Clinical Study Protocol

A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin® in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer

Product	SB8 (proposed bevacizumab biosimilar)	
EudraCT Number	2015-004026-34	
US IND Number (if applicable)	NA	
Protocol Number	SB8-G31-NSCLC	
Study Phase	Phase III	
Version and Effective Date	Amendment 2.0	Aug 18, 2016
	Amendment 1.0	Dec 17, 2015
Sponsor	Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea	

SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.		
Name of Finished Product:	SB8 (proposed bevacizumab biosimilar)		
Name of Active Ingredient:	Bevacizumab		
Title of Study: A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin® in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer			
Protocol No:	SB8-G31-NSCLC	**Phase:**	III
Indication: Metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)			

Objectives:

Primary Objective:

The primary objective is to demonstrate the equivalence of SB8 to Avastin®, in terms of the best overall response rate (ORR) by 24 weeks of chemotherapy in subjects with metastatic or recurrent non-squamous NSCLC.

Secondary Objectives:

The secondary objectives are:

- To evaluate the efficacy of SB8 compared to Avastin® by
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Duration of response (DOR)
- To evaluate the safety and tolerability of SB8 compared to Avastin®
- To evaluate the pharmacokinetics of SB8 compared to Avastin®
- To evaluate the immunogenicity of SB8 compared to Avastin®

Exploratory Objective:

The exploratory objective is:

- To evaluate the best ORR by 11 and 17 weeks

Study Design:

This is a Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of SB8 compared to Avastin®. Subjects with metastatic or recurrent non-squamous NSCLC without known activating epidermal growth factor receptor (EGFR) gene mutations or anaplastic lymphoma

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kinase (ALK) gene translocations will be randomised in a 1:1 ratio, stratified by age (< 70 and ≥ 70) and gender to receive either SB8 or Avastin® (administered intravenously 15 mg/kg every 3 weeks) concurrently with chemotherapy (for at least 4 cycles and up to 6 cycles of paclitaxel 200 mg/m^2 plus carboplatin AUC 6 every 3 weeks). Subjects will undergo radiographic assessment of disease status (computed tomography [CT] or magnetic resonance imaging [MRI]) according to the Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST v1.1) after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every four cycles until there is radiographic documentation of progressive disease (PD), unacceptable toxicity, death, or end of study, whichever occurs first. If subjects show response to treatment, defined as complete response (CR)/partial response (PR)/stable disease (SD) after completion of the induction treatment period of combination chemotherapy with SB8 or Avastin®, they will receive SB8 or Avastin® maintenance therapy as per randomisation until disease progression, unacceptable toxicity, death, or end of study (EOS). Adverse Event (AE) information will be collected until end of treatment (EOT) visit (at least 21 days after last IP administration and prior to subsequent therapy).

Approximately 50% of the enrolled subjects will have blood samples collected for PK analysis of SB8 or Avastin®, at pre-dose and post-dose of Cycle 1, 3, 5, and 7.

All randomised subjects will be evaluated for ADA against SB8 or Avastin® at Baseline (pre-dose of Cycle 1) and during treatment (pre-dose of Cycle 3, 5, and 7) and EOT visit.

Number of Subjects:

A total of approximately 678 subjects (339 per treatment group) will be enrolled into this study.

Target Population:

Subjects with metastatic or recurrent non-squamous NSCLC without known activating EGFR gene mutations or ALK gene translocations

Eligibility Criteria:

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Aged ≥ 18 years (if local regulations are different in this regard, follow the local regulations).
2. ECOG performance status of 0-1 at Screening.
3. Histologically and/or cytologically confirmed metastatic (AJCC 7th edition TNM stage IV) or recurrent non-squamous NSCLC or NSCLC-not otherwise specified (NOS).
4. At least one measurable lesion according to RECIST v1.1.
5. Adequate haematological function at Screening defined as the following:

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a. Absolute neutrophil count (ANC) ≥ 1,500/mm^3 (≥ 1.5 × 10^9/L).

b. Platelet count ≥ 100,000/mm^3 (≥ 100 × 10^9/L).

c. Haemoglobin ≥ 9 g/dL (without transfusion within 14 days prior to Randomisation).

6. Adequate hepatic function at Screening defined as the following:

   a. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (in cases of known Gilbert's syndrome ≤ 3 × ULN).

   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 × ULN (in case of liver metastases < 5 × ULN).

   c. Alkaline phosphatase (ALP) < 3 × ULN (in case of liver metastases < 5 × ULN).

7. Adequate renal function at Screening defined as the following:

   a. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CCr) measured or calculated according to Cockcroft-Gault formula ≥ 50 mL/min.

   b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion should be < 1 g or protein/creatinine ratio in spot urine should be < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).

8. Subjects and their partners of childbearing potential (female or male) including those with history of elective sterilisation (e.g. fallopian tube ligation) who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 6 months after the last administration of investigational product (IP). A pregnancy test result is required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. True abstinence will be considered sufficient for subjects who do not have a partner.

9. Subjects must be able to provide informed consent, which must be obtained prior to any study related procedures.

Exclusion criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. For mixed tumour with the component of squamous cell carcinoma, it should be categorised according to predominant histology. Any component of small cell carcinoma of the lung is to be excluded.

2. Known activating mutations in EGFR gene or transforming re-arrangements of ALK gene.

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3. Radiological or clinical evidence of tumour invasion into blood vessels or close to large vessels that may have risk of bleeding at the discretion of Investigator.
4. History of systemic anti-cancer therapy administered in the first-line setting for metastatic or recurrent disease of NSCLC.
5. Any systemic anti-cancer therapy including neoadjuvant or adjuvant chemotherapy administered for NSCLC and completed less than 12 months prior to Randomisation.
6. Previously treated with a monoclonal antibody and/or molecule targeting VEGFR-related and/or EGFR-related signalling pathways.
7. Radiotherapy within 14 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered as measurable lesion unless there has been demonstrated progression in the lesion.).
8. Major surgical procedure within 28 days prior to Randomisation (e.g., requiring more extensive procedure than local anaesthesia [involving general anaesthesia or respiratory assistance or regional anaesthesia] or open lung biopsy) or expected major surgical procedure during the study.
9. Minor surgical procedure within 7 days prior to Randomisation (e.g., requiring local anaesthesia or following procedures: mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle biopsy [EBUS & TBNA], pleural biopsy, thoracentesis, pleurodesis, catheter insertions/removal, tooth extraction, superficial incision.
10. Subject with non-healing wound.
11. Symptomatic brain metastasis and/or leptomeningeal disease. Baseline brain imaging is strongly recommended to evaluate for presence of brain metastases. If brain metastases are found, they can be treated according to local practice at the discretion of investigator. Treatment options for brain metastases may include whole brain radiation, radiosurgery, craniotomy, etc. as deemed medically appropriate by the investigator. Subjects should have no neurologic symptoms off corticosteroids for at least 1 day to ensure that subjects do not have symptomatic brain metastasis. If subjects initially developed symptomatic brain metastases that resolved after treatment, they could be considered ‘asymptomatic’ and eligible for the study if they have no residual neurological dysfunction off corticosteroids for at least 1 day.
12. Previous malignancy other than NSCLC in the last 5 years except for locally curable cancers that have been in complete remission and need no subsequent therapy, such as basal or squamous cell cancer of the skin, carcinoma in situ of the cervix or breast, or superficial bladder cancer.
13. Life expectancy is less than 3 months.

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14. Evidence of clinically significant haemorrhagic diathesis or underlying coagulopathy.
15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [≥ 75 mg/day], regular use of aspirin, dipyridamole, ticlopidine and/or cilostazol); anticoagulant therapy within 28 days prior to Randomisation (e.g., with warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitor, and thrombolytic agent including tissue plasminogen activator, anistreplase, streptokinase, urokinase).
16. History of active gastroduodenal ulcer within 3 months prior to Randomisation.
17. Uncontrolled hypertension (blood pressure: systolic > 150 mmHg and/or diastolic > 100 mmHg) despite antihypertensive therapy or hypertensive crisis or hypertensive encephalopathy.
18. Any of the following events within 6 months prior to Screening:
    a. Myocardial infarction or unstable angina.
    b. Pulmonary embolism.
    c. History of congestive heart failure (CHF) (New York Heart Association, NYHA, Class ≥ II).
    d. Coronary/peripheral artery bypass graft surgery.
    e. Stroke or transient ischemic attack.
    f. Deep vein thrombosis.
    g. Abdominal fistulae as well as non-GI fistulae, GI perforation and/or fistulae, GI-vaginal fistulae, or intra-abdominal abscess.
    h. Gastrointestinal bleeding, haematemesis or haemoptysis (≥ 1/2 teaspoon of red blood) or any other major bleeding events.
19. Symptomatic peripheral sensory, motor, autonomic neuropathy NCI-CTCAE v4.03 grade ≥ 2 and/or ototoxicity grade ≥ 2, except if due to trauma or mechanical impairment.
20. Serologically confirmed active or chronic hepatitis B or hepatitis C (asymptomatic inactive carriers are allowed at investigator's discretion per local standards).
21. Acquired immunodeficiency syndrome or known seropositivity for human immunodeficiency virus (HIV).
22. Live/attenuated vaccine within 12 weeks prior to Randomisation (killed/inactivated or recombinant vaccine is allowed.).
23. Known allergy or hypersensitivity to any of the treatment components.

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24. Risk of osteonecrosis of jaw (ONJ) (e.g., treated with intravenous bisphosphonates and/or invasive dental procedures within 28 days prior to Randomisation).
25. Uncontrolled malignant pleural effusion (e.g., recurrent despite drainage or sclerosing agents).
26. Pregnancy or lactation period.
27. Subjects unwilling to follow the study requirements.
28. Inappropriate other medical conditions for the study at the discretion of Investigator.
29. Currently enrolled in another interventional clinical study.
30. Previous administration of other investigational product(s) within 28 days prior to Randomisation.

Planned Study Period:

Recruitment is expected to last approximately 2 years. Treatment will be given to randomised subjects until disease progression, unacceptable toxicity, death, or 12 months from Randomisation of the last subject, whichever occurs first. Subjects will be followed for survival status and whether subsequent systemic anti-cancer therapy is received or not by clinic visit or telephone contact every 3 months until withdrawal of consent or death or 12 months from Randomisation of the last subject.

Investigational Products:

- Name: SB8 (proposed bevacizumab biosimilar) or EU sourced Avastin®
- Route of administration: intravenous (IV) infusion
- Dose: 15 mg/kg every 3 weeks, the initial dose should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Non-investigational Products:

- Paclitaxel 200 mg/m^2 IV infusion over 3 hours every 3 weeks on Day 1 for at least 4 cycles and up to 6 cycles in the absence of disease progression or unacceptable toxicity
- Carboplatin AUC 6 IV infusion over 30 minutes every 3 weeks on Day 1 for at least 4 cycles and up to 6 cycles in the absence of disease progression or unacceptable toxicity

Main Criteria for Evaluation

Primary endpoint

- The best ORR by 24 weeks of chemotherapy (best ORR is defined as the proportion of subjects whose best overall response is either complete response [CR] or partial response

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[PR] according to RECIST v1.1)

Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles according to RECIST v1.1 and tumour size will be assessed by both Investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review.

Secondary endpoints

The secondary efficacy endpoints are:

- Progression free survival (PFS), defined as the time from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of EOT visit or the last tumour assessment date if the date of EOT is not available.
- Overall survival (OS), defined as the time from the date of Randomisation to the date of death regardless of the cause of death. Subjects who are alive at the time of analysis will be censored at the date of last known alive.
- Duration of response (DOR), defined as the time from documented tumour response (complete or partial) until documented disease progression. Only the subjects who achieve an initial tumour response will be evaluated for DOR.

Safety endpoint is:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)

Safety of subjects will be monitored by physical examination, ECOG performance status and vital sign assessment. Biochemical and haematological laboratory parameters will also be measured.

AEs will be collected and classified according to NCI-CTCAE v4.03.

The pharmacokinetic endpoints are:

- C_{trough} at pre-dose of Cycle 1, 3, 5, and 7
- C_{max} at post-dose of Cycle 1, 3, 5, and 7

Blood sampling for PK will be collected in approximately 50% of the enrolled subjects.

The immunogenicity endpoint is:

- Incidence of anti-drug antibodies (ADAs) at pre-dose of Cycle 1, 3, 5, 7, and at the EOT visit (at least 21 days after last IP administration and prior to subsequent therapy)

Exploratory endpoint is:

- Best ORR by 11and 17 weeks

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Statistical Methods

Analysis set

Randomised set (RAN) will consist of all subjects who receive a randomisation number at the Randomisation.

Full analysis set (FAS) will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to by intention-to-treat principle. However, subjects who do not qualify for randomisation and are inadvertently randomised into the study will be excluded from FAS, provided these subjects do not receive any IP during the study.

Per-protocol set (PPS) will consists of all FAS subjects who complete at least two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. Major protocol deviations that will lead to exclusion from the PPS will be pre-specified, and PPS will be determined prior to unblinding the treatment codes.

Safety set (SAF) will consist of all subjects who received the study drug at least once. This analysis set will be used for the safety analyses. The subjects will be analysed based on the actual treatment they received.

PK population will consist of subjects allocated to PK sub-study who have at least one measurable serum concentration of bevacizumab.

Efficacy analysis

For US FDA or other regulatory agency submissions for those who are in favour of risk ratio, the primary efficacy analysis for demonstrating the equivalence of SB8 to Avastin® will be done for the ratio of the best ORR (best ORR of SB8/best ORR of Avastin®) by 24 weeks in the FAS. The equivalence will be declared if the two-sided 90% confidence interval (CI) of the best ORR ratio is contained within the pre-defined equivalence margin of [0.737, 1.357]. The similar analysis will be performed for the PPS to support the primary efficacy result.

For EMA, MFDS or other regulatory agency submissions for those who are in favour of risk difference, the primary efficacy analysis will be performed for the difference of the best ORR (best ORR of SB8 – best ORR of Avastin®) by 24 weeks between SB8 and Avastin® in the PPS, and the equivalence will be declared if the two-sided 95% CI of the best ORR difference is contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The similar analysis will be performed for the FAS to support the primary efficacy result.

