

5. At least one measurable target lesion according to RECIST 1.1 (Appendix 13.4) as confirmed by CIR; bone-only and brain-only metastases are not allowed. Lesions previously treated with radiotherapy are non-target lesions unless clear progression was documented.

6. Eastern Cooperative Oncology Group performance status of 0 or 1 and life expectancy > 3 months based on Investigator's judgment.

7. Adequate hematological function, defined as:

   - Platelet count ≥ 100,000/μL without the need for transfusion in the 2 weeks prior to Screening.
   - Prothrombin time (PT), International normalized ratio (INR) or activated partial thromboplastin time (aPTT) < 1.5 ×the upper limit of normal (ULN).
   - Absolute neutrophil count ≥ 1,500/μL without any medical interventional treatment (ie, granulocyte-colony stimulating factors [G-CSFs] and/or herbal remedies).
   - Hemoglobin ≥ 9 g/dL, without the need for transfusion in the 2 weeks prior to Screening.

8. Adequate hepatic function as evidenced by meeting all of the following requirements:

   - Total bilirubin: ≤ 1.5 × ULN.
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP): ≤ 3 × ULN.
   - If liver metastases are present, ALT or AST ≤ 5 × ULN; if liver and/or bone metastases ALP ≤ 5 × ULN.

9. Adequate renal function, as evidenced by meeting all of the following requirements:

- Serum creatinine ≤ 1.5 × ULN and creatinine clearance > 50 mL/minute or estimated glomerular filtration rate (GFR) > 50 mL/minute.
- Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, proteinuria must be < 2 g in 24 hours or an equivalent protein/creatinine ratio of < 2000 mg/g creatinine (or < 226.0 mg/mmoL creatinine).

10. Female patients with childbearing potential (excluding women who have undergone surgical sterilization or menopause. Menopause is defined as the status where no menstrual periods continue for 1 year or more without any other medical reasons), are eligible if they have negative serum pregnancy testing within 7 days prior to first dosing and are willing to use an effective method of birth control/contraception to prevent pregnancy until 3 months after the end of study. Male patients must consent using effective method of contraception until 3 months after the end of study.

    Note: Contraceptive methods that are considered highly effective are, for example, total abstinence, an intrauterine device, a double-barrier method (such as condom plus diaphragm with spermicide, a contraceptive implant, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release], or have a vasectomized partner with confirmed azoospermia).

4.3.2 Exclusion Criteria

Patients will not be entered in the study for any of the following reasons:

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.
2. Known ROS-1 positive tumor.
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.
4. Prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGFR, including Avastin®.
5. Prior systemic therapy for metastatic disease.
6. Prior systemic anticancer therapy, or radiotherapy for locally advanced nsNSCLC if completed < 6 months prior to the diagnosis of relapsing disease.

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.

8. Known brain metastasis or other CNS metastasis that is either symptomatic or untreated. Metastases that have been treated by complete resection and/or radiotherapy demonstrating stability or improvement are not an exclusion criterion provided they are 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.

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

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 is acceptable.

11. A significant thrombotic or hemorrhagic event ≤ 6 months prior to Screening (includes 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).

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.

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

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

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.

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

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.

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.

19. Clinically significant active infection requiring systemic therapy.

20. Active Hepatitis B infection (according to local site standards) or active Hepatitis C infection (Hepatitis C virus [HCV] antibody positive); the patient could be included in the study if he/she is HCV RNA negative, details see Section 6.2.2.

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

22. Patient considered unsuitable for inclusion by the Investigator (eg, 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).

23. Pregnant or lactating women.

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.

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 is eligible provided the infection is under control.

    For China sites 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 is eligible provided the infection is under control.

    - Anti-cancer 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 anti-cancer 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 is not eligible.

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

27. Any person who is:

- an employee of the Principal Investigator, study center, IQVIA or Sponsor.
- a relative of an employee of the study center, the Investigators, IQVIA or the Sponsor.

4.3.3 Subject Restrictions

Patients should agree on the following:

- Refrain from strenuous exercise (including contact/collision sports) for 72 hours prior to randomization and for the duration of the study.
- Adhere to study requirements for contraceptives.
- Adhere to the concomitant medication restrictions (excluded medications are specified in Section 5.8.1).
- Ability to stop regular use of aspirin (> 325 mg/day) or other non-steroidal anti-inflammatory drugs (NSAIDs) with antiplatelet activity or treatment with dipyramidole, ticlopidine, clopidogrel or cilostazol within 10 days of first dose of study drug.
- Ability to stop oral, inhaled or topical corticosteroids, or to limit the dose to not exceed 10 mg/day prednisolone or equivalent. During the 4 weeks prior to Day 1, the dose must be stable.
- Willingness to stop traditional anticancer or anti-infective remedies after ICF is signed during the conduct of the study.

Surgical procedures

For elective surgery during the study, the interval between termination of the bevacizumab infusion and subsequent elective surgery should be at least 28 days. If emergency surgery is performed, precautions should be taken to minimize the potential risk of bleeding and thrombosis associated with this class of agents, infusion should be stopped and close monitoring for bleeding, wound healing and thromboembolic complications should be initiated. Patients with anticipated elective surgery will not be enrolled into the study.

4.3.4 Subject Withdrawal

In the event of any of the following conditions, study drug (BAT1706 or Avastin®) should not be administered and the patient should be permanently withdrawn from the study:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess) and fistula formation involving an internal organ.
- Wound dehiscence and wound healing complications requiring medical intervention.
- Serious hemorrhage (ie, requiring medical intervention).
- Severe arterial thromboembolic events.
- Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism.
- Hypertensive crisis or hypertensive encephalopathy.
- Posterior Reversible Encephalopathy Syndrome.
- Nephrotic syndrome.
- At least 4 weeks prior to elective surgery.
- Severe hypertension not controlled with medical management.
- Proteinuria (≥ 2 g/24 hours) persisting despite interruption of BAT1706 or Avastin®.
- Severe infusion reactions (≥ Grade 3).
- Patient who become pregnant during the course of the study.
- Treatment delay of > 6 weeks (> 9 weeks interval between 2 administrations).

All patients are free to withdraw from participation in the clinical study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances where there is a compelling safety reason to allow the patient to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the patient to continue in the study.

In addition, patients will be withdrawn from study drug and from the study in the following circumstances:

- The Investigator decides that the patient should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the study drug

is to be discontinued and appropriate measures are to be taken. The Sponsor or Sponsor designee is to be notified immediately.

- The patient is unwilling to continue in the study.
- Lack of compliance with protocol.
- The Investigator or the Sponsor, for any reason, stops the study.

If a patient discontinues study treatment, he/she will have the EoT Visit procedures and survival follow-up performed as shown in the Schedule of Events (Table 1). All patients will be followed for survival, until death or the end of the study 24 months after randomization, whichever is earlier. If a patient withdraws consent, the date and primary reason will be documented in the source documents. Patients who withdraw consent before the first tumor assessment will be replaced.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Investigational Medicinal Product

BAT1706 will be supplied as 100 mg/4 mL. The dose is 15 mg/kg.

Comparator

EU-Avastin® will be supplied as 100 mg/4 mL. The dose is 15 mg/kg.

Concomitant drugs

The initial dose of paclitaxel is 200 mg/m²However, for Chinese patients (according to local label), paclitaxel will be administered at a dose of 175 mg/m²

In all patients, the initial dose target of carboplatin is area under the curve (AUC) 6 mg/mLminute.

For all patients in case of anticipated excessive toxicity (eg, elderly patients, prior toxicity during chemo-radiotherapy), the Investigator may start the first course of chemotherapy using paclitaxel at a dose of 175 mg/m²(or use a paclitaxel dose of 200 mg/m²after prophylactic administration of G-CSF), and/or carboplatin AUC 5 mg/mLminute.

Mode of Administration

- BAT1706 or EU-Avastin® infusion must be administered first, ie, prior to the administration of paclitaxel and carboplatin. The prepared infusion solutions will be administered as an IV infusion through a dedicated line. It must NOT be administered as an IV push or bolus. Drug infusions will take place under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary. The initial dose for the first BAT1706 or EU-Avastin® infusion should be delivered over 90 minutes. If the first infusion is well tolerated, the second and subsequent infusion may be administered over 60 minutes. Drug administration start/stop and dosing amounts will be recorded in the electronic case report form (eCRF). No dose modifications are allowed. No more than 6-week delay is allowed (maximum of 9 weeks between 2 administrations).
- Paclitaxel infusion is recommended to be given IV over 3 hours or according to local standard practice or package inserts after adequate pre- and concomitant prophylactic medication (see details in Section 5.6.1.1). Please refer to the prescribing information

for the formulation, preparation, and storage of paclitaxel.[14] Dose modifications are allowed twice according to the guidelines in Section 5.6.1.3.

- Carboplatin is administered intravenously according to local standard practice or package insert after the end of paclitaxel infusion. Please refer to the prescribing information for the formulation, preparation, and storage of carboplatin.[15-16] Dose modifications are allowed twice according to the guidelines in Section 5.6.1.3.

5.2 Identity of Investigational and Comparator Products

Table 3 provides the details of investigational and comparator products.

Table 3 Investigational and Comparator Products

Investigational product	Dosage form and strength	Manufacturer
BAT1706 [redacted]	Solution for infusion (25 mg/mL) 100 mg/4 mL solution in a single use vial	Bio-Thera Solutions, Ltd.
Comparator	**Dosage form and strength**	**Manufacturer**
EU-Avastin®: Composition: bevacizumab, trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate, polysorbate 20, and water for injection	Solution for infusion (25 mg/mL) 100 mg/4 mL solution in a single use vial	Roche Pharma AG.

Abbreviation: EU = European Union.

Stability and Storage

No preservative is used in BAT1706/EU-Avastin®; therefore, the vials are intended for single use only. [redacted] Do not use vials beyond the expiration date.

Preparation of BAT1706/EU-Avastin® for Intravenous Administration

The recommended dose is 15 mg/kg every 3 weeks when used in combination with carboplatin and paclitaxel chemotherapy. The dose of BAT1706/EU-Avastin® should be recalculated in

case of body weight change ≥ 10% and if not due to fluid retention, which needs to be treated appropriately.

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. It is recommended that the necessary amount of BAT1706/EU-Avastin® will be withdrawn and diluted in 0.9% sodium chloride. Recommended concentration is from 1.4 mg/mL to 16.5 mg/mL. The volume to be administered for each patient will be calculated based on the patient's weight. Discard any unused portion left in the vial, as the product contains no preservatives.

Details of the identity of paclitaxel and carboplatin are provided in the package inserts.[14-16]

5.3 Packaging and Labeling

All study drugs will be supplied to the study center by the Sponsor.

Both BAT1706 and EU-Avastin® will be packaged and labelled in accordance with text that is in full regulatory compliance with each participating country.

Handling and storage instructions for paclitaxel and carboplatin will be included in a separate Pharmacy Manual.