Safety analyses

All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the grade of severity will be reported by NCI-CTCAE v4.03. AEs will be summarised descriptively by treatment group. Changes in vital signs and clinical laboratory measurements will be summarised descriptively by treatment group. All other safety variables will be summarised

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descriptively by treatment group.

Pharmacokinetic analyses

The PK blood samples will be collected in approximately 50% of the enrolled subjects. The PK parameters will be summarised descriptively by treatment group at selected cycles.

Immunogenicity analyses

Incidence of ADAs will be summarised by treatment group and cycle and listed by treatment group.

Sample size calculation

Regarding the calculation of the equivalence margin for the ratio of the best ORR by 24 weeks, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered.

The overall ratio of the best ORR and its 70% CI from above four studies are calculated to be CCI [redacted] using the fixed effect method from meta-analysis. Retaining the CCI [redacted]% of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks.

For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] will be used due to the similar derivation.

With 305 completers in each treatment group, the two-sided 90% CI of the best ORR ratio is expected to lie within [0.737, 1.357] with approximately 80% power, and the two-sided 95% CI of the best ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected best ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.

FLOWCHARTS

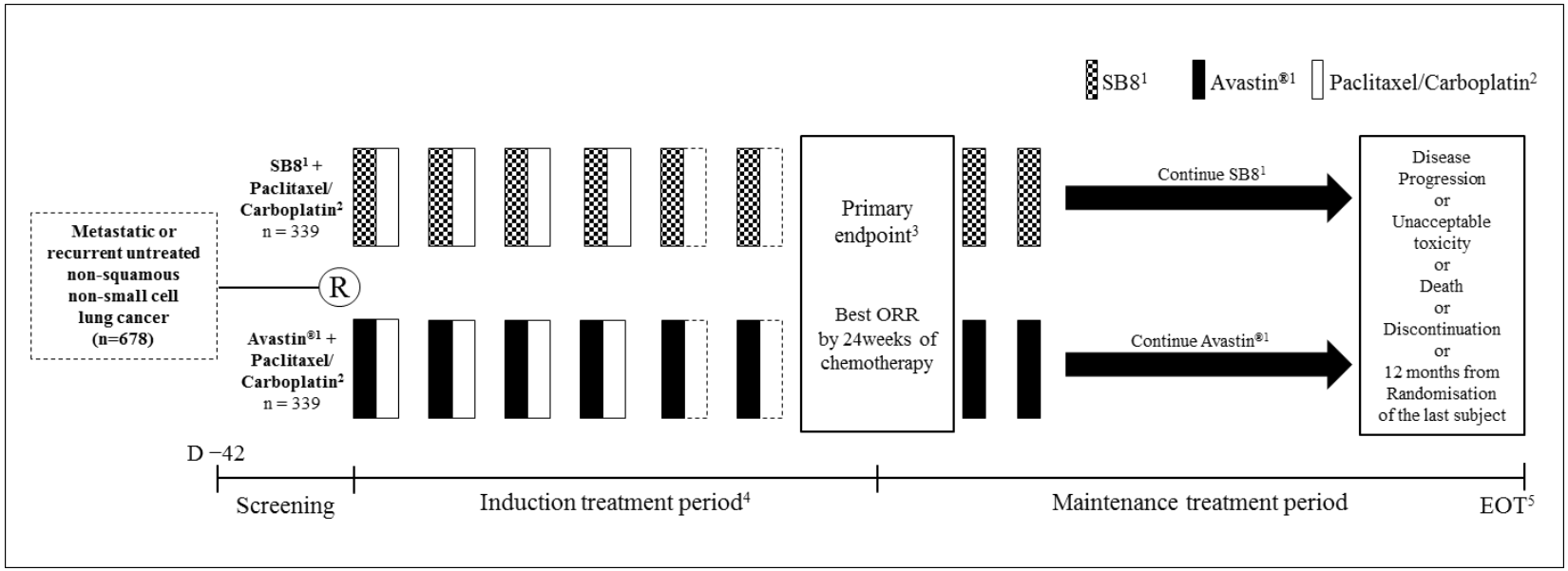

Figure 1. Graphical Study Design

® = Randomisation; ORR = overall response rate; EOT = end of treatment

[1]SB8 or Avastin® 15 mg/kg IV infusion every 3 weeks on Day 1.

[2]Paclitaxel 200 mg/m^2 IV infusion over 3 hours every 3-week on Day 1 for at least 4 cycles and up to 6 cycles.
Carboplatin AUC 6 IV infusion over 30 minutes every 3-week on Day 1 for at least 4 cycles and up to 6 cycles.

[3]Primary endpoint is the best ORR by 24 weeks of chemotherapy with SB8 or Avastin®.

[4]Physical examination, vital sign, ECOG performance status, reviewing the laboratory values including haematology, biochemistry, urinalysis, and reviewing IP compliance will be performed at each cycle. Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles since cycle 6 until disease progression or death or end of study. Tumour response will be assessed using CT or MRI following Image Acquisition Guideline that will be provided by Sponsor.

[5]EOT is defined as discontinuation of treatment due to disease progression, unacceptable toxicity, death, or last administration of IP before end of study. EOT visit will be performed at least 21 days after last IP administration and prior to subsequent therapy. Subjects will be followed for survival status and whether subsequent systemic anti-cancer therapy is received or not by clinic visit or telephone contact every 3 months from EOT until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up or initiation of subsequent therapy for NSCLC) or EOS date, defined as when deaths of all the randomised subjects have been observed, or 12 months from Randomisation of the last subject, whichever occurs first.

Table 1. Schedule of Activities

Assessments	**Screening**	**Induction Treatment Period[22]**						**Maintenance Treatment Period[24]**			**EOT[25]**	**F/U[26]**
Cycle		**1**	**2**	**3**	**4**	**5[23]**	**6[23]**	**7**	**Every cycle since Cycle 6**	**Every 4 cycles since Cycle 6**		**Every 3 months**
Day of Cycle	**Within 42 days prior to Randomisation**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Visit window (days)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**
Informed consent[1]	✓											
Demographic information[2]	✓											
Medical history[3]	✓											
Physical examination including height (Screening visit only) and weight[4]	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
Vital signs[5]	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
ECOG status	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
Haematology[6]	✓	✓[10]	✓	✓	✓	✓	✓	✓	✓		✓	
Coagulation test[7]	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)		(✓)	
Biochemistry[8]	✓	✓[10]	✓	✓	✓	✓	✓	✓	✓		✓	
Urinalysis[9]	✓	✓[10]	✓	✓	✓	✓	✓	✓	✓		✓	
Serology (HBV/HCV infection test)[11]	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)		(✓)	
Pregnancy test (serum or urine)[12]	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)		✓	
12-lead ECG	✓										✓	
Tumour assessment[13]	✓		✓		✓		✓			✓		
Randomisation		✓[14]										
SB8 or Avastin®[16]		✓[15]	✓	✓	✓	✓	✓	✓	✓			
Paclitaxel/Carboplatin[17]		✓[15]	✓	✓	✓	✓	✓					
Blood sample for immunogenicity[18]		✓		✓		✓		✓			✓	
Blood sample for PK[19]		✓		✓		✓		✓				
Concomitant and previous medication[20]	✓	Continuously										(✓)

Assessments	**Screening**	**Induction Treatment Period[22]**						**Maintenance Treatment Period[24]**			**EOT[25]**	**F/U[26]**
Cycle		**1**	**2**	**3**	**4**	**5[23]**	**6[23]**	**7**	**Every cycle since Cycle 6**	**Every 4 cycles since Cycle 6**		**Every 3 months**
Day of Cycle	**Within 42 days prior to Randomisation**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
Visit window (days)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 7**
AEs and SAEs[21]	✓	Continuously										(✓)
Survival status		Continuously										✓

AEs = adverse events; ECG = electrocardiogram; EOT = end of treatment; ECOG = eastern cooperative oncology group; F/U = follow-up; PK = pharmacokinetics; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SAEs = serious adverse events

1. Written informed consent must be obtained before any study related assessments.
2. Demographic data includes the date of birth, gender, race and ethnicity.
3. Medical history and major surgical procedures including malignancy other than NSCLC and those medical conditions described in the exclusion criteria, in the last 5 years.
4. Complete physical examination for Screening visit, including height and weight; abbreviated physical examination including weight at subsequent visit. Physical examination should be performed pre-dose on dosing days.
5. Vital signs include blood pressure, pulse rate, and body temperature. If a vital sign result is outside the expected range for the subject's age, gender and race, then it should be repeated after 5 minutes' rest.
6. Blood sampling for haematology and biochemistry should be collected at pre-dose within 3 days prior to the administration of IPs of each cycle. Haematology tests include haemoglobin, platelet count, WBC including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).
7. Blood coagulation test, international normalised ratio (INR) will be performed at Screening. Additional blood coagulation test will be performed at the discretion of Investigator if there are any suspicious cases.
8. Biochemistry tests include creatinine, urea (blood urea nitrogen [BUN]), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), albumin, and electrolytes (sodium, potassium, chloride).
9. If urine dipstick is ≥ 2+ (other ways of urinalysis are also acceptable), 24 hours urine protein excretion is < 1 g or protein/creatinine ratio in spot urine is < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).
10. Haematology, biochemistry and urinalysis need to be completed within 28 days prior to randomisation. They may not need to be repeated on Day 1 of Cycle 1 if the tests have been performed within 14 days prior to administration of IPs.
11. Hepatitis B and hepatitis C tests should be performed during Screening period according to local practice. Known history of HIV infection will be confirmed separately at the discretion of Investigator. Additional HBV/HCV tests will be performed at the discretion of Investigator if there are any suspicious cases.
12. For all women with reproductive potential including women who had menopause onset within 2 years prior to Randomisation, serum or urine pregnancy test must be performed within 2 weeks prior to Randomisation. A serum or urine pregnancy test should be performed at EOT visit. Additional pregnancy test will be performed at the discretion of Investigator if there are any suspicious cases.
13. Tumour assessments should be performed at Screening (within a maximum of 21 days prior to Randomisation) and after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles until disease progression, unacceptable toxicity, death, or end of study. If tumour assessment was already performed according to the schedule but next IP administration needs to be delayed due to any reasons, tumour assessment does not need to be repeated. At least one measurable lesion should be confirmed prior to Randomisation. If the baseline tumour assessment was not performed within 21 days prior to Randomisation, it should be repeated. Tumour response will be assessed using CT or MRI following Image Acquisition Guideline that will be provided by Sponsor. The same modality used at Screening will be used throughout the study.

14. All screening procedures must be completed and reviewed within 42 days prior to randomisation. All eligibility criteria must be reviewed and confirmed prior to Randomisation.
15. The first dose of IP and non-IPs should be administered within 7 days after Randomisation.
16. SB8 or Avastin® will be administered via IV infusion before paclitaxel and carboplatin at a dose of 15 mg/kg every 3 weeks for at least 4 cycles and up to 6 cycles, and then SB8 or Avastin® maintenance monotherapy will be administered at a dose of 15 mg/kg every 3 weeks until disease progression, unacceptable toxicity, death, or end of study.
17. Paclitaxel 200 mg/m^2 and carboplatin AUC 6 will be administered as an IV infusion on Day 1 of each cycle every 3 weeks for at least 4 cycles and up to 6 cycles. Subjects will also receive the pre-medications (e.g., steroids and anti-emetics) and adequate hydration on dosing days.
18. Blood sampling for immunogenicity will be performed in all randomised subjects. Blood sampling for immunogenicity will be taken at pre-dose on Day 1 of Cycle 1, 3, 5, and 7, and at the EOT visit (at least 21 days after last IP administration and prior to subsequent therapy). If the administration of IPs is delayed for any reasons after pre-dose blood sampling for immunogenicity, blood sampling for immunogenicity does not need to be repeated in delayed visit for the treatment.
19. Blood sampling for PK analysis will be performed at pre-dose and post-dose of IP (within 15 minutes after the end of infusion) of Cycle 1, 3, 5, and 7 in approximately 50% of the enrolled subjects. If the administration of IPs is delayed for any reasons after pre-dose blood sampling for PK is collected, pre-dose blood sampling for PK does not need to be repeated in delayed visit for the treatment, however, post-dose blood sampling for PK analysis should be performed within 15 minutes after the end of infusion. In all cases, the exact date and time of PK sampling and administration of IP must be carefully recorded in the source documentation to ensure the data are usable.
20. Concomitant and previous (within 28 days prior to Screening) medications will be recorded at Screening and concomitant medications are to be monitored continuously during the study treatment and after EOT visit, if such information is related to SAEs.
21. All AEs will be reported in the eCRF from the time when the informed consent form is signed until the EOT visit (progression of NSCLC and death due to progression of NSCLC are not to be reported as an AE or SAE). After the EOT visit, only SAEs will be reported using the paper SAE report form.
22. Subject will receive either SB8 or Avastin® concurrently with chemotherapy for at least 4 cycles and up to 6 cycles. After completion of the induction treatment period, maintenance treatment with IPs monotherapy will be a start.
23. Induction chemotherapy at Cycle 5 and 6 may be replaced with the maintenance therapy at the discretion of Investigator. In this case, all other activities except for non-IPs infusion must follow originally planned activities at each cycle.
24. SB8 or Avastin® maintenance monotherapy will be continued every 3 weeks until disease progression, unacceptable toxicity, death, withdrawal of consent, or end of study.
25. EOT is defined as discontinuation of treatment due to disease progression, unacceptable toxicity, death, consent withdrawal, or last administration of IP before end of study. EOT visit will be performed at least 21 days after last IP administration and prior to subsequent therapy.
26. Subjects will be followed for survival status and whether subsequent systemic anti-cancer therapy is received or not by clinic visit or telephone contact every 3 months from EOT until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up, or initiation of subsequent therapy for NSCLC) or EOS date, defined as when deaths of all the randomised subjects have been observed, or 12 months from randomisation of the last subject, whichever occurs first.

LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
AUC	Area Under the Curve
BSA	Body Surface Area
CCr	Creatinine Clearance
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum Concentration
CNS	Central Nervous System
CRO	Contract Research Organisation
CT	Computed Tomography
C_{trough}	Trough Concentration
CR	Complete Response
DOR	Duration of Response
DSMB	Data and Safety Monitoring Board

EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EPAR	European Public Assessment Reports
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GFR	Glomerular Filtration Rate
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board

IV	Intravenous
IWRS	Interactive Web Recognition System
MFDS	Ministry of Food and Drug Safety
MRI	Magnetic Resonance Imaging
NAb	Neutralising Antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NSCLC	Non-small Cell Lung Cancer
NSAID	Non-steroid Anti Inflammatory Drug
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PK	Pharmacokinetics
PPS	Per-protocol Set
PC	Paclitaxel/carboplatin
PR	Partial Response
PS	Performance Status
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAF	Safety Set

SAP	Statistical Analysis Plan
SD	Stable Disease
SLD	Sum of Longest Diameters of Target Lesions
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
US	United States of America
Vc	Volume Distribution of the Central
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell Count

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1. INTRODUCTION

1.1. Background

Lung cancer is the second most common cancer in men and the third most common in women, accounting for about 13% of cancer diagnoses, but it is the leading cause of cancer-related deaths in industrialised countries. In Europe 2012, estimated new cases of lung cancer are 410,000 and deaths from lung cancer are 353,000 [Ferlay, 2013]. The 5-year relative survival rate varies depending on the stage at diagnosis, from 22.9% to 2.8% for patients with local and distant stage disease, respectively [SEER Cancer Statistics, 1975-2009].

Approximately half of non-squamous non-small cell lung cancer (NSCLC) patients have advanced stage at diagnosis beyond curative resection [Jemal, 2009]. The median overall survival with metastatic NSCLC is only 4-5 months and survival rate at one year 10% with best supportive care [Rapp, 1988]. A meta-analysis has represented that combination chemotherapy leads to improvements of overall survival compared to best supportive care. Current combination chemotherapy showed a response rate of 19-32% and a median overall survival of 7.9 to 11.3 months [NSCLC Collaborative Group, 1995; Schiller, 2002].

The efficacy and safety of Avastin®, in combination to platinum-based chemotherapy, in the first-line treatment of patients with NSCLC, were investigated in studies E4599 [Sandler, 2006] and AVAiL (BO17704) [Reck, 2009]. E4599 study reported significantly improved overall survival (OS) and progression-free survival (PFS) with bevacizumab plus platinum-based chemotherapy versus chemotherapy alone (median OS 12.3 vs. 10.3 months [$p = 0.003$], median PFS 6.2 vs. 4.5months [$p < 0.001$]). AVAiL study has demonstrated significant PFS prolongation with bevacizumab compared with placebo. Adding bevacizumab for chemotherapy showed better treatment effect in non-squamous NSCLC.

Recently, a few tyrosine kinase inhibitors (TKI) demonstrated overwhelming benefit for subjects with epidermal growth factor receptor (EGFR) gene mutations and anaplastic lymphoma kinase (ALK) gene re-arrangements. In IPASS study, EGFR TKI has shown significantly prolonged PFS compared with standard chemotherapy (24.9% with gefitinib vs. 6.7% with paclitaxel-carboplatin in 12 months PFS rates) [Mok, 2009]. Another study of crizotinib versus chemotherapy in advanced ALK-positive lung cancer, the median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group [Shaw, 2013]. However, approximately 15% of patients with NSCLC in the United States and European Union have EGFR gene mutations and about 5% of patient with NSCLC have ALK gene re-arrangements. Also patients with unknown genetic alterations or with genetic alterations but who cannot receive TKI treatment for various reasons are generally treated with platinum-based chemotherapy as first-line chemotherapy.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has

been shown to benefit patients with a variety of cancers. There are studies that the addition of bevacizumab to platinum-based chemotherapy of patients with non-squamous NSCLC has a significant survival benefit. Considering the proper number of cycles of chemotherapy, no survival benefit was shown with administration of more than 4 cycles. Lately, in another study, all patients were given 4 cycles of chemotherapy followed by maintenance therapy with bevacizumab alone, OS was approximately 13.6 months. This result of OS is not inferior to that from another study with 6 cycles of chemotherapy [Patel, 2013].

Therefore, paclitaxel and carboplatin with bevacizumab for at least 4 and up to 6 cycles and then maintenance therapy with bevacizumab is one of rational options for non-squamous NSCLC.

1.2. Investigational Product: SB8

1.2.1. Overview of SB8

SB8 is under development as a similar biological medicinal product to Avastin® (bevacizumab, Roche Registration Ltd.). Avastin® is currently indicated for the treatment of patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, non-small cell lung cancer, advanced and/or metastatic renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, and carcinoma of the uterine cervix [Avastin® SmPC, 2015]. SB8 and Avastin® have identical primary structure and the active substance for both products is bevacizumab produced in a Chinese Hamster Ovary (CHO) mammalian cell line transformed by recombinant deoxyribonucleic acid (DNA) technology. Bevacizumab is a recombinant humanised monoclonal IgG1 antibody that selectively binds to and inhibits the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis.

SB8 was extensively characterised and compared to Avastin® using “state-of-the-art” methods. These studies were in accordance with the principles laid out in the comparability guidelines including the ‘Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (revision 1)’ [EMEA/CHMP/BWP/49348/2005]. The biosimilarity set of analytical methods is appropriately designed and covers the analysis of the primary structure, higher order structure, post-translational modifications, and bioassays. It was demonstrated that SB8 has similar structural and physicochemical characteristics with Avastin®.

SB8 is presented as a concentrate for infusion in a single-use vial containing either 100 mg of bevacizumab in 4 mL or 400 mg of bevacizumab in 16 mL. Both presentations of SB8 contain 25 mg/mL of bevacizumab and the concentration of the excipients is also identical between the 100 mg and 400 mg presentations. A 25 mg/mL solution of SB8 is a sterile, clear to slightly

opalescent, colourless to pale brown solution for intravenous (IV) infusion and preservative-free (pH 5.0).

1.2.2. Non-clinical Data of SB8

The summary of the data from non-clinical studies including repeated dose toxicity study in non-human primates is described in Investigator's brochure (IB).

As outlined in the 'Guideline on similar biological medicinal products containing monoclonal antibodies' [EMEA/CHMP/BMWP/42832/2005], a risk-based approach was taken to the non-clinical evaluation of SB8. A series of *in vitro* pharmacodynamics studies was performed in order to demonstrate comparability between SB8 and the reference product (Avastin®). In addition, *in vivo* non-clinical toxicology has been performed in cynomolgus monkeys with SB8 and Avastin®. Toxicokinetic and *in vivo* pharmacodynamics evaluation were also performed as a part of *in vivo* toxicity study.

1.2.3. Clinical Data of SB8

Based on the biosimilarity between SB8 and Avastin® demonstrated through extensive quality and non-clinical similarity exercises, a Phase I study was conducted in healthy male subjects to compare the PK, safety, tolerability and immunogenicity of SB8 to Avastin® and a Phase III study will be conducted in subjects with metastatic or recurrent non-squamous NSCLC to compare the efficacy, safety, PK, and immunogenicity of SB8 to Avastin®. Information on the safety of SB8 based on the product information of Avastin® is presented in the Investigator's Brochure (IB).

1.3. Comparator Drug: Avastin®

1.3.1. Clinical Pharmacokinetics of Avastin®

The PK of Avastin® has been studied in patients with solid tumours. Formal drug-drug interaction studies have not been performed with Avastin®.

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

Metabolism: assessment of bevacizumab metabolism in rabbits following a single IV dose of 125I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is

similar to endogenous IgG (i.e., primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver). Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

Elimination: the value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

1.3.2. Clinical Data of Avastin®

1.3.2.1. Avastin® in Non-small Cell Lung Cancer

Avastin® has clinical activity in patients with NSCLC in combination with chemotherapy. Two pivotal Phase III studies demonstrated that the combination of bevacizumab and chemotherapy significantly prolonged OS or PFS compared with chemotherapy alone in patients with locally advanced metastatic or recurrent NSCLC [Sandler, 2006; Reck, 2009]. Therefore, Avastin® is currently approved for use as combination in patients with NSCLC, with platinum-based chemotherapy for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.

Avastin® was investigated in 2 large multicentre, randomised studies in patients with locally advanced, metastatic or recurrent NSCLC.

E4599 Study [Sandler, 2006]

The E4599 study enrolled 878 patients with locally advanced (stage IIIb with malignant pleural effusion), metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0), both by IV infusion (PC) on Day 1 of every 3-week cycle for up to 6 cycles or PC in combination with Avastin® at a dose of 15 mg/kg IV infusion Day 1 of every 3-week cycle. After completion of six cycles of PC chemotherapy or upon premature discontinuation of chemotherapy, patients on the Avastin® + carboplatin + paclitaxel arm continued to receive Avastin® as a single agent every 3 weeks until disease progression.

The overall response rate was achieved 59 of 392 patients (15%) in the PC group and 133 of

381 patients (35%) in the Avastin® + PC group.

AVAiL study [Reck, 2009]

In this randomised, Phase III study, patients with locally advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy were randomly assigned to gemcitabine + cisplatin (GC) or Avastin® 7.5 mg/kg + GC, or Avastin® 15 mg/kg + GC. Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 IV infusion on Day 1 and gemcitabine 1250 mg/m^2 IV infusion on Days 1 and 8 of every 3-week cycle for up to 6 cycles (GC) with placebo or GC with Avastin® at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the Avastin® containing arms, patients could receive Avastin® as a single-agent every 3 weeks until disease progression or unacceptable toxicity.

The ORR was significantly higher in Avastin® plus GC (34.1% in the Avastin® 7.5 mg/kg + GC, 30.4% in the Avastin® 15 mg/kg + GC) than GC (20.1%).

1.4. Rationale for the Study

Bevacizumab is a vascular endothelial growth factor (VEGF)-specific angiogenesis inhibitor indicated for the treatment of non-squamous NSCLC. In 2006 in the US, it was approved for the first-line treatment of unresectable, locally advanced, recurrent or metastatic NSCLC in combination with paclitaxel and carboplatin [Avastin® Prescribing Information, 2015]. In 2007 in the EU, it was approved for first-line treatment of patients with metastatic, unresectable advanced or recurrent NSCLC other than predominantly squamous cell histology [Avastin® SmPC, 2015]. Two drug chemotherapy regimens which combine a platinum agent with paclitaxel, docetaxel, vinorelbine, irinotecan, and gemcitabine are usually accepted as standard of care for the treatment of advanced NSCLC. Up to date, there is no evidence that one platinum-based regimen was superior to another in term of efficacy [Schiller, 2002], indicating that determining the platinum compound is mainly based on health care professional's preference. In the community of thoracic oncology there is the perception that the best efficacy of anti-angiogenic agents may be achieved in combination with taxanes. In E4599 study, median OS and PFS was increased by 2 months and 1.7 months respectively when bevacizumab was added to first-line PC therapy compared with PC alone [Sandler, 2006]. In AVAiL study, median PFS was significantly increased (6.7 months vs. 6.1 months) in high dose bevacizumab group compared with placebo [Reck, 2009]. The purpose of this study is to evaluate the equivalence of clinical efficacy of Avastin® combined PC and SB8 combined PC in first-line treatment of non-squamous NSCLC.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to demonstrate the equivalence of SB8 to Avastin®, in terms of the best overall response rate (ORR) by 24 weeks of chemotherapy in subjects with metastatic or recurrent non-squamous NSCLC.

Best ORR is defined as the proportion of subjects whose best overall response is either complete response [CR] or partial response [PR] according to RECIST v1.1; tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles according to RECIST v1.1 and assessed by both Investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of SB8 compared to Avastin® by
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Duration of response (DOR)
- To evaluate the safety and tolerability of SB8 compared to Avastin®
- To evaluate the pharmacokinetics of SB8 compared to Avastin®
- To evaluate the immunogenicity of SB8 compared to Avastin®

2.3. Exploratory Objective

The exploratory objective is:

- To evaluate the best ORR by 11 and 17 weeks

3. STUDY DESIGN

3.1. Overview of Study Design

This is a Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of SB8 compared to Avastin®. Subjects with metastatic or recurrent non-squamous

NSCLC without known activating epidermal growth factor receptor (EGFR) gene mutations or anaplastic lymphoma kinase (ALK) gene translocations will be randomised in a 1:1 ratio, stratified by age (< 70 and ≥ 70) and gender to receive either SB8 or Avastin® (administered intravenously 15 mg/kg every 3 weeks) concurrently with chemotherapy (for at least 4 cycles and up to 6 cycles of paclitaxel 200 mg/m^2 plus carboplatin AUC 6 every 3 weeks). Subjects will undergo radiographic assessment of disease status (computed tomography [CT] or magnetic resonance imaging [MRI]) according to the Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST v1.1) after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles until there is radiographic documentation of progressive disease (PD), unacceptable toxicity, death, or end of study, whichever occurs first. If subjects show response to treatment, defined as complete response (CR)/partial response (PR)/stable disease (SD) after completion of the induction treatment period of combination chemotherapy with SB8 or Avastin®, they will receive SB8 or Avastin® maintenance therapy as per randomisation until disease progression or unacceptable toxicity or death, or end of study. Adverse Event (AE) information will be collected until end of treatment (EOT) visit (at least 21 days after last IP administration and prior to subsequent therapy).

Approximately 50% of the enrolled subjects will have blood samples collected for PK analysis at pre-dose and post-dose of Cycle 1, 3, 5, and 7.

All randomised subjects will be evaluated for ADA against SB8 or Avastin® at Baseline (pre-dose of Cycle 1) and during treatment (pre-dose of Cycle 3, 5, and 7) and EOT visit.