5.4 Method of Assigning Subjects to Treatment Group

Once the patient meets all inclusion criteria and no exclusion criteria and has provided an informed consent, patient will then be randomly assigned in a blinded manner to either Arm A or Arm B with a 1:1 ratio. The randomization will be performed using the Interactive Web Response System (IWRS) based on the following stratification factors:

- NSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV).
- Gender (male or female).
- Ethnicity (Asian or non-Asian).

Patients will be assigned a patient number in the order in which they are enrolled in the study. Each vial of study drug will be labeled with a unique medication identification number. The IWRS will assign the correct vial for the allocated treatment group and visit and the medication identification will be linked to an individual patient.

Access to the randomization code will be controlled and documented (see Section 5.7 for further details).

5.5 Selection of Bevacizumab Dose in the Study

In the EU, US, and many other countries, Avastin® has received health authority approval for the treatment of nsNSCLC, in combination with carboplatin and paclitaxel, for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.

The dose of BAT1706 selected for this study is based on the clinically effective dose of the currently available dosage form of Avastin® in that indication.[4-5]

The primary focus of this study is to demonstrate clinical equivalence of BAT1706 (proposed biosimilar to Avastin®) with EU-Avastin®. The recommended dose of Avastin®, administered as an IV infusion, is 15 mg/kg of body weight given once every 3 weeks. Therefore in this study, patients randomized to receive BAT1706 or EU-Avastin® will receive 15 mg/kg once every 3 weeks.

5.6 Treatment Regimen, Schedule, and Mode of Administration

The treatment regimen is every 3 weeks (21 days) administrations for up to 6 cycles for chemotherapy and BAT1706 or EU-Avastin®, followed by maintenance monotherapy with BAT1706 or EU-Avastin® until progression or excessive toxicity with a maximum of 12 months in this study. Thereafter, patients who still benefit and tolerate therapy will be enrolled in the LTE study using the same regimen as during maintenance therapy with a maximum of 12 additional months.

The duration of participation for each patient of this study is expected to be about 12 months, which exceeds the median number of cycles administered in non-Asian patients (7 cycles) while it slightly exceeds the median number of cycles administered in Asian patients (11 cycles).[12,13] However, since patients with EGFR mutation are excluded in this study, and the mutation confers a longer PFS time, the median number of cycles in Asian patients (in whom the mutation is present in up to 50% of adenocarcinoma) is expected to be ≤ 11 cycles.[17]

Patients intolerant to chemotherapy after 2 dose reductions can start monotherapy with BAT1706 or EU-Avastin® or start another line of anti-cancer therapy after investigator's judgment. The drug sequence is as follows: To better evaluate the tolerability of BAT1706 or EU-Avastin® only BAT1706 or EU-Avastin® is administered on Day 1 of Cycle 1, and paclitaxel and carboplatin are given on Day 2. As of Cycle 2, BAT1706 or EU-Avastin® is given first, then paclitaxel followed by carboplatin on the same day.

Patients must be under close surveillance from the start of the infusion to allow detecting hypersensitivity reactions which may occur within minutes. Severe hypotension, bronchospasm or generalized rash/erythema requires immediate discontinuation of infusion and appropriate treatment. The infusion may be slowed for minor symptoms such as flushing or local cutaneous reactions. Patients experiencing severe hypersensitivity reactions should be discontinued from the study.

Patients may be hospitalized for observation at the discretion of the Investigator (such instances of hospitalization will not be recorded as a serious adverse event [SAE]).

BAT1706 or EU-Avastin® dose modification for intolerance is NOT permitted during this study. Any deviation will be recorded in the eCRF. Dose modifications for intolerance to chemotherapy are allowed twice.

In the event of a life-threatening reaction, including anaphylaxis, hypersensitivity reaction, renal failure, severe cardiopulmonary event and severe muco-cutaneous reaction, BAT1706 or EU-Avastin® will be discontinued and no additional BAT1706 or EU-Avastin® will be administered.

If extravasation occurs during infusion of the study drug, the infusion must be stopped. Restart the remainder of the infusion either in the area of the same arm which is proximal to the body or in the other arm. The PK sample will always be drawn from the opposite arm of the infusion arm.

Patients who miss the allocated day for study drug infusion will be contacted and another visit will be arranged as soon as practically possible to administer study drug. No dose reduction is planned and a maximum of 9 weeks interval between 2 administrations is accepted. If the patient has not recovered, he/she is withdrawn from study. In case treatment is delayed for intolerance to BAT1706/EU-Avastin®, the chemotherapy must be postponed to coincide with the new cycle.

For more information regarding chemotherapy regimens, please refer to Section 5.6.1.

The treatment regimen for BAT1706/EU-Avastin® plus chemotherapy is provided in Table 4.

Table 4 Treatment Regimen of BAT1706/EU-Avastin® plus Paclitaxel and Carboplatin

Regimen	Dose	Mode
BAT1706/EU-Avastin®	15 mg/kg	IV
Paclitaxel	200 mg/m^2 (administered according to standard institutional practice)	IV
Carboplatin	target AUC 6 mg/mLminute (according to local standard practice or package insert)	IV

Abbreviations: AUC = area under the curve; EU = European Union; IV = intravenous
Note: BAT1706/EU-Avastin® infusion should be administered prior to paclitaxel and carboplatin.

BAT1706/EU-Avastin® dose and schedule will remain unchanged during the maintenance period when given as single agent. The same study drug (BAT1706 or EU-Avastin®) will be continued during maintenance therapy based on the allocation at the time of randomization.

Administered dose of all study drugs, date/time of start of infusion, date/time of end of infusion and any interruptions must be documented in the eCRF. Interruptions should be documented as the time that infusion is stopped and restarted.

5.6.1 Chemotherapy

5.6.1.1 Premedication

Systematic premedication is not warranted before BAT1706 or Avastin® infusion on Day 1 of Cycle 1. Diphenhydramine (or its equivalent) can be given according to local practice.

All patients must receive premedication prior to carboplatin/paclitaxel administration to prevent severe hypersensitivity reactions. On Day 2 of Cycle 1, and on Day 1 in all subsequent cycles, all patients will be given 20 mg dexamethasone IV, diphenhydramine (or its equivalent) 50 mg IV, and cimetidine (300 mg) or ranitidine (50 mg) IV according to each drug label and per local standard practice. Premedication should be completed 30 to 60 minutes before paclitaxel infusion. Once BAT1706 or Avastin® is no longer given in combination with paclitaxel and the patient has tolerated BAT1706 or Avastin® infusions, premedication can be stopped; however, this will depend on each individual case per Investigator's judgment, and local standard practice.

5.6.1.2 Chemotherapy Regimen

Administration of backbone chemotherapy will be according to the standard preparation and infusion procedures of each study center. Patients should receive paclitaxel prior to carboplatin.

All patients will be treated with standard combination chemotherapy consisting of paclitaxel (175 mg/m^2 initial dose for Chinese patients and 200 mg/m^2 for patients from other countries)

followed by carboplatin target AUC 6 mg/mL•minute ever y 3 weeks for up to 6 cycles with adequate pre- and concomitant medication. For the first course of chemotherapy, in case of anticipated excessive toxicity (e.g, elderly patients, prior toxicity during chemo-radiotherapy), the Investigator may start paclitaxel at a dose of 175 mg/m^2 and/or carboplatin target AUC 5 mg/mL•minute. Alternatively, paclitaxel 200 mg/m² can be administered after prophylactic use of G-CSF.

The carboplatin dose will be calculated using the Calvert formula, taking into account the GFR and given in dose of AUC:

Carboplatin-dosage in mg = (target AUC) ×(GFR + 25) on Day 1 of each 3 -week cycle.

Glomerular filtration rate is to be based on the Cockroft-Gault formula for creatinine clearance:

$$\text{GFR (mL/min)} = \frac{C \times (140 - \text{age [years]}) \times (\text{weight [kg]})}{72 \times \text{serum creatinine (mg/dL)}}$$

where C = 0.85 for female patients and C = 1.00 for male patients.

The Cockcroft–Gault formula will be used to calculate the creatinine clearance/GFR (required for the Calvert's formula). As clinically recommended, GFR will be capped at 125 mL/minute (even if the result obtained is higher) to avoid potential overdosing. Accordingly, the maximum total dose of carboplatin would be 900 mg per cycle.

5.6.1.3 Dose Modifications in Case of Toxicity

A maximum of 2 dose reductions is allowed for hematological and non-hematological toxicity after paclitaxel and carboplatin (Table 5). Once the dose is reduced, no re-escalation is allowed. If toxicity persists despite dose reduction to chemotherapy dose Level-2, the patient must stop chemotherapy. Chemotherapy dose reductions can be cumulative from cycle to cycle as required based on toxicity.

Table 5 Dose Modifications for Paclitaxel and Carboplatin according to Starting Dose

Regimen	**Level-0 (starting dose)**	**Level-1**	**Level-2**	**Level -3**
Paclitaxel (mg/m^2)	200	150	100	Off-treatment
Carboplatin (target AUC [mg/mLmin])	6	4.5	3	Off-treatment

Regimen	Level-0 (starting dose)	Level-1	Level-2	Level -3
Paclitaxel (mg/m^2)	175	130	90	Off-treatment
Carboplatin (target AUC [mg/mLmin])	5	4	3	Off-treatment

Abbreviation: AUC = area under the curve

Drug toxicity will be assessed using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 dated 14 Jun 2010.

In case of insufficient recovery at the planned date for the next cycle, dose modification and treatment delay will be made according to Table 6 and Table 7. A maximum treatment delay of 6 weeks is accepted (9 weeks interval between administrations); beyond that delay the patient is withdrawn from study. Patients with severe hypertension, moderate to severe proteinuria, will not receive further treatment with BAT1706/Avastin® if the AE cannot be adequately controlled within 14 days.

During the combination treatment period, any chemotherapy delay mandates a BAT1706/Avastin® infusion delay and vice-versa. All 3 drugs of this regimen (BAT1706/Avastin® + paclitaxel + carboplatin) should always be administered together during the treatment period if the patient fulfills the criteria for receiving the next treatment cycle.

Recommended dose modifications:

Please refer to the prescribing information for paclitaxel and carboplatin for details.[14-16]

Table 6 Dose Modifications for Hematologic Toxicities (Regardless of Causality)

Toxicity		**Paclitaxel/Carboplatin**
Grade 3 Neutropenia of any duration or Grade 4 < 7 days	1st event	Interrupt until recovery to > 1500/mm^3 Preferably reinitiate at original dose, unless Investigator deems dose reduction by one level is necessary based on individual patient status. Discuss with Medical Monitor Sponsor
	2nd event	Interrupt until recovery to > 1500/mm^3 Consider dose reduction by one level at Investigators discretion, discuss with Medical Monitor Sponsor
	3rd event	Interrupt until recovery to > 1500/mm^3 Use dose reduction by one level
	4th event despite dose reduction	Use dose reduction by one level. Off-treatment if 2 dose reductions already done
Grade 4 Neutropenia ≥ 7 days	1st event	Interrupt until recovery to > 1500/mm^3 Reinitiate at next lower dose level.
	2nd event despite dose reduction	Interrupt until recovery to > 1500/mm^3 Reinitiate at previous lower dose level.
	3rd event despite dose reduction	Off-Treatment
Febrile Neutropenia with Absolute Neutrophil Count < 1,000/mm^3	1st event	Hold dose until ANC > 1500/mm^3 and T < 37℃ Reinitiate at next lower dose level
	2nd event despite dose reduction	Hold dose until ANC > 1500/mm^3 and T < 37℃ Reinitiate at next lower dose level
	3rd event despite dose reduction	Off-Treatment
Thrombocytopenia ≥ 50,000 to < 100,000/mm^3	all events	Hold dose until recovery to ≥ 100,000/mm^3 No change in dose
Grade ≥ 3 Thrombocytopenia	≥ 25,000/mm^3 to < 50,000/mm^3, 1st event	Hold dose until recovery to > 100,000/mm^3 Reinitiate at original dose level
	≥ 25,000/mm^3 to < 50,000/mm^3, 2nd event	Hold dose until recovery to >100,000/mm^3 Reinitiate at next lower dose level
	< 50,000/mm^3 despite previous dose reduction	Off-Treatment
Grade 4 Thrombocytopenia or Grade 3 with Bleeding Requiring Platelet Transfusion	< 25,000/mm^3, 1st event	Hold dose until recovery to > 100,000/mm^3 Reinitiate at next lower dose level
	< 25,000/mm^3 despite previous dose reduction	Off-Treatment
Any Grade Non-hemolytic Anemia		Transfusion indicated for Grade ≥ 3 Anemia No change in dose.

Abbreviation: ANC = absolute neutrophil count

If treatment is held for > 1 week for granulocyte recovery, or if a febrile neutropenic episode (≥ 38.5℃ with a granulocyte count < 1000/mm^3) occurs at any time during therapy, prophylactic filgrastim (Neupogen®) or pegfilgrastim (Neulasta®) will be administered (according to the package insert) with all subsequent cycles. If other uses of G-CSF are allowed, according to regular institutional practice and the Principal Investigator's judgment.

Criteria for dose reductions and discontinuation of therapy for some specific non-hematologic toxicities are summarized in Table 7.

Table 7 Dose Modifications for Selected Non-Hematologic Toxicity (Regardless of Causality)

Toxicity	Paclitaxel/Carboplatin
Metabolic	
Hyperglycemia	No Change
Hypoglycemia	No Change
Gastrointestinal-related/Mucositis	
≥ Grade 3 Nausea/Vomiting (1st Event)	No change
≥ Grade 3 Nausea/Vomiting (2nd Event)	Decrease both drugs dose by one dose level
Grade 1 - 2 Diarrhea	No change
≥ Grade 3 Diarrhea lasting > 24 hours despite maximum anti-diarrheal management (1st event)	Hold study drugs until recovery to ≤ Grade 1 or to baseline Reinitiate at original dose level
≥ Grade 3 Diarrhea lasting > 24 hours despite maximum anti-diarrheal management (2nd Event)	Hold study drugs until recovery to ≤ Grade 1 or to baseline Reinitiate at original dose level
Grade 1 - 2 Mucositis	Hold study drugs until recovery to ≤ Grade 1 or to baseline Reinitiate at original dose level
≥ Grade 3 Mucositis (1st event)	Hold study drugs until recovery to ≤ Grade 1 or to baseline Decrease current dose by one dose level
≥ Grade 3 Mucositis (2nd event)	Hold study drugs until recovery to ≤ Grade 1 or to baseline. Decrease current dose by one dose level
Hepatobiliary	
≥ Grade 2 Aspartate aminotransferase or Alanine aminotransferase and ≤ Grade 1 Total Bilirubin	Hold until LFTs ≤ Grade 1. Restart paclitaxel at same dose when bilirubin is within normal limit. Decrease paclitaxel dose by one dose level when bilirubin = Grade 1. No dose adjustment for carboplatin
≥ Grade 3 Aspartate aminotransferase or Alanine aminotransferase or ≥ Grade 2 Total Bilirubin	Hold until LFTs ≤ Grade 1. Restart paclitaxel at same dose when bilirubin is within normal limit. Decrease paclitaxel dose by one dose level when bilirubin = Grade 1. No dose adjustment for carboplatin
Allergic/Hypersensitivity to Paclitaxel	
≥ Grade 3 allergic/ hypersensitivity despite adequate premedications	Off-treatment
Neuropathy	
Neuropathy Grade 2	Hold study drugs until recovery to ≤ Grade 1 or to baseline. Decrease paclitaxel by one dose level. No dose adjustment for carboplatin.
Neuropathy ≥ Grade 3	Hold study drugs until recovery to ≤ Grade 1 or to baseline. Decrease paclitaxel by two dose levels. No dose adjustment for carboplatin.

Abbreviation: LFT=liver function test

For dose modifications for other events not cited above, it is suggested to follow the hospital standards and carefully capture any modification in the eCRF page.

5.7 Blinding

This is a randomized, double-blind, active comparator study with limited access to the randomization code. The treatment each patient will receive will not be disclosed to the Investigator, study center staff, patient, Sponsor or Sponsor designee or the DSMB. The treatment codes will be held by the Sponsor.

The process for breaking the blind will be handled through the IWRS. Investigators are strongly discouraged from requesting the blind be broken for an individual patient, unless there is a patient safety issue that requires unblinding and would change patient management. Any center that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study. If the blind is broken, it may be broken for only the patient in question.

The Sponsor or Sponsor designee must be notified immediately if a patient and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a patient's treatment code must be documented in the patient's source documents and eCRFs.

Additionally, Sponsor or Sponsor designee may be required to unblind the patient if the AE meets criteria of a suspected unexpected serious adverse reaction in order to fulfil expedited regulatory reporting requirements.

The DSMB may assess unblinded data if needed.

5.8 Prior and Concomitant Treatments

5.8.1 Excluded Medications

Patients are not allowed to take the following medications:

- As of screening and throughout full study including LTE, no anticancer or immune-stimulating agents should be used (either standard, investigational or Chinese herbal medicines).
- Anti-infectives from Chinese herbal medicines should not be used as the drug-drug interaction is unknown but standard antibiotics must be used any time as required from screening to end of LTE.
- Any NSAIDs (including aspirin in doses over 325 mg/day) within 10 days prior to administration of the study drug and for the duration of the study; paracetamol, up to 4 g per day, will be allowed.

- Any live/attenuated virus vaccination within 12 weeks before Screening, and during study participation until the final Follow-Up Visit.
- Any oral anticoagulation (eg, warfarin, rivaroxaban, dabigatran, acenocumarol, etc.) treatment.

5.8.2 Allowed Medications

Patients are allowed to continue with concomitant medication for pre-existing disease as long as they are not part of the list of excluded medicines (Section 5.8.1). In the interest of patient safety and acceptable standards of medical care, the Investigator will be permitted to prescribe treatment(s) at his/her discretion for treatment-emergent adverse events (TEAEs). All treatments administered during the patient's participation in the study (prescription or over-the-counter, including vitamins and/or herbal supplements) must be recorded in the source documents and patients' eCRF (medication, dose, treatment duration and indication).

5.8.3 Allowed Radiotherapy

A short course of local radiotherapy for bone metastasis with palliative intent is allowed during participation in the study, but radiotherapy for relapsing or new brain metastases is not allowed. In such case, the patient should be withdrawn from study.

5.9 Medical Care of Subjects after End of Study

The Sponsor will not provide any additional care to patients after they leave the study because such care should not differ from what is normally expected for patients with advanced nsNSCLC.

5.10 Treatment Compliance

Records of treatment compliance for each patient will be kept during the study. Any deviations from the intended regimen must be recorded in the source document and eCRFs.

5.11 Study Medication Accountability

The Investigator, a member of the study center staff, or a hospital pharmacist must be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the Sponsor's instruction and adherence to GCP guidelines as well as local or regional requirements. These forms must be made available, upon request, for inspection at any time.

All study drug supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All remaining partially used and/or unused study drugs

will be returned to the Sponsor or Sponsor's designee after study completion/termination, or destroyed with the permission of the Sponsor in accordance with applicable laws and study site procedures. If the study drug is to be destroyed, the Investigator will provide documentation in accordance with Sponsor's specifications.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

6.0 EFFICACY, SAFETY, IMMUNOGENICITY, AND PHARMACOKINETIC ASSESSMENTS

6.1 Efficacy

6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR at Week 18 (ORR_{18}) based on tumor response evaluated according to RECIST 1.1 (Appendix 13.4) as assessed by CIR. Patients not achieving Week 18 assessment will be considered non-responders if they dropped out earlier in case of intolerance, documented disease progression, withdrawal of consent, lost to follow-up, or death. The ORR_{18} is calculated as the proportion of patients achieving a PR or a CR at Week 18. Confirmation of response is not required.

Each patient will be assigned to one of the following RECIST 1.1 categories based on independent CIR, irrespective of protocol deviations or missing data:

- CR: complete response.
- PR: partial response.
- SD: stable disease.
- PD: progressive disease.
- NE: not evaluable (insufficient data).

Tumor assessments will be performed at Weeks 6, 12, and 18, regardless of whether a treatment cycle is delayed and whether or not this assessment coincides with the completion of the cycle. Then after, tumor assessments will be performed after every 3 cycles (approximately every 9 weeks [assessed within Days 15-21 after the treatment of the third cycle is given]). Window for tumor assessment is 1 week at the maximum during the first 18 weeks. The results must be available for treatment decision before the planned next cycle.

Patients who discontinued study drug without disease progression will continue to undergo tumor assessments every 9 weeks until disease progression or a maximum of 12 months. Tumor assessment at the EoT Visit is only necessary if more than 4 weeks have passed since the previous assessment (window for these assessments is within 1 week of the EoT Visit).

Contrast-enhanced CT or MRI of at least the chest and abdomen, including the adrenals and the liver, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. Brain CT or MRI scan, and bone scans or X-rays should be

performed at screening if clinically indicated and during treatment period as clinically indicated. If the bone scan is positive at screening, it will be repeated at no less than 12-week intervals. Plain X-ray of bone lesions are used at time of regular tumor assessments as clinically indicated between isotopic bone scans. Positron emission tomography scans are not accepted for sole assessment of efficacy but can be used to identify new lesions if a baseline PET scan was done. Throughout the study it is critical that the same methodology and scan acquisition techniques used at Screening are used throughout the study to ensure comparability. If a patient is unable to undergo a contrast CT due to allergy or renal insufficiency during follow-up, a chest CT without contrast, combined with MRI images of the target lesions with gadolinium contrast, is preferred if tolerated by the patient. Further detail will be provided by CIR contracted for this study.

All imaging for tumor assessments performed until Week 18 will be sent for CIR. The results of the CIR (independent blinded assessment of tumor response) will be used for the primary efficacy analyses. Details will be described in the imaging charter.