3.2. Rationale for Study Design

3.2.1. Rationale for Dose Selection of SB8 or Avastin®

The safety and efficacy of Avastin®, in addition to platinum-based chemotherapy, in the first-line treatment of patients with non-squamous NSCLC, was investigated in studies E4599 and AVAiL. In E4599 study, patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC 6), both by IV infusion (PC) on Day 1 of every 3-week cycle for up to 6 cycles or PC in combination with Avastin® at a dose of 15 mg/kg IV infusion Day 1 of every 3-week cycle. After six cycles of paclitaxel-carboplatin chemotherapy or upon premature discontinuation of chemotherapy, patients on the Avastin® + PC treatment group continued to receive Avastin® as a single agent every 3 weeks until disease progression. Median OS and PFS are 12.3 months and 6.4 months in the bevacizumab combined PC group, as compared with 10.3 months and 4.8 months in the PC group [Sandler, 2006]. In AVAiL study, patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 IV infusion on Day 1 and gemcitabine 1250 mg/m^2 IV infusion on Days 1 and 8 of every 3-week cycle for up to 6 cycles gemcitabine and cisplatin (GC) with placebo or GC with Avastin® at a dose of 7.5 or 15 mg/kg IV infusion Day 1 of every 3-week cycle. In the Avastin® containing treatment group, patients could receive Avastin® as a single-agent every 3 weeks until disease progression or

unacceptable toxicity. There are significant PFS prolongation, when bevacizumab group was compared with placebo group (placebo 6.1 months, Avastin® 7.5 mg/kg 6.7 months, Avastin® 15 mg/kg 6.5 months). However, OS was not significantly increased in bevacizumab for the 7.5 and 15 mg/kg group, respectively, versus placebo, possibly due to high use of efficacious second-line therapies [Reck, 2009].

3.2.2. Rationale for Selection of Chemotherapy Regimen

Over the past decade, a number of new agents have become available for the treatment of metastatic NSCLC, including the taxanes, gemcitabine, and vinorelbine. The combination of one or more of these agents with a platinum compound has resulted in high response rates and prolonged survival at one year in Phase II studies [Sandler, 1995; Abratt, 1995; Crino, 1995; Langer, 1995; Le Chevalier, 1995]. The improvements offered by cisplatin-based regimens, though significant in terms of survival and quality of life, were modest at best. Carboplatin, which possesses a toxicity profile favourable to that of its parent analogue cisplatin, yielded survival rates superior to that of the cisplatin-combination chemotherapy arms in a large randomised study of patients with metastatic NSCLC. With the introduction of taxanes in the early 1990s, paclitaxel demonstrated single-agent activity of 21% to 24%, with a 40% 1-year survival rate in metastatic disease. The next generation of Phase I/II studies evaluated the efficacy of paclitaxel in combination with carboplatin. Results with this regimen have shown substantial promise, and 1-year survival rates as high as 54% have been reported [Chandra, 1998]. Also, taxanes appears to be potent at inhibiting angiogenesis. Sweeney et al., demonstrated that docetaxel inhibited endothelial cell proliferation and tubule formation in vitro in a dose-dependent fashion [Sweeney, 2001].

3.2.3. Rationale for Pharmacokinetic Assessment

A randomised, three arm, parallel, single-dose comparative PK study was conducted in healthy male volunteers to demonstrate similarity in PK profiles of SB8 and EU sourced Avastin® and US sourced Avastin®. However, since target-mediated clearance of bevacizumab can be more accurately investigated in patients, additional PK assessments will be performed in this comparative efficacy study to provide supportive evidence to PK similarity.

3.2.4. Rationale for Immunogenicity Assessments

Immune responses may affect both safety and effectiveness such as altering PK, inducing anaphylaxis, or promoting development of neutralising antibodies (NAbs) that neutralise the product as well as its endogenous protein counterpart. For subject safety and for demonstrating biosimilarity, immunogenicity will be assessed in this study according to the recommended guideline.

3.3. Number of Subjects

Approximately 678 subjects (339 per treatment group) will be randomised in this study over a planned recruitment period of approximately 2 years.

4. STUDY POPULATION

4.1. Overview

The study population for this study is subjects with metastatic or recurrent non-squamous NSCLC.

4.2. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Aged ≥ 18 years (if local regulations are different in this regard, follow the local regulations).
2. ECOG performance status of 0-1 at Screening.
3. Histologically and/or cytologically confirmed metastatic (AJCC 7th edition TNM stage IV) or recurrent non-squamous NSCLC or NSCLC-not otherwise specified (NOS).
4. At least one measurable lesion according to RECIST v1.1.
5. Adequate haematological function at Screening defined as the following:
    a. Absolute neutrophil count (ANC) ≥ 1,500/mm^3 (≥ 1.5 × 10^9/L).
    b. Platelet count ≥ 100,000/mm^3 (≥ 100 × 10^9/L).
    c. Haemoglobin ≥ 9 g/dL (without transfusion within 14 days prior to Randomisation).
6. Adequate hepatic function at Screening defined as the following:
    a. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (in cases of known Gilbert's syndrome ≤ 3 × ULN).
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 × ULN (in case of liver metastases < 5 × ULN).
    c. Alkaline phosphatase (ALP) < 3 × ULN (in case of liver metastases < 5 × ULN).
7. Adequate renal function at Screening defined as the following:

a. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CCr) measured or calculated according to Cockcroft-Gault formula ≥ 50 mL/min.

b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion should be < 1 g or protein/creatinine ratio in spot urine should be < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).

8. Subjects and their partners of childbearing potential (female or male) including those with history of elective sterilisation (e.g., fallopian tube ligation) who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 6 months after the last administration of IP. A pregnancy test result is required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. True abstinence will be considered sufficient for subjects who do not have a partner.

9. Subjects must be able to provide informed consent, which must be obtained prior to any study related procedures.

4.3. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. For mixed tumour with the component of squamous cell carcinoma, it should be categorised according to predominant histology. Any component of small cell carcinoma of the lung is to be excluded.

2. Known activating mutations in EGFR gene or transforming re-arrangements of ALK gene.

3. Radiological or clinical evidence of tumour invasion into blood vessels or close to large vessels that may have risk of bleeding at the discretion of Investigator.

4. History of systemic anti-cancer therapy administered in the first-line setting for metastatic or recurrent disease of NSCLC.

5. Any systemic anti-cancer therapy including neoadjuvant or adjuvant chemotherapy administered for NSCLC and completed less than 12 months prior to Randomisation.

6. Previously treated with a monoclonal antibody and/or molecule targeting VEGFR-related and/or EGFR-related signalling pathways.

7. Radiotherapy within 14 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered as measurable lesion unless there has been demonstrated progression in the lesion.).

8. Major surgical procedure within 28 days prior to Randomisation (e.g., requiring more extensive procedure than local anaesthesia [involving general anaesthesia or respiratory assistance or regional anaesthesia] or open lung biopsy) or expected major surgical procedure during the study

9. Minor surgical procedure within 7 days prior to Randomisation (e.g., requiring local anaesthesia or following procedures; mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle biopsy [EBUS & TBNA], pleural biopsy, thoracentesis, pleurodesis, catheter insertions/removal, tooth extraction, superficial incision.

10. Subject with non-healing wound.

11. Symptomatic brain metastasis and/or leptomeningeal disease. Baseline brain imaging is strongly recommended to evaluate for presence of brain metastases. If brain metastases are found, they can be treated according to local practice at the discretion of investigator. Treatment options for brain metastases may include whole brain radiation, radiosurgery, craniotomy, etc. as deemed medically appropriate by the investigator. Subjects should have no neurologic symptoms off corticosteroids for at least 1 day to ensure that subjects do not have symptomatic brain metastasis. If subjects initially developed symptomatic brain metastases that resolved after treatment, they could be considered ‘asymptomatic’ and eligible for the study if they have no residual neurological dysfunction off corticosteroids for at least 1 day.

12. Previous malignancy other than NSCLC in the last 5 years except for locally curable cancers that have been in complete remission and need no subsequent therapy, such as basal or squamous cell cancer of the skin, carcinoma *in situ* of the cervix or breast, or superficial bladder cancer.

13. Life expectancy is less than 3 months.

14. Evidence of clinically significant haemorrhagic diathesis or underlying coagulopathy.

15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [≥ 75 mg/day], regular use of aspirin, dipyridamole, ticlopidine and/or cilostazol); anticoagulant therapy within 28 days prior to Randomisation (e.g., with warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitor, and thrombolytic agent including tissue plasminogen activator, anistreplase,

streptokinase, urokinase).

16. History of active gastroduodenal ulcer within 3 months prior to Randomisation.

17. Uncontrolled hypertension (blood pressure: systolic > 150 mmHg and/or diastolic > 100 mmHg) with antihypertensive therapy, or hypertensive crisis or hypertensive encephalopathy.

18. Any of the following events within 6 months prior to Screening:

    a. Myocardial infarction or unstable angina.

    b. Pulmonary embolism.

    c. History of congestive heart failure (CHF) (New York Heart Association, NYHA, Class ≥ II).

    d. Coronary/peripheral artery bypass graft surgery.

    e. Stroke or transient ischemic attack.

    f. Deep vein thrombosis.

    g. Abdominal fistulae as well as non GI fistulae, GI perforation and/or fistulae, GI-vaginal fistulae, or intra-abdominal abscess.

    h. Gastrointestinal bleeding and/or haematemesis or haemoptysis (≥ 1/2 teaspoon of red blood) or any other major bleeding events.

19. Symptomatic peripheral sensory, motor, autonomic neuropathy NCI-CTCAE v4.03 grade ≥ 2 and/or ototoxicity grade ≥ 2, except if due to trauma or mechanical impairment.

20. Serologically confirmed active or chronic Hepatitis B or Hepatitis C (asymptomatic inactive carriers are allowed at investigator's discretion per local standards)

21. Acquired immunodeficiency syndrome or known seropositivity for HIV.

22. Live/attenuated vaccine within 12 weeks prior to Randomisation (killed/inactivated or recombinant vaccine is allowed.).

23. Known allergy or hypersensitivity to any of the treatment components.

24. Risk of occurrence of osteonecrosis of jaw (ONJ) (e.g., treated with intravenous bisphosphonates and/or invasive dental procedures within 28 days prior to Randomisation).

25. Uncontrolled malignant pleural effusion (e.g., recurrent despite drainage or sclerosing

agents).

26. Pregnancy or lactation period.

27. Subjects unwilling to follow the study requirements.

28. Inappropriate other medical conditions for the study at the discretion of Investigator.

29. Currently enrolled in another interventional clinical study.

30. Previous administration of other investigational product(s) within 28 days prior to Randomisation.

4.4. Subject Withdrawal

Once randomised to study treatment, subjects may withdraw from the study or study specific procedures at any time. The subject must be discontinued from all study treatment (IPs and/or non-IPs) in the event of any of the following, but follow-up for safety information should be continued until death or EOT visit (see Sections 5.1.5. and 5.1.6.):

- Radiographic progression of disease at the discretion of Investigator
- Unequivocal clinical progression of disease at the discretion of Investigator (e.g., the occurrence of malignancy-associated disseminated intravascular coagulation, respiratory failure requiring ventilator care.)
- Death of any cause
- Unacceptable toxicity including AEs not manageable by symptomatic therapy or schedule modification or dose modification (see Section 6.4)
- AEs requiring permanent discontinuation of IP (see Section 6.4.2)
- Protocol deviations that may affect the subject's safety seriously if continued on treatment, agreed by the Investigator and the Sponsor
- Pregnancy
- Treatment delay of more than 3 weeks from the schedule, which is counted from the planned starting date of each cycle (i.e., 6 weeks from the last administration of IP)
- Lack of subject's compliance
- Consent withdrawal by subject

- Unblinding (except unblinding for the purpose of regulatory reporting)

If subjects withdraw consent, the Investigator must inquire the reason to determine if it is related to the study (e.g., documented lack of efficacy, AE or pregnancy). In such cases the reason for withdrawal must be recorded clearly and should not be classified as consent withdrawal. If the subject does not return for a scheduled visit, every effort should be made to contact the individual. Subject's decision to withdraw consent and discontinue the study procedure will not prejudice the future medical treatment in any way.

All the subjects who withdraw from the study will be asked to return to the Investigational site for the EOT visit procedures to be performed (see Section 5.1.5.) and to have a follow-up telephone contact or clinic visit. The subject must be reminded that clinical data which have been acquired so far will be kept in the study database for the sake of integrity of data, unless the subject expresses his/her willingness to remove all of his/her data from the study database.

5. STUDY PROCEDURES AND ASSESSMENT

5.1. Procedures by Study Period

5.1.1. Screening Period

Screening should be performed within 42 days before Randomisation. All subjects must provide written informed consent prior to any study related procedures being performed.

The following procedures and assessments should be performed within 42 days before Randomisation. Retesting or re-evaluation is allowed within the screening period, but the latest assessment will be used to determine the eligibility. Re-screening or re-consenting after 42 day screening period has elapsed is not allowed.

- Informed consent
- Demographic data
- Medical history and major surgical procedures (see Section 6.2.5.) including malignancy other than NSCLC and those medical conditions described in the exclusion criteria, in the last 5 years (see Section 4.3.).
- ECOG performance status (see APPENDIX 1)
- Physical examination including vital signs (blood pressure, pulse rate, and body temperature), height and weight
- Ongoing AEs from the acquisition of the informed consent

- Review of previous or concomitant medication (within 28 days prior to informed consent; within 12 weeks prior to informed consent in case of vaccines)

- Haematology, biochemistry, urinalysis, and serology (retesting is allowed during the Screening period). **Haematology, biochemistry and urinalysis need to be completed within 28 days before randomisation.**

  - Haematology: haemoglobin, WBC including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count.

  - Blood coagulation test: international normalised ratio (INR). If there is significant deviation in the value (i.e., INR > 1.5), it is highly recommended that the investigator determine the cause (i.e., warfarin – which would be excluded) and reversibility. If the Investigator determines that the subject is at a high risk of bleeding as a result of abnormal INR, subject should be excluded according to section 4.3 (exclusion criterion 14).

  - Biochemistry: serum creatinine, urea (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, albumin, sodium, potassium, chloride

  - Urinalysis (dipstick): leukocytes, nitrite, urobilinogen, protein, pH, Hb, specific gravity, ketone, bilirubin, glucose (other ways of urinalysis are also allowed), if urine dipstick is ≥ 2+, 24 hours urine protein excretion should be < 1 g or protein/creatinine ratio in spot urine should be < 1 g/g creatinine (or < 226.0 mg/mmol creatinine)

  - Serology: test for Hepatitis B and hepatitis C should be performed during Screening period according to local practice. Known history of HIV infection will be confirmed separately at the discretion of Investigator.

  - If other laboratory tests not listed above are checked by local practice and found to be abnormal, it is recommended that Investigator use the best clinical judgement to determine if the abnormal values would affect patient safety while participating in the study.