6.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Progression-free survival rate at 12 months, defined as the proportion of patients being alive without documented progression 12 months after randomization, using Kaplan-Meier method.
- Progression-free survival time defined as the time from the date of randomization to the date of documented clinical or radiological progression or death due to any cause using Kaplan-Meier method.
- Overall survival rate at 12 months, defined as the proportion of patients being alive 12 months after randomization using Kaplan-Meier method.
- Overall survival time defined as the time from randomization to death of any cause using Kaplan-Meier method.
- ORR at Week 6 (ORR_6) and ORR at Week 12 (ORR_{12}), based on tumor response as assessed by CIR, and best ORR of confirmed responses at end of study assessed by local radiologist/Investigator if after Week 18 according to RECIST 1.1.
- Duration of response defined as the time from first documentation of a response (CR or PR) and the first documentation of progression (assessed by local radiologist/Investigator if after Week 18) according to RECIST 1.1.

6.2 Safety

All AEs (non-serious and serious) will be evaluated for safety. Clinical laboratory results, vital signs, Electrocardiograms (ECGs) and the performance of physical examination will also be evaluated as specified in the Schedule of Events (Table 1). Special attention should be paid for anaphylactic reactions/hypersensitivity reactions/infusion related reactions; arterial and venous thromboembolic events, febrile neutropenia, gastrointestinal perforations, hypertension, proteinuria, pulmonary hemorrhage, other hemorrhages, and wound healing complications/abscess/fistulas.

6.2.1 Adverse Events

Definition of AE: An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from study drug.
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to a clinical symptom or any type of intervention, whether prescribed in the protocol or not.

  A laboratory result should be considered by the Investigator to be an AE if it:

1. Results in the withdrawal of study drug.
2. Results in withholding of study drug pending some investigational outcome.
3. Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia).

4. Results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE with regard to the patient's medical profile.

Definition of SAE: An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death. However, death due to progressive disease is not reported as an SAE.
- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  Following hospitalizations are not considered to be SAEs because there is no 'adverse event' associated with the hospitalization:

  - Surgical operations planned before informed consent (where the illness or disease existed before the patient was enrolled in the study and the condition requiring the hospitalization has not changed after study drug administration).
  - Hospitalization for administration of chemotherapy.
  - Elective hospitalizations for pre-existing conditions that did not worsen.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event)

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

An Unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the study drug. The action taken and the outcome must also be recorded.

Severity

The term severe is a measure of intensity of an event; a severe event is not necessarily serious. Severity of all AEs will be graded by the Investigator according to NCI-CTCAE version4.03, dated 14 June 2010.

Relationship

Causal relationship assessment to study drug treatments is required for reporting AEs. To promote consistency, the following guidelines should be taken into considerations along with good clinical and scientific judgment when determining the relationship of study drug treatments to an AE:

Definitely Related:	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to the withdrawal of the drug should be clinically plausible.
Possibly Related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.
Unlikely Related:	A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and for which other drugs, chemicals or underlying disease provide a plausible explanation.
Not Related:	A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely the alternative etiology.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.

- Evidence that the event is reproducible when the drug is re-introduced (positive rechallenge).
- No medically sound alternative etiologies that could explain the event (eg, pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (eg, Stevens-Johnson syndrome).
- An indication of dose-response (ie, greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (eg, pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (eg, after 5 half-lives) (negative dechallenge).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (eg, situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

All efforts should be made to classify the AE according to the above categories.

Action taken

The action taken for each AE will be defined as:

- None.
- Infusion interrupted.
- Infusion slowed.

- Infusion stopped.
- Other.

Outcome

The outcome of each AE will be defined as:

- Resolved.
- Stabilized.
- Ongoing.
- Resolved with sequelae.
- Fatal.
- Lost to follow-up.

6.2.1.1 Reporting of Adverse Events

Period: From ICF signing to first study medication administration - All AEs related to the study procedures (eg, blood withdrawal etc.).

Period: From the start of the first study medication administration until 28 days after discontinuation/completion of the study medication or up to Week 53 after randomization- All AEs, regardless of relationship to the study medication/study procedures. During the LTE study, only adverse events of special interest (AESIs) and SAEs until 28 days after the subject's last dose will be collected.

All AEs are to be recorded on the appropriate AE pages in the eCRF. The Investigator should complete all the details requested including event's name, dates of onset, date of resolution, severity, action taken, outcome, relationship to study drug. Each event should be recorded separately.

When recording AEs, the diagnosis of the underlying illness or disorder should be used as the event term or description on the eCRF, and symptoms of the illness or disorder should not be reported as separate AEs. It is expected that whenever possible the clinical term, rather than the laboratory term, for the AE will be used by the reporting Investigator (eg, "anemia" versus "low hemoglobin value").

All AEs must be followed up to resolution, stabilization, or until the patient is lost to follow-up, whichever occurs first.

6.2.1.2 Reporting of Serious Adverse Events and Pregnancy

Any SAE, including death due to any cause (except death due to progressive disease), which occurs during this study, whether or not related to the study drug, must be reported immediately (within 24 hours of the study center's knowledge of the event).

Any SAE, regardless of causality assessment, must be collected from ICF signing till the last visit occurring 28 days after the patient's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the Investigator to be related to the study drug should be reported to the Sponsor regardless of the length of time that has passed since study completion.

All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) in English. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described. Once the SAE has been recorded in the EDC system, the Sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the paper SAE report form to meet the 24-hour timeline requirement (contacts and instructions to be provided in separate documentation). Once the EDC becomes available, the Investigator must enter all SAE data as reported on the backup paper SAE report form on the applicable eCRF pages.

In the case of fatal or life-threatening events, these should be reported immediately by telephone. The immediate report should be followed up within 24 hours by completing the relevant page in eCRF. The detail contact information for reporting of SAEs is provided in the Investigator Site File.

The SAE report will contain as much available information concerning the SAE to enable the Sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements. Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described.

Progression of underlying malignancy

Progression of the underlying malignancy should not be recorded as an AE. Signs and symptoms of the underlying NSCLC should only be reported if:

- Newly emergent (ie, not present at baseline) and the association with the underlying malignancy and old/new metastatic lesions is unclear and/or

- The Investigator attributed deterioration of the NSCLC signs and symptoms directly to the study drug. Should there be any uncertainty regarding the attribution of the NSCLC to the AE, it should be reported as an AE/SAE accordingly.

Adverse Events of Special Interest (AESIs)

The following are considered events of interest:

- Hypertension ≥ Grade 3.
- Proteinuria ≥ Grade 3.
- Gastrointestinal perforation, gastrointestinal abscesses and gastrointestinal fistulae (any grade).
- Wound healing complications ≥ Grade 3.
- Hemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ Grade 2 hemoptysis).
- Arterial thromboembolic events (any grade).
- Venous thromboembolic events ≥ Grade 3.
- Posterior Reversible Encephalopathy Syndrome (any grade).
- Chronic heart failure ≥ Grade 3.
- Non-gastrointestinal fistula or abscess ≥ Grade 2.

These AESIs can be classified as serious or non-serious but require reporting to the Sponsor, similar to SAE reporting timeline, even if they do not meet any of the seriousness criteria. These events will be captured using the SAE procedure.

Pregnancy

Any pregnancy that occurs after administration of study drug must be reported immediately (within 24 hours of Investigator's awareness) on a Pregnancy Report Form. The same procedure must be followed if a female partner(s) of a male study patient becomes pregnant after the patient has been enrolled. All pregnancies must be followed to outcome. The Investigator must obtain written authorization (medical records release) from a female partner of a male patient prior to obtaining follow-up.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs.

A patient who becomes pregnant must be withdrawn from the study.

6.2.1.3 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

The Sponsor will evaluate reported SAEs for expedited reporting as assessed against the most current approved version of the IB. Until an AE is identified in the Reference Safety Information of the IB, it is considered unexpected, regardless of whether the AE has been submitted previously as an expedited report.

Expedited reporting will be performed by the Sponsor or Sponsor designee in accordance with local and regional law and established guidance. Upon receiving an expedited report, the Investigator must review and retain the notice with the IB and shall be responsible for submitting expedited reports to their IRBs/IECs in accordance with institutional guidelines. Regardless of institutional guidelines, Investigators shall submit expedited reports to their IRBs/IECs in the event that the Sponsor identifies an expedited report to represent a new and/or unforeseen risk.

6.2.2 Clinical Laboratory Evaluations

Clinical laboratory tests during the study will be performed by a local laboratory. The Schedule of Events (Table 1) shows the visits and time points at which blood for clinical laboratory tests and urine for urine tests will be collected in the study.

The following laboratory parameters will be measured:

- Infection screen (for Hepatitis B and Hepatitis C):
- Hepatitis B is defined as active according to local site standards.
- Active Hepatitis C is defined as positive test for confirmatory HCV RNA. If HCV antibody tested positive, the result should be confirmed by a positive HCV RNA. Patients with negative HCV RNA could be considered for the study.

- Screening for HIV, syphilis, and tuberculosis to be performed according to local practice and local regulatory guidance.
- Hematology: hemoglobin, hematocrit, platelets, white blood cells, lymphocytes, neutrophils, and complete blood cell count with differential.
- Serum chemistry: creatinine, AST, ALT, ALP, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, glucose, total cholesterol, total protein, albumin, sodium, potassium, chloride, and calcium.
- Urinalysis: protein, glucose, and blood.

- Coagulation: INR and aPTT or PT.
- Pregnancy testing for females of child-bearing potential only: Human Chorionic Gonadotropin in serum and urine.

At Screening, a first set of laboratory tests will take place as soon as a patient starts the screening procedures. In case CBC was done > 7 days prior to Day 1 of Cycle 1, CBC will be repeated to confirm eligibility. And for subsequent cycles, laboratory tests must be performed within a maximum of 3 days prior to Day 1 of each cycle (ie, before BAT1706 or Avastin® administration). Hematology tests will be repeated on Day 8 of each cycle during combination therapy. The results must be available before each study drug infusion. Similarly, unscheduled hematology/serum chemistry assessments may be performed whenever clinically indicated.

In case therapeutic doses of anticoagulants are started during the treatment period, coagulation tests will be repeated not more than 3 days prior to each cycle. If anticoagulants are used for study-related AE, Investigator should take appropriate actions, including but not limited to dose interruption and dose reduction. If the patient has not recovered within the permitted window, no further treatment can be administered and the EoT must take place. Urine dipstick will be assessed within 7 days prior to randomization and then every cycle during treatment period. In case proteinuria is observed, 24-hour urine test should be performed.

Qualified medical staff at the site will review, initial, and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate, at the discretion of the Investigator. Clinically significant laboratory values will be recorded as AEs if they meet the criteria as specified in Section 6.2.1.

6.2.3 Vital Signs, Physical Findings and Other Safety Assessments

6.2.3.1 Vital signs

Vital signs (temperature, blood pressure, and pulse rate) will be performed prior to administration of study drug at the visits indicated in Table 1. Blood pressure and pulse rate will be measured after the patient has rested comfortably for at least 5 minutes using a manual or digital sphygmomanometer.

The Investigator must immediately assess all vital signs findings at each visit. If the Investigator finds any clinically relevant abnormalities, these must be reported as AEs/SAEs as appropriate.

6.2.3.2 Physical examination

Physical examination will be performed prior to administration of study drug at Screening and at the visits indicated in Table 1.

Height will only be measured at Screening. Weight will be measured at Screening and then every cycle for body surface area adjustment of dose, if change is ≥ 10%.

Any clinically significant changes from admission will be recorded as AEs. The physical examination will be performed by a physician and will include the examination of the following: general appearance, abdomen, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, skin, thyroid/neck, lymph nodes, and neurological/psychiatric. The infusion site will be assessed and findings will be recorded as AEs.

Magnetic resonance imaging may be performed in case there is suspicion for PRES.

6.2.3.3 Electrocardiogram

Electrocardiograms will be performed prior to administration of study drug at the visits indicated in Table 1. Additional ECGs will be performed if clinically indicated. Local ECG readings will be used throughout the study.

A computerized 12-lead ECG will be performed with the patient in a supine position after the patient has rested comfortably for at least 5 minutes. Standard ECG parameters, including heart rate, QRS, PR, RR, QT, and the QT interval corrected for heart rate using Fridericia's formula (QTcF) will be measured.

The original ECG traces and variables must be stored in the patients' medical records as source data. The Investigator or designee will evaluate the ECG from a clinical perspective and the result (whether the ECG result is normal or abnormal) will be recorded on the appropriate section of the eCRF and on the ECG trace signed and dated by Investigator or designee. Any ECG abnormality that the Investigator considers as an AE should be reported as such.

6.2.4 Safety Monitoring

A DSMB consisting of members who are independent from the Sponsor will be established. The DSMB analyses will be performed as specified in the DSMB charter.

The DSMB will review patient safety data on an on-going basis based on descriptive statistics of TEAEs after the first 20 patients have been treated for 6 weeks in each arm; then after, if no unexpected safety signal was identified, the study will continue and the safety data will be reviewed at regular intervals after approximately every 200 patients are evaluated after they

received the first 4 cycles. At each DSMB review, if no unexpected changes in the known safety profile for Avastin® are observed for BAT1706, the DSMB will recommend continuing the study. The blind will be broken only in case a serious safety signal is identified.

6.3 Immunogenicity

Blood samples will be collected to test for ADA and NADA at the visits indicated in Table 1 and Table 2.

For all immunogenicity samples, the date and time of sampling will be accurately recorded.

Approximately 6 mL of whole blood per time point for ADA and NADA will be collected.

Wherever possible, immunogenicity blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venipuncture. The immunogenicity samples should be obtained from the forearm not used for the BAT1706 or EU-Avastin® IV administration.

In case of positive test for ADA/NADA at the EoT visit or at SFUV 12 months after the first dose, whichever comes first, ADA/NADA blood sample should continue to be collected every 9 weeks until 2 tests are negative (no later than 24 months after randomization); one PK sampling will be collected in case the first positive ADA/NADA result is found at the SFUV/EoT Visit.

In the event of early withdrawal from treatment, every effort should be made to take immunogenicity samples as part of the EoT Visit procedures, if possible, with date/time of sample and date/time of dose prior to this sample recorded.

Blood sample, collection, processing, storage, and shipment handling details will be presented in a separate Laboratory Manual.

6.4 Pharmacokinetic Assessments

The PK and popPK analysis will be explored in a subgroup of 200 patients, from samples collected only at designated sites in China, Turkey, and Ukraine.

Blood samples for the determination of serum concentrations of bevacizumab will be taken by venipuncture at the times specified in the schedule of assessments (Table 1 and Table 2). Approximately 4 mL of whole blood per time point for PK will be collected.

The exact date/time of each blood sample collection will be recorded in the patient's eCRF. Blood samples for PK analyses should be collected in appropriate blood collection tubes as defined in the study manuals. The Sponsor will provide the Investigator with a manual

containing details for the preparation of blood samples to be collected. Shipment and analysis instructions will be provided to the Investigator in a separate manual.

The following information will be captured for blood sample collection in each patient's eCRF:

1. Patient's number.
2. Start date/time and stop date/time of the most recent dose administration prior to the PK sample, if applicable.
3. Date and time of each blood sample collected for PK analysis.
4. Start date/time and stop date/time of subsequent dose administration, if applicable.

6.5 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of NSCLC.

The safety assessments to be performed in this study, including hematology analyses, serum chemistry tests, urine test, and assessment of TEAEs, are standard evaluations to ensure patient safety. Early assessments of ADA/NADA at Days 15 and 43 will be done in order to detect an early immune response, followed by assessments every 6 to 9 weeks. Serum level of bevacizumab will be measured at the same time points as ADA/NADA and up to 3 months after last dose in case ADA/NADA are positive at EoT visit.

The RECIST 1.1 guideline (Appendix 13.4) is well established and scientifically accepted and will be used for the evaluation of tumor response. The NCI-CTCAE version 4.03 dated 14 Jun 2010, a standard for assessment of safety in oncology clinical studies, will be used for the assessment of AEs in nsNSCLC patients.

7.0 STUDY PROCEDURES

7.1 Screening Period

Screening (Day -21 to -1)

Patients must be screened within 21 days prior to randomization. The purpose of screening period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each patient and prior to the conduct of any screening procedures or assessments. Re-screening is allowed to re-evaluate eligibility of the patient if prior exclusion criteria could be resolved. Medical monitor's approval is required.

At Screening, a first set of laboratory tests will take place as soon as a patient starts the screening procedures. In case CBC was done > 7 days prior to Day 1 of Cycle 1, CBC will be repeated to confirm eligibility.

During the Screening visit, the following procedures will be performed/collected:

- Informed consent.
- Eligibility assessment including CIR to confirm the presence of at least one measurable target lesion according to RECIST 1.1 (Appendix 13.4).
- EGFR and ALK mutation status if applicable.
- Demographics (including date of birth, gender, and ethnicity).
- Relevant medical/surgical history (including lung cancer history and other past and current medical disease with clinical significance; prior anticancer treatments, including adjuvant chemo and/or radiotherapy).
- Laboratory/safety assessments:
    - Infection screen (serum virology of Hepatitis B and C, and HIV, syphilis, and tuberculosis).
    - Laboratory testing (hematology, chemistry, coagulation and urine test).
    - Serum pregnancy test (for females of child-bearing potential): within 7 days of prior to first dosing.
    - Vital signs (see Section 6.2.3.1).
    - Physical examination including height (see Section 6.2.3.2).

- 12-lead ECG (see Section 6.2.3.3).
- Assessment of AEs.
- Previous and concomitant therapy/medications assessments.

- Disease assessments:
  - Tumor assessment (see Section 6.1).
  - ECOG performance status.

7.2 Treatment Period

7.2.1 Cycle 1

Eligible patients with confirmed measurable target lesion by CIR will be randomized and allocated to treatment as per the IWRS within 3 days before Day 1 of Cycle 1 (baseline). The following procedures will also be performed/collected:

- Assessment of eligibility.
- Laboratory/safety assessments:
  - Hematology: Days 1 and 8.
  - Chemistry, coagulation and urine test: Day 1.
  - Vital signs (see Section 6.2.3.1): Days 1 and 8.
  - Physical examination (see Section 6.2.3.2): Days 1 and 8.
    Note: Weight is measured at every cycle. If weight change is ≥ 10%, the dose will be adjusted according to the new body surface area.
  - 12-lead ECG (see Section 6.2.3.3): Day 1.
  - Assessment of AEs – continuous.
  - Concomitant therapy/medications assessments – continuous.
- Disease assessment:
  - Survival – continuous.
- Other assessments:
  - Blood PK (if applicable) and ADA/NADA samples: Refer to Table 2.

Blood samplings on Day 1 *before infusion* can be made within 7 days prior to dosing at time of laboratory tests.

- Study treatment (see Section 5.0):
    - Randomization (within 3 days before Day 1 of Cycle 1).
    - Administration of BAT1706 or EU-Avastin®: Day 1.
    - Administration of premedication: prior to carboplatin/paclitaxel administration: On Day 2 (see Section 5.6.1.1).
    - Administration of carboplatin/paclitaxel: Day 2.

7.2.2 Cycles 2 to 6

The following procedures will be performed/collected:

- Laboratory/safety assessments:
    - Hematology: Days 1 and 8.
    - Chemistry, coagulation and urine test: Day 1.
    - Urine pregnancy test (for females of child-bearing potential): Day 1 of Cycles 3 and 5 (serum pregnancy test to be performed in case of positive urine pregnancy test).
    - Vital signs (see Section 6.2.3.1): Day 1.
    - Physical examination, including weight (see Section 6.2.3.2): Day 1
      Note: Weight is measured at every cycle to adjust body surface area if change is ≥ 10%.
    - 12-lead ECG (see Section 6.2.3.3): Day 1.
    - Assessment of AEs – continuous.
    - Concomitant therapy/medications assessments – continuous.
- Disease assessments:
    - Tumor assessment (see Section 6.1): Weeks 6, 12, and 18.
    - ECOG performance status: Day 1 of Cycles 3 and 5.
    - Survival – continuous.

- Other assessments:
    - Blood PK (if applicable) and ADA/NADA samples: Refer to Table 2.
- Study treatment (see Section 5.0):
    - Administration of BAT1706 or EU-Avastin®: Day 1.
    - Administration of premedication: Day 1.
    - Administration of carboplatin/paclitaxel: Day 1.

7.2.3 Cycles 7 to 17: Maintenance Period

The following procedures will be performed/collected:

- Laboratory/safety assessments:
    - Laboratory testing (hematology, chemistry, coagulation and urine test): Day 1.
    - Urine pregnancy test (for females of birth potential): Day 1 every 6 weeks (serum pregnancy test to be performed in case of positive urine pregnancy test).
    - Vital signs (see Section 6.2.3.1): Day 1.
    - Physical examination, including weight (see Section 6.2.3.2): Day 1
      Note: Weight is measured at every cycle to adjust body surface area if change is ≥ 10%.
    - Assessment of AEs – continuous.
    - Concomitant therapy/medications assessments – continuous.
- Disease assessments:
    - Tumor assessment (see Section 6.1): Weeks 27, 36, and 45 or after every 3 cycles.
    - ECOG performance status: Day 1 every 6 weeks.
    - Survival – continuous.
- Other assessments:
    - Blood PK (if applicable) and ADA/NADA samples: Refer to Table 2.

- Study treatment (see Section 5.0): BAT1706 or EU-Avastin® every 3 weeks until disease progression or until the total duration of study treatment reaches 12 months, then BAT1706 only in the LTE study for an additional 12 months (ie, for up to a total of 24 months after initial randomization).

7.3 End of Study and Follow-up Period

7.3.1 End of Treatment Visit/Safety Follow-up Visit

All patients who receive at least one infusion of BAT1706 or EU-Avastin® and who discontinue the study at any time after Day 1 (but do not withdraw their consent) will be required to undergo all of the evaluations at SFUV/EoT that will take place 28 days ±2 days after they received the last dose during the study with a maximum at Week 53.