- Serum (or urine) pregnancy test for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation should be performed within 2 weeks prior to Randomisation. For all other women, documentation of the medical history confirming that the subject is not of childbearing potential must be required.

- 12-lead ECG

- Baseline tumour assessment (within a maximum 21 days prior to Randomisation) of lung and locoregional lymph nodes by CT scan or MRI. Upper abdominal cavity including the adrenal glands must be included in imaging study. If the baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. Baseline tumour assessment should be done after allowed surgical procedure to suspected target or non-target lesions (see Sections 4.3. and 5.2.1.). Tumour assessment before subject signed informed consent will be acceptable to use as baselines tumour assessment and may not be repeated if it is done within 21 days prior to Randomisation and performed according to Section 5.2.1.

- Additional CT scan, MRI, PET-scan, or bone scan will be performed at the discretion of Investigator (optional), if there are symptoms or clinical suspicion of distant metastasis.

5.1.2. Randomisation

If the subject signs the ICF, the Investigator should check the whole eligibility criteria of the subjects prior to Randomisation.

5.1.2.1. Randomisation Method

The randomisation numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and site personnel. A subject randomisation list will be produced by the interactive web response system (IWRS) provider using a validated system that automates the random assignment of subject numbers to randomisation numbers. These randomisation numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomisation list will be produced by or under the responsibility of the Sponsor using a validated system that automates the random assignment of medication numbers to medication packs containing each of the IPs.

5.1.2.2. Stratification Factors

Randomisation will be stratified by

- Age at randomisation: < 70 vs. ≥ 70

- Gender: male vs. female

5.1.3. Induction Treatment Period (Cycle 1 to Cycle 6)

The first dose of IPs should be administered within 7 days after Randomisation.

Induction treatment period consists of 4 to 6 cycles of a 3-week cycle. The Investigator may

determine the duration of induction chemotherapy according to tumour response and toxicity profiles of individual subject. The visit window allowed for each visit is ± 3 days.

All procedures and assessments must be performed within 3 days before the administration of IPs of each cycle, unless otherwise specified.

The following procedures and assessments will be performed at each subsequent scheduled visit.

- Physical examination including vital signs (blood pressure, pulse rate, and body temperature) and weight
- ECOG performance status
- Haematology, biochemistry, and urinalysis (if urine dipstick is ≥ 2+, see Section 7.3.2.) – Repeated laboratory tests may not be needed if tests have been performed within 14 days prior to Day 1 of Cycle 1.
- Blood coagulation test if clinically suspected
- Pregnancy test (serum or urine) if clinically suspected
- Serology: tests for HBV or HCV will be repeated during the course of the study only when clinically suspected.
- AEs assessment from previous cycles
- Review of concomitant medication
- Premedication of IP and/or Non-IPs (if necessary, see Section 6.6.1.)
- Administration of IP and non-IPs on Day 1 of each cycle for at least 4 cycles and up to 6 cycles

If a treatment is delayed, concerned laboratory tests will be repeated within 3 days before the administration of IPs of each cycle.

The other assessments will be performed at the following schedule:

- Imaging tumour assessment of target and non-target lesion by CT scan or MRI will be performed after IP administration of Cycle 2, 4, and 6 and before planned Day 1 of Cycle 3, 5, and 7 (upper abdominal cavity including the adrenal glands must be included in imaging study.). If tumour assessment was already performed according to the schedule but next IP administration needs to be delayed due to any reasons, tumour assessment does not need to be repeated.

- If progressive disease is suspected clinically, the Investigator may additionally perform tumour assessment during the induction treatment period.
- Blood sampling for PK (approximately 50% of enrolled subjects) at pre-dose and post-dose of IP (within 15 minutes after the end of infusion) of Cycle 1, 3, and 5
- Blood sampling for immunogenicity in all randomised subjects at pre-dose of Cycle 1, 3, and 5.

In case of early switch to maintenance treatment period, subject blood sampling will be collected as originally planned at Cycle 3 and/or 5, if applicable.

5.1.4. Maintenance Treatment Period

If subjects show response to treatment, defined as complete response (CR) or partial response (PR), or stable disease (SD) after completion of the induction treatment period of combination chemotherapy with SB8 or Avastin® (at least 4 cycles and up to 6 cycles), they will receive SB8 or Avastin® maintenance therapy as per randomisation until disease progression, unacceptable toxicity, death, or end of study. The visit window allowed for each visit is ± 3 days.

The following procedure and assessments will be performed within 3 days prior to Day 1 of each scheduled cycle, unless otherwise specified:

- Physical examination including vital signs (blood pressure, pulse rate, and body temperature) and weight
- ECOG performance status
- Haematology, biochemistry, and urinalysis (if urine dipstick is ≥ 2+, see Section 7.3.2.)
- Blood coagulation test if clinically suspected
- Pregnancy test (serum or urine) if clinically suspected
- Serology: tests for HBV or HCV will be repeated during the course of the study only when clinically suspected.
- AEs assessments
- Review of concomitant medication
- Administration of IP every 3 weeks on Day 1 of each cycle

If a treatment is delayed, concerned laboratory tests will be repeated within 3 days before the administration of IP of each cycle.

The other assessments will be performed at the following schedule:

- Tumour assessment will be performed every 4 cycles (prior to IP administration). Upper abdominal cavity including the adrenal glands must be included in imaging study.
- If progressive disease is suspected clinically, the Investigator may additionally perform tumour assessment during the maintenance treatment period.
- Blood sampling for PK (approximately 50% of enrolled subjects) at pre-dose and post-dose of IP (within 15 minutes after the end of infusion) of Cycle 3, 5, and 7.
- Blood sampling for immunogenicity at pre-dose of Cycle 3, 5, and 7.

5.1.5. End of Treatment (EOT)

EOT is defined as discontinuation of treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or last administration of IP before end of study. Other conditions that also meet definition of EOT are described in Section 4.4. The EOT visit will be performed at least 21 days after last IP administration and prior to subsequent therapy. In case of study withdrawal for any reasons, every effort should be made to follow the subject for EOT visit. The following procedures will be performed at EOT visit:

- 12-lead ECG
- Physical examination including vital sign (including blood pressure, pulse rate, and body temperature) and weight
- ECOG performance status
- Haematology, biochemistry, and urinalysis (if urine dipstick is ≥ 2+, see Section 7.3.2.)
- Blood coagulation test if clinically suspected
- AEs assessment
- Pregnancy (serum or urine) test (only for female subjects with childbearing potential)
- Review of concomitant medication
- Blood sampling for immunogenicity

5.1.6. Follow-up Period

Subjects will be followed for survival status and whether subsequent therapy is received or not

by clinic visit or telephone contact every 3 months (± 7 days) from EOT until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up or initiation of subsequent therapy for NSCLC) or EOS date, defined as when deaths of all the randomised subjects have been observed, or 12 months from Randomisation of the last subject, whichever occurs first.

SAEs will continue to be reported to Sponsor during the follow-up period. (See Section 7.2.2)

5.2. Efficacy Assessment

Tumour response will be assessed classified according to RECIST v1.1 criteria. Subject must have at least one radiographically measurable lesion in a previously non-irradiated area according to RECIST v1.1 to be eligible for randomisation in this study. All tumour measurements should be performed with the same method of assessment and made by the same Investigator/radiologist for each subject during the study to the extent that this is feasible. Based on the independent central review for tumour assessment, the imaging independent central reviewer will record their own assessments of each subject's imaging eligibility at baseline, best response, disease progression, and related variables. The primary efficacy analysis will be based on the data from the independent central review.

The primary endpoint is:

- The best ORR by 24 weeks of chemotherapy (best ORR is defined as the proportion of subjects whose best overall response is either complete response [CR] or partial response [PR] according to RECIST v1.1)

The secondary endpoints are:

- PFS, defined as the time from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of the EOT visit or the date of last tumour assessment if the EOT visit is not available.

- OS, defined as the time from the date of Randomisation to the date of death regardless of the cause of death. Subjects who are alive at the time of analysis will be censored at the date of last known alive.

- DOR, defined as the time from documented tumour response (complete or partial) until documented disease progression. Only the subjects who achieve an initial tumour response will be evaluated for DOR.

The exploratory endpoint is:

- Best ORR by 11 and 17 weeks

5.2.1. Measurability of Tumour

At baseline, tumour lesion/lymph nodes will be categorised measurable or non-measurable. At least one measurable lesion should be confirmed for this study. Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- Measurable lesion 10 mm by CT/MRI scan (CT scan slice thickness no greater than 5 mm)

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT/MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions are non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

5.2.1.1. Definition of Target and Non-target Lesions

During the baseline assessment before IP administrations, all lesions detected are classified as either target lesions or non-target lesions on CT/MRI scan.

- Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions total, representative of all involved organs should be identified as target lesions and recorded at baseline. Target lesions should be selected based on their size and their suitability for accurate repeated measurements by imagaing.

- Non-target lesions: All other lesions including small lesions and other non-measurable lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up.

For detailed instructions, please refer to Completion Guide for Tumour Assessment Worksheet.

5.2.1.2. Criteria for Tumour Response Evaluation

Evaluation of Measurable Lesions

Tumour response will be evaluated according to the RECIST v1.1 criteria. Subjects should

continue to undergo tumour response assessment until PD, unacceptable toxicity, death or end of study.

In this study, tumour response will be measured using CT scan or MRI (other methods such as X-ray or ultrasound are not permitted for monitoring target lesions) following Image Acquisition Guideline that will be provided by Sponsor. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during the study.

The use of oral and IV contrast, etc., is highly recommended and should be used consistently unless contraindication exists. Tumour evaluations should be made by the same Investigator or radiologist for each subject during the study, if possible.

Baseline total tumour burden must be assessed no more than 21 days prior to Randomisation. If the baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. Baseline tumour assessment will include the adrenal glands and the entire liver. In case of contrast contraindication, MRI or non-contrast CT scans can be performed. Additional PET-scan, or bone scan will be performed at the discretion of the Investigator (optional), if there are symptoms or clinical suspicion of distant metastasis.

Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

For baseline brain imaging, MRI with contrast is preferred but CT scan with IV contrast is acceptable if MRI cannot be obtained (Ex. pacemaker, unavailable MRI facility, etc.). If brain metastases are found but not treated (asymptomatic), they could be potentially listed as target and/or non-target lesions at discretion of investigators. However, **all target and/or non-target lesions should be followed using the same imaging modality throughout the study.**

If brain metastases are found and treated, those should be listed as “non-target” lesions for tumour response evaluation according to RECIST 1.1. If brain metastases are treated and patients are asymptomatic, follow-up brain imaging is not required unless clinically suspected.

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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. (Note: the appearance of one or more new lesions is also considered progression).

Table 2. Criteria for Response Evaluation

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD[a]	No	PR
CR	Not evaluated	No	PR
PR	Non-PD[a] or not all evaluated	No	PR
SD	Non-PD[a] or not all evaluated	No	SD
Not all evaluated	Non-PD[a]	No	inevaluable
PD	Any category	Yes or No	PD
Any category	PD[a]	Yes or No	PD
Any category	Any category	Yes	PD

[a] For non-target lesions, PD is defined as the unequivocal progression, as determined by the Investigator

Evaluation of Non-measurable Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively.

Complete Response (CR)

Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD

Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD)

Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more

new lesions is also considered progression).

5.2.2. Timing of Overall Response Rate Evaluation: All Time Points

The overall response is determined once all the data for the subject is known. For best response determination in the study, confirmation of complete or partial response is NOT required. Best response in this study is defined as the best response across all time points (e.g., a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR).

5.3. Safety Assessment

The safety endpoint is:

- Incidence of AEs and SAEs.

5.3.1. Clinical Safety Assessment

Safety of subjects will be monitored by physical examination, performance status and vital sign assessment. Subjects will be assessed for AEs at each clinical visit and as necessary throughout the study.

5.3.2. Laboratory Assessment

Haematology and biochemistry laboratory tests will be done as part of regular safety assessments.

- Haematology: haemoglobin, WBC including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count.
- A coagulation test (INR) will be performed at Screening and during the study if clinically suspected.
- Biochemistry: creatinine, urea (BUN), ALT, AST, ALP, total bilirubin, albumin, sodium, potassium, chloride
- Urinalysis (dipstick): leukocytes, nitrite, urobilinogen, protein, pH, Hb, specific gravity, ketone, bilirubin, glucose (other ways of urinalysis are also allowed.)
- Pregnancy test in women of childbearing potential (serum or urine)
- Tests for HBV or HCV will be repeated during the course of the study only when clinically suspected.

5.4. Other Assessments

5.4.1. Pharmacokinetic Assessments

Approximately 50% of the enrolled subjects will be participating by default in the PK sub-study for PK assessment and those subjects will be defined at the time of randomisation in the IWRS. Once the number of subjects is reached to the planned number, all further subjects enrolled will not participate in the PK sub-study.

Blood sampling for PK analysis will be performed at pre-dose and post-dose of IP (within 15 minutes after the end of infusion) of Cycle 1, 3, 5 and 7.

If the IP administration is delayed for any reasons after pre-dose blood samples for PK is collected, pre-dose blood sampling for PK analysis does not need to be repeated in delayed visit for the treatment, however, post-dose blood sampling for PK analysis should be performed within 15 minutes after the end of infusion.

In all cases, the exact date and time of the PK sampling and IP administration must be carefully recorded in the source documentation to ensure the data are usable.

Details of the sampling, handling, storage and shipping for PK samples are described in the Study Sample Handling and Logistics Manual.

5.4.2. Immunogenicity Assessments

The purpose of immunogenicity testing is to determine whether ADAs and NAbs against SB8 or Avastin® occur in similar rate and influence the safety or efficacy. Blood sampling for immunogenicity testing will be done as per visiting schedule in all subjects (see Table 1).

All randomised subjects will be evaluated for ADA against SB8 or Avastin® at Baseline (pre-dose of Cycle 1) and during treatment (pre-dose of Cycle 3, 5, and 7) and EOT visit. Details of sampling, handling, storage and shipping for immunogenicity samples are described in the Study Sample Handling and Logistics Manual.