The following procedures will be performed/collected:

- Laboratory/safety assessments:
    - Laboratory testing (hematology, chemistry, coagulation, and urine test).
    - Serum pregnancy test (for females of child-bearing potential).
    - Vital signs (see Section 6.2.3.1).
    - Physical examination (see Section 6.2.3.2).
    - 12-lead ECG (see Section 6.2.3.3).
    - Assessment of AEs – continuous.
    - Previous and concomitant therapy/medications assessments – continuous.
- Disease assessments:
    - Tumor assessment (see Section 6.1): Only required if more than 4 weeks have passed since the previous assessment (window for this assessment is within 1 week of the EoT Visit).
    - ECOG performance status.
- Other assessments:
    - Blood PK (if applicable) and ADA/NADA samples: at the time of hematology's blood sampling (if tested positive for ADA/NADA at the SFUV/EoT visit, ADA/NADA blood samples should continue to be collected every 9 weeks until

2 consecutive tests are negative [no later than 24 months after randomization]). In case the first positive ADA/NADA result is found at the SFUV/EoT Visit, one PK sampling will be collected.

7.3.2 Survival Follow-Up

After the SFUV/EoT Visit, all patients who do not withdraw consent will be monitored for survival status via telephone call every 3 months up to 24 months after randomization.

The Sponsor may also elect to discontinue clinical investigations under this study for any reason, at any time.

7.3.3 Long-Term Extension Study (Cycle 18 onward)

Patients who are still benefiting of therapy after 12 months will be offered to continue to receive BAT1706 in the LTE study (regardless of the arm patient was assigned at randomization), until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for a maximum of 12 additional months (ie, for up to 24 months from initial randomization). The same treatment regimen of every 3 weeks (21 days) will be followed. Patients who enter in the LTE study will undergo the EoT visit within 28 ±2 days after they receive the last dose of study drug with a maximum at Week 104.

The visit window for LTE visits are -1 to +7 days.

The following will be performed/collected:

- Laboratory/safety assessments:
    - Laboratory testing (hematology, chemistry, coagulation and urine test): Day 1.
    - Urine pregnancy test (for females of birth potential): Day 1 every 6 weeks (serum pregnancy test to be performed in case of positive urine pregnancy test).
    - Vital signs (see Section 6.2.3.1): Day 1.
    - Physical examination, including weight (see Section 6.2.3.2): Day 1.
      Note: Weight is measured at every cycle to adjust body surface area if change is ≥ 10%.
    - Continuous assessment of AESIs and SAEs until 28 days after the subject's last dose.
    - Concomitant therapy/medications assessments – continuous.

- Disease assessments:
    - Tumor assessment (see Section 6.1): Patient should be assessed at Investigator's discretion until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision or up to 24 months after randomization, whichever occurs first.
    - Survival: monitored via telephone call every 3 months.
- Study treatment (see Section 5.0): BAT1706 only every 3 weeks until disease progression or up to 12 months.
- Other assessments:
    - ADA/NADA blood samples: Refer to Table 1.

7.3.4 End of Study Definition

The study will be closed when all randomized and treated patients have either died, are lost to follow-up, or have withdrawn consent, or for a maximum of 24 months after the last patient randomized, whichever occurs earlier.

8.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of GCP (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s).
- Local laboratories for clinical laboratory parameters and ECGs.
- Center Initiation visit.
- Early center visits post-enrollment.
- Routine center monitoring.
- Ongoing center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, Sponsor and/or Sponsor designee may conduct periodic audits of the study processes, including, but not limited to study center, center visits, local laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

8.1 Investigator's Responsibility

The Investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "Investigator" as used in this protocol as well as in other study documents, refers to the Investigator or authorized study personnel that the Investigator

has designated to perform certain duties. Sub-Investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

8.2 Training

The study monitor will ensure that the Investigator and study site personnel understand all requirements of the protocol, the investigational status of the study drug, and his/her regulatory responsibilities as an Investigator. Training may be provided at an Investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the Investigator and will serve as the liaison between the study site and the Sponsor.

8.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. Monitoring visits to each site will be conducted by the assigned study monitor as described in the clinical monitoring plan. Monitoring will be in the form of personal visits with the Investigator and their staff as well as any appropriate communications by telephone, fax, mail, or E-mail transmission. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The Investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The Investigator agrees to cooperate with the monitor to ensure any problems detected in the course of these monitoring visits are resolved.

In order for the Investigator to participate in this study, the study monitor must have direct access to source data for data verification. This will be done by comparing data from the eCRFs with data from the patient's clinic or hospital records (permission will be sought from the patient as part of the consent process).

8.4 Non-Compliance with the Protocol

The Investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the patient. In the event(s) of an apparent immediate hazard to the patient, the Investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The Sponsor will also ensure the responsible IEC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the Sponsor may terminate the Investigator's participation. The Sponsor will notify the IEC and applicable regulatory authorities of any Investigator termination.

8.5 Study Documentation and Electronic Case Report Forms

The Investigator is responsible for maintaining complete and accurate source documents.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts.
- Copies or transcribed health care provider notes that have been certified for accuracy after production.
- Recorded data from automated instruments such as IWRS, X-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, ECGs, rhythm strips) regardless of how these images are stored, including microfiche and photographic negatives.
- Records of telephone contacts.
- Diaries or evaluation checklists.
- Drug distribution and accountability logs maintained in pharmacies or by research personnel.
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation).
- Correspondence regarding a study patient's treatment between physicians or memoranda sent to the IRBs/IECs.
- CRF components that are completed directly by patients and serve as their own source.

The Investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

Electronic case report form will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Only authorized study site personnel will record or change data on the eCRFs. All data must be entered in English. The eCRF is essentially

considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified.

The Investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The Investigator or designee as identified on Form FDA 1572 must sign the CRF to attest to its accuracy, authenticity, and completeness.

The handling of data by the Sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the Sponsor or Sponsor designee. Data management and control processes specific to the study will be described in the data management plan.

Adverse events will be coded using current Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

8.6 Quality Assurance Audit

The Sponsor and/or Sponsor's designee may conduct audits to evaluate study conduct and compliance with the protocol, SOPs, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. In addition, inspections may be conducted by regulatory authority at their discretion during the study or after its completion. The Investigator must inform the Sponsor immediately of such request.

9.0 STATISTICS

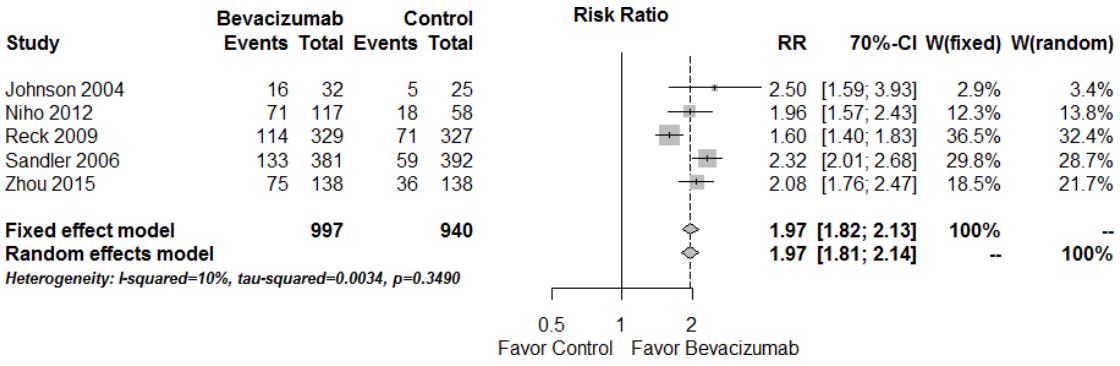
9.1 Determination of Sample Size

The expected ORR used for this study is based on the ORR calculated from our meta-analysis that includes a population of Western and Asian patients (with approximately 23% of Asian patients) with nsNSCLC cancer and unknown EGFR/ALK mutation status. Such an ORR is derived from the reported best ORR in the intent-to-treat (ITT) population or in the subgroup of patients with measurable disease. Although enrolling a higher rate of Asian patients, which would yield an ORR of about 45%, we expect the ORR in our study to be approximately 40% since we will exclude patients with known EGFR mutation or ALK receptor alteration (conferring slightly higher, non-statistically significant, responsiveness) in regions where the targeted agents are available.[17]

To satisfy all regulatory agencies (CFDA, EMA, and US FDA), results will be presented using the risk ratio or the risk difference method to show equivalence.

Sample Size Justification Based on Risk Ratio

To satisfy the CFDA and US FDA, equivalence will be demonstrated using the risk ratio method. The net treatment effect of Avastin® as measured by the ratio of ORRs is 1.97 with a corresponding 70% CI of (1.81, 2.14). Preserving 52% net effect of Avastin®, the equivalence margin will be set to 1.33 on the ratio of ORRs. Preserving 48% net effect of Avastin®, the equivalence margin will be set to 1.36 on the ratio of ORRs.



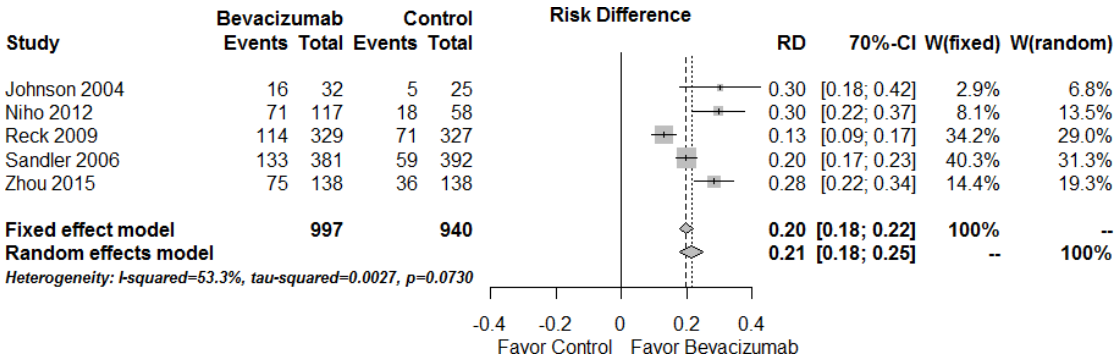
Abbreviations: CI = confidence interval; RR = risk ratio.