6. TREATMENT AND INVESTIGATIONAL PRODUCT

6.1. Definition of Investigational Products and Non-investigational Products

Throughout the study, the IPs mean SB8 and Avastin®. Combination chemotherapy regimens in the induction treatment period are not regarded as IPs since they are considered as standard of care. In this study, carboplatin, and paclitaxel are named as non-IPs.

6.2. Administration of SB8 or Avastin®

6.2.1. Dose and Schedule of SB8 or Avastin®

SB8 or Avastin® will be administered every 3 weeks until disease progression, unacceptable toxicity occurs, death, or end of study. SB8 or Avastin® will be administered intravenously at a dose of 15 mg/kg. Body weight should be recorded at Screening and at every scheduled visit for all subjects.

6.2.2. Formulation, Packaging and Labelling

Bevacizumab is supplied for use as a concentrate for solution (100 mg or 400 mg per vial for SB8, EU sourced Avastin®).

Sponsor or the designated representative team will ensure that the test IP is characterised as appropriate and are manufactured in accordance with any Good Manufacturing Practice (GMP). All IPs will be labelled in accordance with EU, and local regulations and GMP.

6.2.3. Handling and Storage of SB8 or Avastin®

SB8 and Avastin® should be stored at 2-8°C. The temperature should be monitored. If continuous monitoring is not available then manual temperature logs should be generated and recorded to ensure proper storage conditions. If a temperature deviation occurred, responsible person should contact the Sponsor to determine if the drug is still appropriate for use. The IPs should be stored in a secure area and clearly labelled and stored away from other non-IPs or medication to prevent confusion (for example in a clearly marked box on a separate shelf of the refrigerator).

Do not freeze or do not shake SB8 or Avastin® vials. Store the vials within the outer carton to protect them from light. The IPs must not be used beyond the expiration date.

6.2.4. Preparation and Administration of SB8 or Avastin®

6.2.4.1. Preparation of SB8 or Avastin®

IPs should be prepared by a pharmacist or properly trained pharmacy delegate using aseptic technique to ensure the sterility of the prepared solution.

Prior to IP preparation, the dose amount will be calculated by the Investigator according to subject's body weight measured and documented at Baseline and every cycle. The dose calculation is as follows:

- Dose amount (mg) = actual body weight (kg) × 15 mg/kg

- Volume (mL) = $\frac{\text{dose amount (mg)}}{\text{concentration of bevacizumab (mg/mL)}}$

Necessary amount of IP will be withdrawn and diluted to a total volume of 100 mL of 0.9% sodium chloride injection. Detailed process will be described in the Pharmacy Manual.

If any quality issue is encountered, the IPs must not be prepared until the discrepancy has been completely resolved by checking the documentation with the Investigator.

After IP preparation is completed, the label with preparation time, subject identifier, dose amount, and total infusion volume to be given to a subject will be attached on the infusion bag.

6.2.4.2. Administration of SB8 or Avastin®

In the induction treatment period, SB8 or Avastin® will be administered intravenously before starting chemotherapy (paclitaxel and carboplatin) at a dose of 15 mg/kg every 3 weeks. In the maintenance treatment period, SB8 or Avastin® will be administered intravenously at a dose of 15 mg/kg every 3 weeks. The first infusion is given over 90 minutes. If the first dose is well tolerated, second infusions may be given over 60 minutes and subsequently administered over 30 minutes. Do not administer SB8 or Avastin® as an IV push or bolus. Investigators or designee should observe subjects during administration of IPs and for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing of the infusion may help to control infusion-related symptoms and may be resumed when symptoms abate. Subjects who experience infusion-related reactions may be premedicated with paracetamol and antihistamine for subsequent infusions. Subjects should be warned of the possibility of late onset reactions and should be instructed to contact their Investigator if these reactions occur. Dose reductions of SB8 or Avastin® for toxicity are not permitted. Schedule modifications are permitted as described in Section 6.4.2. A detailed guideline for IPs preparation, administration, storage and destruction will be provided in the Pharmacy Manual.

6.2.5. Prohibited Concomitant Medications or Therapies

All concomitant medication use should be recorded. Details to be recorded include: name (generic name preferred), dose number and unit, frequency of administration, route of administration, start and stop dates and the AE it relates to (if applicable).

Medication and therapies that are prohibited prior to Randomisation and/or throughout the study are presented in Table 3.

Table 3. Prohibited Medications and Therapies of NSCLC

Medication or therapies	Time to be prohibited
Anticoagulants or thrombolytic agents:	
Regular use of aspirin	Prior to Randomisation
Aspirin (≥325 mg daily)[a] **After randomisation, low dose aspirin (< 325mg daily) is allowed if medically indicated at the discretion of Investigator.*	From Randomisation to EOT
Antiplatelet agents such as Clopidogrel (≥ 75 mg/day), dipyridamole, ticlopidine and/or cilostazol[b]	Within 10 days prior to Randomisation to EOT
Warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitors, thrombolytic agents including tissue plasminogen activator, anistreplase, streptokinase, urokinase[c] **After randomisation, anticoagulation is allowed if medically indicated*	Within 28 days prior to Randomisation to EOT
Any drugs (include herbal medications) that has not received regulatory approval for any indications	From Randomisation to EOT
Anticancer systemic therapy other than paclitaxel/carboplatin/Avastin®/SB8[d]	From Randomisation to EOT
Major surgical procedure (include open lung biopsy)[e] **If a major surgical procedure is indicated after randomisation, treatment needs to be held for at least 28 days after surgery and subject needs to completely recover from surgery. The maximum allowed delay is 6 weeks from the last IP infusion.*	Within 28 days prior to Randomisation
Minor surgical procedure[f] **If a minor surgical procedure is indicated after randomisation, treatment needs to be held for at least 7 days after surgery and subject needs to completely recover from surgery. The maximum allowed delay is 6 weeks from the last IP infusion.*	Within 7 days prior to Randomisation
Live/attenuated vaccine	Within 12 weeks prior to Randomisation to Cycle 7 Day 1
Intravenous bisphosphonates and/or invasive dental procedure **Allowed after randomisation if determined by investigator as clinically necessary (ex. Bone metastases related to NSCLC or tooth abscess requiring extraction, etc.)*	Within 28 days prior to Randomisation
Radiotherapy[g]	Within 14 days prior to Randomisation to EOT

EOT = end of treatment; NSAIDs = non-steroidal anti-inflammatory drugs

Local anaesthesia is defined as anaesthesia of a small part of the body such as a tooth or an area of skin.

[a] After randomisation, low dose aspirin < 325mg daily is allowed if medically indicated (cardiac prophylaxis, etc.) and there is no bleeding diathesis that would increase the risk of therapy at the discretion of Investigator.

[b]Non-chronic use of NSAIDS (not including aspirin) for symptom management is permitted if there is no bleeding diathesis that would increase the risk of therapy at the discretion of Investigator.

[c]After randomisation, therapeutic anticoagulation (heparin, warfarin, etc.) is allowed if medically indicated in case of new thromboembolic events (i.e., deep venous thrombosis) at the discretion of Investigator. Refer to section 6.4.2 Table 4 for specific guidelines. Non-systemic use of anticoagulants (ex. heparin flush) to maintain patency of intravenous injection devices is allowed.

[d] Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study.
[e] Requiring more extensive procedure than local anaesthesia (involving general anaesthesia or respiratory assistance or regional anaesthesia) or open lung biopsy.
[f] Requiring local anaesthesia or following procedures; mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle aspiration (EBUS & TBNA), pleural biopsy, thoracentesis, pleurodesis, catheter insertion/removal, tooth extraction, superficial incision.
[g] Radiotherapy of palliative purpose to non-progressive non-target lesions is allowed during the treatment period. If target lesions are included in irradiated field, then those lesions should not be evaluated as measurable thereafter. It is strongly recommended that the Investigator consult to the Sponsor at the timing of planning radiotherapy. IP and non-IPs should be suspended during radiotherapy and may be resumed at the discretion of the Investigator.

6.2.6. Investigational Product Accountability

Information on drug disposition required by applicable regulation may consist of the date received, date administered, quantity administered, and the subject to whom the drug was administered. The Investigator is responsible for accounting all used/unused IP. The used IP vial should be disposed and/or destructed after use according to the local regulation. In case that the IP vial is disposed after use, the Investigator is responsible for accounting other materials of used IP such as IP container. The Investigator uses this information to maintain an accurate and complete dispensing and inventory record provided by the Sponsor.

IP supplies are shipped to the Investigator site as needed. The monitor will review drug accounting during routine monitoring visits with the documents containing relevant information provided by the Sponsor. At the completion or termination of the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated and their resolution documented.

All full containers of IP must be returned to the Sponsor/contract distribution centre with the appropriate form. The site and the site monitor are to contact the Sponsor for detailed information before return to the Sponsor is to take place.

Furthermore, due to the fact that the IP is a hazardous substance, and/or its shipment may cause harm to humans, available IP, in an opened vial, may be destroyed at the site with the Sponsor's permission. The site may destroy unused (e.g., left after the vial was opened and/or reconstituted) once accountability of the IP is completed. The IP destruction must be documented on the relevant records. The site may destroy the IP before the site monitoring visits with the Sponsor's agreement and the site monitors will perform the accountability and reconciliation from the records maintained at the site. The accountability, reconciliation, and return procedures also apply to all IPs that are required by the protocol and supplied by the Sponsor.

6.3. Administration of Induction Treatment Period Chemotherapy Regimens

Doses of chemotherapy will be calculated according to the subject's body surface area (BSA) or body weight. Weight and height should be recorded at Baseline and the BSA calculated,

thereafter all subjects should be re-weighted at every cycle. Actual body weights should be used in calculating dose at each cycle. For more information of chemotherapy drugs including contraindications, special warnings and precautions for use, fertility, pregnancy, and lactation, please refer to SmPC of individual drugs.

6.3.1. Paclitaxel

6.3.1.1. Preparation and Storage of Paclitaxel

Refer to the prescribing information in paclitaxel for the formulation, preparation, and storage of paclitaxel. Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study.

6.3.1.2. Dose and Schedule of Paclitaxel

Paclitaxel will be administered by 200 mg/m^2 every 3 weeks for at least 4 and up to 6 cycles during the induction treatment period. Actual body weights should be used in calculating BSA at each cycle. Paclitaxel will be administered as IV infusion over approximately 3 hours after the completion of SB8 or Avastin® administration. Dose and schedule modification for toxicity are permitted (see Section 6.4.).

6.3.2. Carboplatin

6.3.2.1. Preparation and Storage of Carboplatin

Refer to the prescribing information in carboplatin for the formulation, preparation, and storage of carboplatin.

6.3.2.2. Dose and Schedule of Carboplatin

Carboplatin will be administered by Calvert formula (AUC 6) every 3 weeks for at least 4 and up to 6 cycles during the induction treatment period. Carboplatin will be administered as IV infusion over approximately 30 minutes after the completion of paclitaxel. Dose modification and delays for toxicity are permitted (see Section 6.4.).

The Calvert formula incorporates creatinine clearance (CCr) to calculate the subject's carboplatin dose as following:

- Carboplatin dose (mg) = target AUC × (CCr + 25)

CCr must be calculated prior to every dosage of carboplatin using below formula (Cockcroft-Gault equation) and it should NOT exceed 125 ml/min:

Male:

$$\mathrm{CCr} = \frac{(140 - Age[y]) \times body\ weight\ [kg]}{72 \times serum\ creatinine[mg/dL]}$$

Female:

$$\mathrm{CCr}\ = \frac{(140 - Age[y]) \times body\ weight\ [kg]}{72 \times serum\ creatinine[mg/dL]} \times 0.85$$

6.4. Dose and Schedule Modification

6.4.1. General Considerations

Dose and schedule modifications of IPs or non-IPs should follow the guidelines laid out in the following sections. In the induction treatment period, the non-IPs (paclitaxel and carboplatin) and IPs (SB8 or Avastin®) should be administered at same day. Therefore, if a schedule modification for one drug (non-IPs or IPs) is needed, the other drug should be delayed in the same time frame. The allowed maximum delay of IPs or non-IPs administration is 3 weeks from the schedule, which is counted from the planned Day 1 of each cycle (i.e., 6 weeks from the last administration).

If non-IPs (paclitaxel and carboplatin) should be discontinued due to toxicity, the IPs (SB8 or Avastin®) alone can be administered at the discretion of Investigator.

Dose modification of the IPs is not permitted. Administration of the IPs should follow the guidelines as shown in Table 4.

The guidelines of dose and schedule modifications for common toxicities of non-IPs are described in Table 5 and Table 6. If toxicities which are not included in Table 6 occur, dose and schedule modifications should be determined at the discretion of Investigator based on the following general criteria (see also Section 6.4.2.):

1. Dose modifications must be based on the dose level changes in Table 5 and Table 6.
2. Dose modifications must be based on the AE requiring the greatest modification.
3. Once a dose reduction has occurred, the subject should not be re-escalated to higher doses.
4. For grade 3 or 4 toxicities in general, chemotherapy should be held for a maximum of 6 weeks from the last IP administration until resolution to baseline or ≤ grade 1.
5. Subjects may only be re-treated if all related toxicities have resolved to baseline or at the discretion of Investigator.
6. In the induction period, if a dose delay for one drug (IPs or non-IPs) is needed, the other drugs should be delayed in the same time frame.

6.4.2. Schedule Modification of SB8 or Avastin®

Administration of SB8 or Avastin® should follow the guideline as shown in Table 4.

In the induction period, administration of the IPs and non-IPs should be coupled and schedule modification of IPs and non-IPs should follow the same time frame. The allowed maximum delay of IP in this period is 3 weeks from the schedule, which is counted from the planned Day 1 of each cycle (i.e., 6 weeks from the last administration). For haematologic and non-haematologic AEs, the schedule modification of non-IP administration should follow the rules of dose modification (Table 5 and Table 6).

In the maintenance period, SB8 or Avastin® is allowed to be delayed within a maximum of 3 weeks from the schedule, which is counted from the planned Day 1 of each cycle (i.e., 6 weeks from the last administration). When grade 3 or 4 (excluding cardiac or AEs listed in Table 4) AEs are observed within a cycle, hold SB8 or Avastin® until AEs are resolved to ≤ grade 2. If toxicity (except haemoptysis) is not resolved to ≤ grade 2 within 6 weeks from the last IP administration, discontinuation of SB8 or Avastin® and withdrawal of subject from the study may be considered. Continuation of treatment can be decided at the discretion of Investigator if the benefits of continuation overweigh the risk of AE.