The null hypothesis is that either (1) BAT1706 is inferior to Avastin® or (2) BAT1706 is superior to Avastin® based on a pre-specified equivalence margin of (0.75, 1.33) for CFDA, and based on a pre-specified equivalence margin of (0.73, 1.36) for US FDA. The alternative hypothesis is that BAT1706 is equivalent to Avastin®, which can be demonstrated by showing

that the true treatment ratio is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. In other words, equivalence will be declared if the 2-sided 90% CI of the ratio of ORRs (BAT1706: Avastin®) is entirely contained within the equivalence margin of (0.75, 1.33) for CFDA, and within the equivalence margin of (0.73, 1.36) for US FDA. Based on these equivalence margins and reference effect size of 40%, 316 patients per arm (632 patients total) will achieve 80% power for CFDA, and will achieve 87% power for US FDA. The primary analysis will be based on the ITT population, and the supportive analysis will be based on the per-protocol (PP) population. With an expected ORR of 42% in the PP set, 83% power will be achieved with the equivalence margin of (0.75, 1.33), and 90% power will be achieved with the equivalence margin of (0.73, 1.36).

Sample Size Justification Based on Risk Difference

To satisfy the EMA, equivalence will be demonstrated using the risk difference method. The net treatment effect of Avastin® as measured by the difference between ORRs is 0.21 with 70% CI of (0.17, 0.26). Preserving 29% net effect of Avastin®, the equivalence margin will be set to (-0.12, +0.15) for the difference of ORRs.



Abbreviations: CI = confidence interval; RD = risk difference.

The null hypothesis is that either (1) BAT1706 is inferior to EU-Avastin® or (2) BAT1706 is superior to EU-Avastin® based on a pre-specified asymmetrical equivalence margin of (-0.12, 0.15). The alternative hypothesis is that BAT1706 is equivalent to EU-Avastin®, which can be demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. In other words, equivalence will be declared if the 2-sided 95% CI of the difference in the ORR between treatments (BAT1706 and EU-Avastin®) is entirely contained within the equivalence margin of (-0.12, 0.15).

Based on that margin and a reference effect size of 40% at Week 18, 316 patients per arm (632 patients total) will achieve 85% power and 2-side control type I error within 5%. The primary analysis will be based on the ITT population, and the supportive analysis will be based

on the PP population. With an expected ORR of 42% in the PP set, 84% power will be achieved.

9.2 Statistical Methods

Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using number, mean, standard deviation, median, minimum, and maximum values. Time to event endpoints will be analyzed using Cox proportional hazards models stratified according to the randomization stratification factors. Hazard ratios for the comparison of the 2 treatment arms and corresponding 95% CIs will be reported.

Generally, the baseline value to be used in any change from baseline, listings/summaries/graphical presentations or as a covariate in a statistical analysis is defined as the latest available pre-randomization value. If necessary, detailed baseline definitions of specific parameters or assessments will be defined in the Statistical Analysis Plan (SAP).

9.2.1 Data to be Analyzed

Data handling will be the responsibility of IQVIA. The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the SAP prepared by IQVIA and approved by the Sponsor before database lock. The statistical analysis will be performed by IQVIA.

9.2.2 Analysis Populations

The efficacy analyses will be applied for both the PP and ITT population.

Intention-to-Treat (ITT) Population

The ITT population will consist of all randomized patients in accordance with the intended treatment arm, regardless of the treatment actually received. For the primary efficacy analysis of the ITT population, patients who discontinued prior to Week 18 for any reason will be counted as non-responders.

Per-protocol (PP) Population

The PP population is defined as patients who have received at least 3 cycles of study drugs as allocated (BAT1706 or EU-Avastin® and paclitaxel/carboplatin) or less due to early progression, death, or excessive toxicity and have one tumor assessment with no major

protocol deviations that would have significantly impact on primary efficacy or safety outcomes.

All decisions to exclude patients from PP population will be made prior to database release. For the PP efficacy analysis, patients for whom the efficacy endpoint is missing, ie, patients without at least 1 valid post treatment evaluation, are excluded from the PP population, except those who are withdrawn due to excessive toxicity, early progression or death, in which case the patients will be classified as non-responders. It is anticipated that approximately 10% of patients in the ITT population will be excluded from the PP Population.

Safety Population

The safety population will consist of all randomized patients who received at least one dose of study drug (BAT1706 or EU-Avastin®) and allocated into actual-received treatment arm. The safety population will be used as the basis for all safety analyses.

Pharmacokinetic (PK) Population

Pharmacokinetic population is a subgroup of 200 patients from samples collected only at designated sites in China, Turkey, and Ukraine who receive at least one dose of study drug, have at least one measured concentration at a scheduled post-dose PK time point, and have no major protocol deviations that may significantly affect the PK assessment. The PK and popPK analysis will be performed on the PK population.

9.2.3 Missing Data

For the primary efficacy analysis as well as all analyses of responder/survivor proportion endpoints performed on ITT and PP population, patients who do not provide data for the responder/survivor endpoint will be considered non-responders/censor, ie, assigned to the less favorable outcome for the endpoint. Sensitivity analyses to assess the robustness of conclusions to missing data will be carried out if there are more than 5% of patients missing evaluations in either treatment arm. Sensitivity analyses will include an analysis that assumes that outcomes are missing at random. Details of the method for dealing with missing data and of the implementation of the sensitivity analyses will be described in the SAP.

9.2.4 Data Pooling

This is a multi-center study and centers may be pooled together in a country/region level for subgroup or center effect analysis in an exploratory manner if applicable.

9.3 Subject Disposition and Characteristics

Patient disposition will be summarized for patients in ITT population. The total number of patients for each defined analysis population will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the ITT population. Study drug and study duration will be summarized using descriptive statistics for the safety population.

9.4 Efficacy Analyses

9.4.1 Primary Efficacy Analyses

The primary efficacy endpoint is ORR_{18} based on tumor response at Week 18 evaluated according to RECIST 1.1 (Appendix 13.4) as assessed by CIR.

The primary efficacy analyses aim to demonstrate the equivalence between BAT1706 and EU-Avastin® arms. The null hypothesis tested for the primary efficacy analyses is that either (1) BAT1706 is inferior to EU-Avastin® or (2) BAT1706 is superior to EU-Avastin® based on a pre-defined equivalence margin.

For the CFDA and US FDA, to demonstrate equivalence between the 2 treatment groups, the ratio of ORRs will be used. The ratio of ORR_{18} will be calculated. Equivalence will be declared if the 90% CI of the ratio of the ORR_{18} between treatments (BAT1706:EU-Avastin®) is entirely contained within the equivalence margin of (0.75, 1.33) to comply with CFDA requirements, and within the equivalence margin of (0.73, 1.36) to comply with US FDA requirements. For the EMA, the difference between ORR_{18} will be calculated. Equivalence will be declared if the 95% CI of the difference of ORR_{18} between treatments is entirely contained within the asymmetrical equivalence margin of (-0.12, 0.15).

The 2-sided 90% CI of risk ratio or 95% CI of risk difference will be estimated including covariates of stratification factors: NSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and Ethnicity (Asian or non-Asian), for the ITT population as primary analyses and for the PP population as supportive analyses.

The multivariate-adjusted risk ratio and the 90% CI will be estimated by the log-binomial regression model including stratification factors. When the log-binomial model fails to converge, the Poisson regression with robust error variance will be used.

The multivariate-adjusted risk difference and the 95% CI will be estimated by the binomial regression model including stratification factors. If this binomial model for the risk difference fails to converge, the modified Poisson approach can be used as above.

The primary efficacy analyses will take place after all patients have been evaluated for response at Week 18.

9.4.2 Secondary Efficacy Analyses

The secondary efficacy endpoints include ORR_6, ORR_{12}, best ORR of confirmed responses at end of study, DoR, PFS rate at 12 months, PFS time, OS rate at 12 months, and OS time.

The secondary binary efficacy endpoints will be summarized descriptively and analyzed similarly to the primary efficacy endpoint. For time to event variables such as PFS, OS, and DoR, Kaplan-Meier curves will be calculated and displayed. Median survival times and the corresponding 95% CI will be provided. The estimated hazard ratio with 95% CI will be obtained from Cox regression model. The secondary analyses will be conducted based on up to 12-month exposure. A complementary report for safety and survival data will be made 2 years after LPI.

9.4.3 Subgroup Analyses

The primary endpoint and secondary endpoints will be also analyzed in subgroups breaking down by, but not limited to, country/region/demographic, dose of paclitaxel and carboplatin, or stratification factors: Stage (IV or other), gender and ethnicity (Asian or non-Asian). In each subgroup, the analysis will be carried out using the same type of methodology as described for corresponding endpoint. These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. For subgroups without an adequate number of patients, the analysis may not be performed. One additional exploratory analysis to assess the effect of paclitaxel dose differences and carboplatin dose differences on the primary endpoint will be conducted by fitting a logistic regression model of ORR_{18} with independent factors including paclitaxel dose (200 vs 175 mg/m^2), carboplatin dose (AUC 6 vs 5 mg/mLminute), treatment group, and ethnicity (Asian vs non-Asian). Odds ratios and 95% confidence intervals will be presented. Another exploratory analysis to assess the effect of reduced dose of paclitaxel and carboplatin on the primary endpoint will be conducted by a logistic regression model of ORR_{18} with independent factors including paclitaxel dose (>80% vs ≤80% of initial dose at cycle 6), carboplatin dose (AUC >80% vs ≤80% of initial dose at cycle 6), treatment group, and ethnicity (Asian vs non-Asian).

9.5 Safety

The safety population will be applied for all safety analyses.

9.5.1 Adverse Events

Treatment-emergent AEs are AEs that occur, having been absent before the first dose of study drug, or have worsened in severity after the initiating the study drug. Treatment-emergent AEs will be coded using MedDRA version 19.0 and assigned grades based on NCI-CTCAE version 4.03 dated 14 Jun 2010. The number and percentage of patients reporting TEAEs will be tabulated by the worst CTCAE grade, System Organ Class, and Preferred Term as well as the relationship to study drug. Similarly, the number and percentage of patients reporting interested TEAEs (please refer to Section 6.2.1), treatment-emergent SAEs, and TEAEs leading to discontinuation of study treatments will be summarized by CTCAE grade and relationship to study drug.

9.5.2 Clinical Laboratory Evaluations

Descriptive statistics will be provided for both laboratory assessment value and change from baseline by scheduled visits.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE version 4.03, if applicable. A shift table, presenting the frequency tabulation for baseline and the worst post treatment value according to the NCI-CTCAE grade or clinical judgment, will be provided for each clinical laboratory tests.

Abnormal clinical laboratory results deemed of clinical significance or of Grade 3 or 4 will be listed and reported as AEs.

Viral serology and immunodeficiency virus test will be presented in patient characteristics summary table.

9.5.3 Vital Signs Measurements, Physical Findings and Other Safety Evaluations

Descriptive statistics will be provided for vital sign and electrocardiogram parameters by scheduled visits. Physical examination data will be listed.

9.6 Immunogenicity Analyses

The safety population will be used for the immunogenicity analyses associated with number and percentage of patients with positive ADA/NADA will be summarized. The PK population will be used for correlation between serum level of ADA/NADA and bevacizumab exposure; results will be presented by scatter plot as well as Pearson/Spearman correlation coefficient.

9.7 Pharmacokinetic Analyses

The PK and popPK analyses will be explored in a subgroup of 200 patients, from samples collected only at designated sites in China, Turkey, and Ukraine.