Table 4. Schedule modification of SB8 or Avastin®

Adverse Event	CTCAE Grade[a]	Action to be taken
Haemoptysis	1	• If no source was found, and the bleeding resolved within 1 week, reinitiate with the same dose. • If a source of bleeding was discovered, it will be treated according to current medical practice.
	≥2	• Discontinue
Hypertension	≥2	• Hold SB8 or Avastin® until recovery to resting BP of < 150/100 mmHg and then reinitiate with the same dose. Anti-hypertensive medications are allowed and recommended for blood pressure control at the discretion of Investigator.
	4	• Discontinue
Congestive heart failure (left ventricular systolic dysfunction)	3	• Hold until resolution to Grade ≤ 1
	4	• Discontinue
Proteinuria	≥2	• Hold SB8 or Avastin® until recovery to grade ≤ 1, and then reinitiate with the same dose.
Arterial thromboembolism (New onset or worsening CVAs, TIAs, MIs, etc.)	Any	• Discontinue

Adverse Event	CTCAE Grade[a]	Action to be taken
Venous thromboembolism	≤ 3	• Closely monitor. Anticoagulation (heparin, warfarin, etc.) is recommended and allowed per local practice at the discretion of Investigator and patients should not have any grade of pulmonary/CNS haemorrhage or grade ≥ 2 haemorrhagic event while on anticoagulation.
	4	• Discontinue
Increased AST or ALT	≥ 3	• Hold SB8 or Avastin® until recovery to grade ≤ 2, and then continue SB8 or Avastin®.
Other clinically significant AEs[b]	≥ 3	• Hold SB8 or Avastin® until recovery to grade ≤ 2, and then continue SB8 or Avastin®.

CVA=cerebrovascular accident; TIA=transient ischemic attack; MI=myocardial infarction; CNS=central nervous system; ALT= alanine aminotransferase; AST = aspartate aminotransferase; AE = adverse event
[a] NCI-CTCAE v4.03 will be used (see APPENDIX 3)
[b] Other clinically significant AEs will be determined at the discretion of Investigator

The investigator should discontinue administration of IP permanently and remove subjects from the study if experiencing one of the events specified below:

- Gastrointestinal perforations (gastrointestinal perforation, fistulae formation in the gastrointestinal tract, intra-abdominal abscess), fistulae formation involving an internal organ
- Wound dehiscence and wound healing complications requiring medical intervention
- Serious haemorrhage requiring medical intervention (grade ≥ 2)
- Arterial thromboembolic events (any grade)
- Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism
- Grade 4 hypertension (hypertensive crisis or hypertensive encephalopathy)
- Grade 4 congestive heart failure (left ventricular systolic dysfunction)
- Nephrotic syndrome (grade ≥ 3 proteinuria or ≥ 3.5 g/24 h)
- Posterior Reversible Encephalopathy Syndrome (PRES)

- If the investigator determines that situations not listed above but could jeopardise safety of subjects with continuation of IP, IP should be permanently discontinued.

6.4.3. Dose and Schedule Modification of Non-IPs Chemotherapy Agents

6.4.3.1. Paclitaxel and Carboplatin

All dose modifications for paclitaxel and carboplatin are based on the dose level changes in Table 5. A stepwise dose reduction is permitted. If a reduction to dose level -3 is required then subjects must be discontinued from paclitaxel and/or carboplatin treatment. If more than one AE requiring dose-reduction is found (e.g. Grade 4 neutrophil count decreased and Grade 3 platelet count decreased) during the same evaluation period, one dose level reduction is indicated according to Table 6. If both paclitaxel and carboplatin are discontinued due to toxicity, continuation of SB8 or Avastin® as monotherapy is allowed at the discretion of Investigator. Once a dose reduction has occurred, the subject should not be re-escalated to higher doses. Dose modifications must be based on the AE requiring the greatest modification.

Table 5. Dose Levels for Paclitaxel and Carboplatin

	Dose level 0	Dose level -1	Dose level -2	Dose level -3
Paclitaxel	200 mg/m^2	150 mg/m^2	100 mg/m^2	Discontinue
Carboplatin	AUC 6	AUC 4.5	AUC 3	Discontinue

Table 6. Dose Modifications and Delays of Paclitaxel and Carboplatin

NCI-CTCAE[a] Category	AE grade	Modifications for AEs	
Haematological AE			
Neutrophil count decreased	Grade 3 of any duration or Grade 4 < 7days	1st event	• Hold until ≥ 1.5 × 10^9/L • Once recovers, maintain the same dose, but the Investigator may determine to reduce dose by one level based on the general status of the subject.
		2nd event	• Hold until ≥ 1.5 × 10^9/L. • Once recovers, reduce dose by one level.
		3rd event despite dose reduction	• Hold until ≥ 1.5 × 10^9/L. • Once recovers, reduce dose by one level.
		4th event despite dose reduction	• Discontinue

Neutrophil count decreased	Grade 4 ≥ 7 days or Febrile neutropenia with ANC < 1.0×10^9/L *G-CSF is allowed at the discretion of Investigator	1st event	• Hold until ≥ 1.5×10^9/L and body temperature < 38°C • Once recovers, reduce dose by one level.
		2nd event despite dose reduction	• Hold until ≥ 1.5×10^9/L and body temperature < 38°C • Once recovers, reduce dose by one level.
		3rd event	• Discontinue
Platelets count decreased	Grade 1 or 2	≥ 50×10^9/L to < 100×10^9/L	• Hold until ≥ 100×10^9/L. • Once recovers, maintain the same dose.
	Grade 3 without bleeding	1st event: ≥ 25×10^9/L to < 50×10^9/L	• Hold until ≥ 100×10^9/L. • Once recovers, reduce dose by one level.
		2nd event: ≥ 25×10^9/L to < 50×10^9/L	• Hold until ≥ 100×10^9/L. • Once recovers, reduce dose by one level.
		Despite two dose reductions: < 50×10^9/L	• Discontinue.
	Grade 4 or Grade 3 with bleeding	1st event < 25×10^9/L or < 50×10^9/L with bleeding	• Hold until > 100×10^9/L. • Once recovers, reduce dose by one level.
		Despite previous dose reduction for platelet count decrease : < 25×10^9/L	• Discontinue.
Non-hemolytic anemia	Any grade	Any events time	• Manage by transfusions • Maintain the same dose
Non-Haematological AE			
Nausea/vomiting	Grade ≥ 3	1st event	• Maintain the same dose.
		2nd event	• Reduce dose by one level.
		3rd event or later	• Maintain the reduced dose.
Diarrhea lasting > 24 hours despite maximum anti-diarrheal	Grade ≥ 3	1st event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.

management		2nd event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.
		3rd event or later	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the reduced dose.
Mucositis	Grade ≥ 3	1st event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.
		2nd event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.
		3rd event or later	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the reduced dose.
Neurosensory toxicity	Grade 2	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.	
	Grade 3 or 4	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, - Paclitaxel: discontinue Carboplatin: reduce dose by one level.	
AST or ALT or blood bilirubin increased	Increased AST or ALT Grade ≥ 2 and Increased total bilirubin Grade 1	• Hold until AST/ALT recovery to ≤ grade 1 or baseline. • Once AST/ALT recovers, - Maintain the same dose if bilirubin within normal limit. - If bilirubin is still increased to grade 1, Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.	
	Grade ≥ 3 AST or ALT or Grade ≥ 2 total bilirubin	• Hold until AST/ALT and bilirubin recovery to ≤ grade 1 or baseline. • Once AST/ALT and bilirubin recover, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.	
Other clinically significant AEs[b]	Grade 2	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.	
	Grade 3 or 4	• Hold until recovery to ≤ grade 1 or baseline.	

		• Once recovers, reduce dose by one level.

AE = adverse event; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine transaminase; G-CSF= Granulocyte Colony-stimulating Factor; NCI-CTCAE = national cancer institute common terminology criteria for adverse events
[a] NCI-CTCAE v4.03 will be used (see APPENDIX 3)
[b] Other clinically significant AEs will be determined at the discretion of Investigator

6.5. Assessment of Compliance

Compliance will be assessed by the subject's medical records because both IPs and non-IPs are IV infusional drugs. All dosing information including any dose reductions should be recorded in the subject's medical records.

Also any reason for non-compliance should be documented. For example, insufficient compliance is defined when a subject missing more than one IP and non-IPs for reasons other than toxicity, missed scheduled study activities or overdose.

IP accountability and dispensing records must be kept current and contain the following information:

- The identification of the subjects to whom the drug was dispensed.
- The date(s) and quantity of the drug dispensed and exact package to the subject.
- The dispensing and inventory logs must be available for inspection by the medical monitor.

6.6. General Concomitant Medication and Supportive Care Guidelines

All concomitant medication(s) (including premedication and antiemetic therapy) must be reported. In addition, any diagnostic, therapeutic or surgical procedure performed during the treatment period (from Screening to end of treatment), must be recorded. Any medication which is necessary for the management of AEs from chemotherapy may be used at the discretion of the Investigator. For more information of used drugs including contraindications, special warnings and precautions for use, dose modification in case of toxicity, fertility, pregnancy, and lactation, please refer to SmPC of individual drugs.

6.6.1. Premedication for Study Drugs

6.6.1.1. SB8 or Avastin®

Routine premedication for SB8 or Avastin® is not permitted. However, subjects who experience infusion-related reactions after infusion of SB8 or Avastin® may be premedicated with paracetamol and antihistamine for subsequent infusions. Management of infusion-related

reactions is described in Section 6.6.2.

6.6.1.2. Paclitaxel and Carboplatin

Premedication consisting of ranitidine (or other H2-blocker) 50 mg, pheniramine (or other H1-blocker) 4 mg IV slowly, dexamethasone 10 mg IV slowly 30 minutes prior to paclitaxel administration, unless contra-indicated, may be used. Modifications of premedication regimen are permitted according to local practice.

6.6.2. Management for Infusion-related Reactions

SB8 or Avastin® may cause infusion-related reactions such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and/or vomiting. Such reactions typically occur during or very shortly after an infusion. Administration of SB8 or Avastin® should be performed in a setting with emergency equipment and staff who are trained to medical emergencies. If an infusion reaction occurs, the SB8 or Avastin® infusion should be discontinued and the subject will be monitored until resolution of any observed symptoms. The majority of subjects will be resolved for symptoms and subsequently will receive further infusions. Subjects who experience infusion-related symptoms may be premedicated with paracetamol and antihistamines for subsequent infusions. Subjects should be warned of the possibility of late onset reactions and should be instructed to contact their Investigator if these reactions occur. When a severe hypersensitivity reaction such as anaphylaxis occurs, the infusion should be interrupted immediately and supportive care including oxygen, epinephrine, beta-agonists, and corticosteroids should be administered with continuous vital sign monitoring by trained staff until the symptoms are resolved.

6.6.3. Granulocyte Colony-stimulating Factor (G-CSF) Use

G-CSF may be given at the discretion of Investigator and recommend following NCCN Guidelines of Myeloid Growth Factors. In subjects with risk factors for developing febrile neutropenia (sepsis syndrome, aged ≥ 65, severe neutropenia [ANC $< 0.1 \times 10^9$/L], neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalisation at the time of fever, prior episode of febrile neutropenia) prophylaxis with G-CSF will be permitted.

6.6.4. Antibiotics Use

At the discretion of Investigator, antibiotics may be administered according to NCCN Guidelines of Cancer-related Infections or ASCO Guidelines in febrile neutropenia cases.

6.6.5. Other Supportive Care

All supportive therapies (e.g., physical therapy, blood transfusions) are permitted as appropriate

and according to the local practice.

Subjects with anemia can be treated according to the local practice. Intravenous bisphosphonate therapy is permitted during the study if clinically indicated (e.g., bone metastases for NSCLC) (see Section 6.2.5.).

7. SAFETY MONITORING AND REPORTING

7.1. Adverse Events

7.1.1. Adverse Event Definition

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal (investigational) product or other protocol-imposed intervention and which does not necessarily have to have a causal relationship with this treatment or intervention. An AE can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any dose of a medicinal (investigational) product or other protocol-imposed intervention, regardless of attribution.

All AEs during the period of observation (as specified in Section 7.1.2.) including the event that occurred prior to administration of an IP should be collected as an AE.

Pre-existing conditions and any abnormal findings from assessments at the time of screening which are not related to protocol-imposed intervention should not be reported as AEs, however pre-existing conditions which worsen (i.e., change in severity) that meets the definition of an AE during the study are to be reported as AEs.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

The AE that emerge during the treatment with an IP (i.e., treatment-emergent adverse event) will be analysed for the purposes of safety analyses.

7.1.1.1. Progression of Underlying Disease

Progression of NSCLC is not to be reported as an AE if it is clearly consistent with the suspected progression of the NSCLC as defined by the criteria as specified in Section 5.2.1.2. Such an AE should not be reported as a SAE even if it meets the seriousness criteria.

However, if there is any uncertainty about an AE being due only to the NSCLC, it should be reported as an AE or SAE.

In case of local regulations demanding the treating Investigator to report progression of underlying disease as AE, then the Investigator must fulfil due diligence to the regulatory authorities. However, such cases will not be counted as AE in the Clinical Study Report of this study.

7.1.1.2. Clinically Significant Abnormalities

If there are any abnormalities discovered during the laboratory test, physical examination, vital signs and/or other safety assessments and the abnormality is assessed clinically significant by the Investigator, it should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening or if the abnormality is consistent with a current diagnosis. If it is not specified or defined elsewhere in the protocol, clinically significant abnormality may include the events that led to an intervention, including withdrawal of the IP, dose reduction, significant additional concomitant medication, and others evaluated as clinically significant by the Investigator.

All laboratory abnormalities that require intervention (e.g., transfusion, IV infusion) should be reported as clinically significant AEs according to NCI-CTCAE v4.03. If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be collected as an AE. If the abnormality can be characterised by a precise clinical term, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia". Observations of the same clinically significant abnormality from visit to visit should not be repeatedly collected as AEs, unless their severity, seriousness, or etiology changes.