The PK analyses will be performed on the PK population. Serum bevacizumab concentrations will be listed and summarized by treatment using appropriate descriptive statistics. Graphical presentations of concentration-time data by treatment will be provided, as appropriate. Additional population PK modeling and/or correlation between bevacizumab exposure and response (safety, immunogenicity and/or efficacy) data may be evaluated separately, as appropriate. If performed, a separate analysis plan will be prepared and results will be reported separately from the clinical study report.

10.0 ETHICS

10.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will provide the Sponsor or Sponsor designee with documentation of IRB/IEC approval of the protocol and informed consent before the clinical study may begin at the study centers. The Investigator should submit the written approval to Sponsor or representative before enrollment of any patient into the study.

Sponsor or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or IQVIA of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the clinical study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the clinical study, the Investigator will provide the IEC with a brief report of the outcome of the clinical study, if required.

10.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the clinical study will be conducted.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human patients. The study will be conducted in compliance with GCP and the applicable national regulations to assure that the rights, safety and well-being of the participating study patients are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient will be entered into the clinical study. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the clinical study, and that the patient is free to withdraw from the clinical study at any time. Written consent must be given by the patient and/or legal representative, after the receipt of detailed information on the clinical study.

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. The Investigator will provide each patient with a copy of the signed and dated consent form.

10.4 Subject Data Protection

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the Investigator, the Investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between the Sponsor/Contract Research Organization and the institution/Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between the institution/Investigator and the Sponsor or Sponsor designee.

11.0 STUDY ADMINISTRATION

11.1 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the clinical study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

No records should be disposed of without the written approval of the Sponsor.

11.2 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient randomized into the clinical study.

The Investigator will allow the Sponsor, IQVIA, and authorized regulatory authorities to have direct access to all documents pertaining to the clinical study, including individual patient medical records, as appropriate.

11.3 Investigator Information

11.3.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997); the US CFR Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

11.3.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 13.1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the clinical study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

11.3.3 Publication Policy

The data generated by this clinical study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Study Agreement.

11.4 Financing and Insurance

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this clinical study. The terms of the insurance will be kept in the study files.

12.0 REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15;127(12):2893-917.

2. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012 Mar;13(3):239-46.

3. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013 Jun 20;368(25):2385-94.

4. Avastin® Summary of Product Characteristics (European Union). Roche Registration Limited. 14 January 2015.

5. Avastin® Package Insert (United States). Genentech, Inc. May 2015.

6. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-50.

7. Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol. 2002 Mar 1;20(5):1335-43.

8. Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol. 2011 Oct 1; 29(28):3825-31.

9. Investigator's Brochure: BAT1706: Proposed Biosimilar to Avastin® (Bevacizumab). Edition 01 dated 28 October 2015.

10. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004 Jun 1;22(11):2184-91.

11. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol. 2009 Mar 10;27(8):1227-34.

12. Niho S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer. 2012 Jun;76(3):362-7.

13. Zhou C, Wu YL, Chen G, Liu X, Zhu Y, Lu S, et al. BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2015 Jul 1;33(19):2197-204.

14. Taxol® (paclitaxel) Injection (Patient Information Included): Package Insert. Bristol-Myers Squibb Company.

15. Paraplatin® (carboplatin aqueous solution) Injection: Package Insert. Bristol-Myers Squibb Company.

16. Physician Prescribing Information of Paraplatin Injection. Bristol-Myers Squibb Company.

17. Liang WH, Zhang YX, Kang SY, Pan H, Shao WL, Deng QH, et al. Impact of EGFR mutation status on tumor response and progression free survival after first-line chemotherapy in patients with advanced non-small-cell lung cancer: a meta-analysis. J Thorac Dis. 2014 Sep; 6(9): 1239–1250.

13.0 APPENDICES

13.1 Signature of Investigator

PROTOCOL TITLE: A Multicenter, Randomized, Double-blind, Phase III Study of BAT1706 versus EU-Avastin® plus Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer

PROTOCOL NO: BAT1706-003-CR

This protocol is a confidential communication of Bio-Thera Solutions, Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Bio-Thera Solutions, Ltd.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to Bio-Thera Solutions, Ltd/ IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name of Center: _____

_____

_____

13.2 Estimated Blood Sample Volumes per Patient

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening Period	Infection screen	5
	Hematology	2
	Serum chemistry	5
	Coagulation	3
	Serum Pregnancy Test (if applicable)	2
	Approximate Total	*17*
Treatment Period		
Cycle 1	Hematology	2 ×2
	Serum Chemistry	5
	Coagulation	3
	ADA/NADA	6 ×2
	PK (if applicable)	4 ×5
	Approximate Total	*44*
Cycles 2, 4	Hematology	2 ×2
	Serum Chemistry	5
	Coagulation	3
	PK (if applicable)	4
	Approximate Total for each cycle	*16*
Cycles 3, 5	Hematology	2 ×2
	Serum Chemistry	5
	Coagulation	3
	ADA/NADA	6
	PK (if applicable)	4
	Approximate Total for each cycle	*22*
Cycle 6	Hematology	2 ×2
	Serum Chemistry	5
	Coagulation	3
	ADA/NADA	6
	PK (if applicable)	4 ×5
	Approximate Total for each cycle	*38*
Cycles 7, 10, 13, 16	Hematology	2
	Serum Chemistry	5
	Coagulation	3
	ADA/NADA	6
	PK **(if applicable)**	4
	Approximate Total for each cycle	*20*
Cycles 8, 9, 11, 12, 14, 15, 17	Hematology	2
	Serum Chemistry	5
	Coagulation	3

	Approximate Total for each cycle	*10*
End of Treatment Visit/ Safety Follow up Visit	Hematology	2
	Serum Chemistry	5
	Coagulation	3
	Serum Pregnancy Test (if applicable)	2
	ADA/NADA (if applicable)	6
	PK (if applicable)	4
	Approximate Total	*22*
LTE Study (if applicable)	Hematology	2
	Serum Chemistry	5
	Coagulation	3
	Serum Pregnancy Test (if applicable)	2
	ADA/NADA (if applicable)	6
	Approximate Total	*18*

Abbreviations: ADA = anti-drug antibody; LTE = long-term extension; NADA = neutralizing anti-drug antibody; PK = pharmacokinetic(s).

13.3 Eastern Cooperative Oncology Group (ECOG) — Performance Status Scale

Classification	Criteria
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work (Karnofsky 70-80)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair (Karnofsky 10-20)

13.4 Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria In Solid Tumors)

INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Guidelines for the BAT1706-003-CR study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this trial.

DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study.

Measurable disease is defined by the presence of at least one measurable lesion which has not been irradiated within 12 weeks prior to the date of randomization.

Measurable:

- For tumor lesions: the longest diameter in the plane of measurement has to be recorded with a minimum size of 10 mm by CT scan when CT scan slice thickness is no greater than 5 mm or by magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.
- For nodal lesions: at baseline and in the follow-up, only the short axis of lymph node will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed at baseline.

Non-measurable:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis at baseline). Nodes with < 10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTL).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Measurable previously irradiated lesions where other measurable lesions are available for assessment as target lesions and lesions irradiated within 12 weeks of randomization.

- Skin lesions assessed by clinical examination.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the BAT1706-003-CR study, CT or MRI examinations of the chest and abdomen, including adrenals, will be used to assess tumor burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI with contrast (Gadolinium) should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination

In the BAT1706-003-CR study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI

scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray

Chest X-ray

In the BAT1706-003-CR study, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

In the BAT1706-003-CR study, plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the BAT1706-003-CR study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is patientive and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the BAT1706-003-CR study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

In the BAT1706-003-CR study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology

In the BAT1706-003-CR study, histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (PD) (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of

clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the BAT1706-003-CR study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

Fludeoxyglucose-Positron emission tomography scan

In the BAT1706-003-CR study, fludeoxyglucose (FDG)-positron emission tomography (PET) scans may be used as a method for identifying new lesions if a baseline FDG-PET scan is done, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. Only combined PET/CT with full diagnostic CT part can be used. A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

TUMOR RESPONSE EVALUATION

Refer to Table 1 Schedule of Events on the tumor assessment time point.

Target lesions (TL)

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then the sum of the diameters of those parts should be recorded.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, an estimate of the size of the lesion should be provided.
- When a TL has had any intervention eg, radiotherapy, embolization, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL.

Complete Response (CR) Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm.

Partial Response (PR) At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.

Stable Disease (SD) Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD) At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Not Evaluable (NE) Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a target lesion response.

Non-Target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Complete Response (CR) Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non CR/Non PD Persistence of one or more NTL.

Progression (PD) Unequivocal progression of existing NTL. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

Not Evaluable (NE) Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.

To achieve ‘unequivocal progression’ on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in the table below.

Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Target lesions	Non-target lesions	New lesions	Overall response

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; NA = not applicable (only relevant if there were no target lesions/non-target lesions at baseline).

CENTRAL REVIEW

Radiological examinations performed in the conduct of this study for RECIST response assessments must be retained at the study site as source data and a copy anonymized for personal identifiers eg, name, initials, be available for collection by the Sponsor for centralized review if required.

13.5 PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History

Document	Date	Substantial	Region
Amendment 4	20-Jun-2019	Yes	Global
Amendment 3	08-Feb-2019	No	Global
Amendment 2	19-Sep-2018	Yes	Global
Amendment 1	26-Feb-2018	Yes	Global
Original Protocol	23-Mar-2017	-	-

Amendment [4] (20 June 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Requested by FDA Advise/Information Letter for IND #138278 dated 25 March 2019:

- To delete the phrase "with the 2-sided control type I error within 10%" on page 79 of the protocol because the comparative evaluation of overall response rates for BAT1706 and EU-Avastin® will be based on whether the 90% CI of the risk ratio falls entirely between the predetermined similarity margins.
- To revise the following statement, "The main conclusion shall be driven from both the ITT and per-protocol (PP) analysis sets," to be consistent with the statement, "The 2-sided 90% CI of risk ratio or 95% CI of risk difference will be estimated for the ITT population as primary analyses and for the PP population as supportive analyses." The primary analysis should be based on the ITT population, which includes all randomized patients.
- To specify that the stratification factors to be used in the primary analysis will be based on the stratification variables for randomization as recorded in the IWRS.

List of Main Changes in Amendment:

Protocol text:

- Section 9.1: "with the 2-sided control type I error within 10%" is deleted.

- Section 9.1: The statement “The main conclusion shall be driven from both the ITT and per-protocol (PP) analysis sets,” is replaced with the statement “The primary analysis will be based on the ITT population and the supportive analysis will be based on the per-protocol (PP) population.”

- Section 9.4.1: The stratification factors are added in the primary analysis and it is updated to “The 2-sided 90% CI of risk ratio or 95% CI of risk difference will be estimated including covariates of stratification factors: NSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and Ethnicity (Asian or non-Asian), for the ITT population as primary analyses and for the PP population as supportive analyses.”

In addition, minor corrections of typographical errors and inconsistencies have been made. Such changes are not listed in this protocol amendment summary.