7.1.2. Period of Observation for Adverse Events

AEs will be reported from the time the informed consent form (ICF) is signed until the EOT visit. After the EOT visit, only SAEs will be reported.

The Investigator does not need to actively monitor subjects for AEs once the clinical study has ended. However, SAEs that occurred after the EOS should be reported to the Sponsor if the Investigator becomes aware of the SAEs.

Unresolved AEs until the EOT should be followed up until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up, or initiation of subsequent therapy for NSCLC), or EOS date, defined as when deaths of all the randomised subjects have been observed, or 12 months from Randomisation of the last subject, whichever occurs first. The Investigator should observe the AEs for appropriate medical care of the patient until AE resolution or stabilisation.

7.1.3. Reporting Adverse Events

AEs are to be reported and reviewed by the Investigator. When reporting an AE, a diagnosis (when possible and appropriate) rather than each individual sign and symptom should be reported.

Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 7.2.1. for SAE definition). If an AE is classed as an SAE, it must be reported to Sponsor, or its designated representative, promptly according to the timeline specified in Section 7.2.2.

For a SAE, a diagnosis with a description of signs and symptoms as well as other supporting information that led to the diagnosis should be described in the SAE report form and reported to the Sponsor, or its designated representative, according to the procedures described in Section 7.2.2.

7.1.4. Severity Assessment

The Investigator is responsible for assessing and reporting the severity of AEs in accordance with NCI-CTCAE v4.03.

The following general guideline can be used to describe the severity of the AE. A grading (severity) scale for each AE is provided in NCI-CTCAE v4.03 (see APPENDIX 3).

Table 7. Severity Grade of NCI-CTCAE v4.03

GRADE	Clinical Description of Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

ADL = activities of daily living
[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.1.5. Causality Assessment

The Investigator is responsible for assigning a causal relationship to each AE. The causal relationship between the IP and the AE should be defined as not related (no) or related (yes).

Events should be classified as “related” if there is a reasonable possibility that the IP caused the

AE. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Events should be classified as “not related” if there is no reasonable possibility that the IP caused the AE.

7.1.6. Emergency Unblinding for Safety Reasons

Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject’s safety by their Investigator or a regulatory body. In general, unblinding of subjects during the conduct of the clinical study is not allowed unless there are compelling medical or safety reasons to do so. The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual. If the blind is broken, it may be broken only for the subject in question. The Sponsor must be notified before or immediately after a subject and/or the Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject’s treatment code must be documented in the subject’s source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information. After unblinding (except unblinding for the purpose of regulatory reporting), subjects will be discontinued from the study.

7.1.7. Expectedness Assessment

Expectedness of AEs will be assessed by referring to the safety information in IB of the relevant safety section. More detailed information on expectedness assessment will be explained in IB. The latest SmPC of Avastin®, Annex I of EPAR Product Information posted on EMA website, will be used to assess the expectedness for the comparators.

7.1.8. Withdrawal Due to Adverse Events

Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons. Subjects withdrawn due to an AE should be followed up until the time point specified in the protocol. When a subject withdraws from the study due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 7.2.2.

Subjects who discontinue the administration of IPs because of serious or significant safety issues should be followed closely until the events are fully and permanently resolved or stabilised.

7.2. Serious Adverse Events

7.2.1. Serious Adverse Event Definition

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defects
- Is medically important

If the SAE is considered progression of NSCLC, it should not be reported as a SAE in accordance with Section 7.1.1.1.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning.

7.2.1.1. Life-threatening

The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at 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.

7.2.1.2. Hospitalisation

AEs reported from clinical studies associated with hospitalisation or prolongation of hospitalisation are considered serious. Staying at the observation unit in the emergency room for more than 24 h qualifies for hospitalisation. Any events leading to a subsequent emergency room visit for less than 24 h should be in the discretion of Investigator to assess seriousness as medically important.

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment laboratory abnormality)
- Social admission for convenience (e.g., admission of a subject who does not have a carer)
- Administrative admission (e.g., for a yearly physical exam)
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)

Pre-planned treatments or surgical procedures should be noted in the Screening documentation for the individual subject

7.2.2. Reporting Serious Adverse Event

SAEs before EOT visit must be immediately reported at least within 24 h of the Investigator becoming aware of the event to Sponsor or its designated representative using the SAE report form in the eCRF. SAEs that occurred after the EOT visit must be reported at least within 24 h of the Investigator becoming aware of the event to Sponsor or its designated representative using the paper SAE report form. Contact information for SAE reporting will be provided in SAE Report Completion Instruction.

In particular, if the SAE is fatal or life-threatening, Sponsor must be notified immediately, irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. Sponsor will then follow expedited reporting procedures according to local and international regulations as appropriate.

The Investigator is obligated to pursue and provide information to Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured in the SAE report form. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant

medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

All SAEs will be followed until event resolution or stabilisation (for chronic events), if possible, even when a subject is withdrawn from treatment. For chronic events that does not fully resolve until years later, the outcome should be reported as "resolved with sequelae" as soon as the event has stabilised or returned to baseline. Follow-up information for the SAE should be actively sought and submitted as the information becomes available.

7.3. Adverse Events of Special Interest (AESI)

7.3.1. Hypertension

Hypertension NCI-CTCAE v4.03 grade ≥ 3 should be classified as AESI.

7.3.2. Proteinuria

If subject is discovered to have ≥ 2+ proteinuria on urine dipstick (or other ways of urinalysis) and demonstrate 24 hours urine protein excretion ≥ 1 g or protein/creatinine ratio in spot urine ≥ 1 g/g creatinine (or ≥ 226.0 mg/mmol creatinine), should be classified as AESI.

7.4. Pregnancy

Any pregnancy, including those of female partners of male subjects treated with the IP, should be reported to the Sponsor. If the female partner of a male subject becomes pregnant, a written consent must be obtained from the female partner before collecting any pregnancy-related data. All pregnancies associated with the subject, from the time the subject receives the first dose of IP until 6 months after the last dose of IP should be reported to Sponsor. Pregnancy reports should be made within 24 h of the Investigator becoming aware of the pregnancy using the Pregnancy report form.

Although pregnancy is not an AE, all pregnancies must be followed up until 6-8 weeks after the outcome of the pregnancy becomes available, unless the subject is lost to follow-up. The pregnancy outcome should be notified to Sponsor by submitting a follow-up Pregnancy report form. If the outcome of the pregnancy meets SAE criteria then the Investigator should report this case according to the SAE reporting procedure (see Section 7.2.2.).

7.5. Independent Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will be assigned for this study. The DSMB will consist of external experts (e.g., medical oncologists, clinical pharmacologists or biostatisticians) and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the

DSMB Charter and in the DSMB Statistical Analysis Plan (SAP).

In addition, an ongoing blinded review of AEs, including clinical laboratory data will be continuously undertaken by the Sponsor medical monitor and pharmacovigilance team.

8. STATISTICAL CONSIDERATION AND ANALYTICAL PLAN

8.1. Analysis Sets

The following sets will be used for the analyses performed in the study:

- Randomised set (RAN): RAN will consist of all subjects who receive a randomisation number at the randomisation.
- Full analysis set (FAS): FAS will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to by intention-to-treat principle. However, subjects who do not qualify for randomisation and are inadvertently randomised into the study will be excluded from FAS, provided these subjects do not receive any IP during the study.
- Per-protocol set (PPS): PPS will consist of all FAS subjects who complete at least two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. Major protocol deviations that will lead to the exclusion from the PPS will be pre-specified, and the PPS will be determined prior to unblinding treatment codes.
- Safety set (SAF): SAF will consist of all subjects who received the study drug at least once. This analysis set will be used for safety analyses. The subjects will be analysed based on the treatment they received.
- Pharmacokinetic population: this set will consist of subjects allocated to PK sub-study who have at least one measured serum concentration of bevacizumab.

8.2. Statistical Methods and Analytical Plan

8.2.1. Demographics and Baseline Characteristics

The Baseline value will be defined as the last available measurement value prior to the time of first IP administration.

Subject demographics and baseline characteristics will be summarised by treatment group for the RAN. Continuous variables (e.g., age, weight, height, disease duration) will be summarised with descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Categorical variables (e.g., gender, race, ethnicity, ECOG status) will be summarised with

counts and percentages.

Comparison of treatment groups will be performed using the chi-square test or F-test as appropriate. The results of these tests will be provided including the *p*-value for descriptive purposes and will not be used as a formal basis to determine the factors to be included in statistical models. If baseline imbalances are detected for any of the factors, additional analyses may be performed to adjust for these baseline differences.

Relevant medical history and continuing medical conditions will be summarised by treatment group for the RAN.

Duration of exposure to study drug and number of IV infusions will be summarised by treatment group with descriptive statistics using the SAF. Prior and concomitant medications and significant non-drug therapies will be summarised by treatment group with frequency and percentage.

8.2.2. Efficacy

8.2.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is the best ORR by 24 weeks of chemotherapy. The best ORR is defined as the proportion of subjects whose best overall response is either CR or PR according to RECIST v1.1 during the induction treatment period. If a subject has either CR or PR at least once during the induction treatment period, the subject will be considered as the responder. Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6 before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles according to RECIST v1.1. Tumour size will be assessed by both investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review.

The primary efficacy analysis will aim to demonstrate equivalence in the best ORR between SB8 and Avastin®. The null hypothesis tested for the primary efficacy analysis will be either (1) SB8 is inferior to Avastin® or (2) SB8 is superior to Avastin® based on a pre-defined equivalence margin.

For US Food and Drug Administration or other regulatory agency submissions for those who are in favour of risk ratio, the primary efficacy analysis will be performed in the FAS for the ratio of best ORR (best ORR of SB8/ best ORR of Avastin®) by 24 weeks, and the equivalence will be declared if the 90% confidence interval (CI) of the best ORR ratio is contained within the pre-defined equivalence margin of [0.737, 1.357]. The similar analysis will be performed for the PPS to support the primary analysis.

For EMA, MFDS or other regulatory agency submissions for those who are in favour of risk

difference, the primary efficacy analysis will be performed in the PPS for the difference of the best ORR (best ORR of SB8 – best ORR of Avastin®) by 24 weeks, and the equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The similar analysis will be performed for the FAS to support the primary analysis.

The primary efficacy analysis will be performed using the log binomial model with treatment. The sensitivity analysis will be performed using the log binomial model with the covariates of age (< 70, ≥ 70 years), sex (female, male), region (country or pooled centres) and treatment to explore the robustness of the primary efficacy results.

In the primary efficacy analysis for FAS, the response of the patients without any post-baseline tumour assessment will be imputed as following:

- Missing data from patients who withdrew the study due to progression disease (PD), lack of efficacy and AEs without any tumour assessment will be considered as non-responder.
- Missing data from patients who withdrew the study with reasons other than PD, lack of efficacy and AEs without any tumour assessment will be imputed using multiple imputation method.
- Missing data from patients who remained in the study but do not have any valid tumour assessment will be imputed using multiple imputation method.

In the primary efficacy analysis for the PPS, missing data will not be imputed.

8.2.2.2. Secondary Efficacy Analyses

The secondary efficacy endpoints of PFS, OS and DOR will be analysed for PPS and FAS. PFS and OS will be analysed using the Kaplan-Meier method with median survival time and its 95% CI by treatment. The analysis using the stratified Cox proportional hazard model will be additionally performed to adjust the covariates used in the sensitivity analysis. DOR will be summarised using descriptive statistics by treatment.

8.2.2.3. Exploratory Efficacy Analysis

The exploratory efficacy endpoint is the best ORR by 11 and 17 weeks and will be analysed with the similar manner of the primary endpoint analysis.

8.2.3. Safety

All reported terms for AEs will be coded using MedDRA. No statistical testing will be performed for AEs. For all AE and SAE tables, subjects will be counted once for each preferred

term and each system organ class.

A treatment-emergent AE (TEAE) will be defined as any AE with an onset date on or after the date of the first administration of IP. AEs which are already present before the first IP and increase in severity after the first IP will be considered as TEAEs. Pre-existing AEs before the first IP with no increase in severity after the first IP will not be considered as TEAEs.

All TEAEs and SAEs will be summarised by the frequency and percentage of subjects experiencing events by system organ class, preferred term and treatment group. SAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing during the pre-treatment period will be listed by subject.

Changes in vital signs and clinical laboratory measurements will be summarised descriptively by treatment group. Other safety variables (e.g., infusion reaction) will be summarised and listed.

All safety analyses will be performed using the SAF.

8.2.4. Pharmacokinetics

The PK blood samples will be collected in approximately 50% of the enrolled subjects. The PK parameters (C_{trough} and C_{max}) will be summarised descriptively by treatment group at each cycle.

8.2.5. Immunogenicity

The incidence of anti-drug antibodies and neutralising antibodies will be summarised by treatment group and cycle for SAF.

8.3. Determination of Sample Size

Regarding the calculation of the equivalence margin for the ratio of the best ORR by 24 weeks, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered. The overall response rate for Avastin® was reported as 34.9% (133 of 381 patients), 34.7% (114 of 329 patients), 32.4% (11 of 34 patients) and 56.2% (68 of 121 patients) compared to the overall response rate of 15.1% (59 of 392 patients), 21.7% (71 of 327 patients), 18.8% (6 of 32 patients) and 33.9% (20 of 59 patients) for chemotherapy, in E4599, AVAiL, AVF0757 and JO19907 respectively.

The overall ratio of the best ORR and the 70% CI from above four studies are calculated to be [redacted] using the fixed effect method from meta-analysis. Retaining the [redacted]% of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks.

For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] will be used due to the similar derivation.

For the calculation of the equivalence margin for the difference of the best ORR by 24 weeks, E4599 [Sandler, 2006] and AVAiL [Reck, 2010] studies were considered. The overall response rate for Avastin® was reported as 34.9% (133 of 381 patients) and 37.8% (130 of 344 patients), compared to the overall response rate of 15.1% (59 of 392 patients) and 21.6% (75 of 347 patients) for chemotherapy, in E4599 and AVAiL, respectively.

The overall difference in the best ORR and its 95% CI from these two studies are calculated to be CCI % [CCI %, CCI %] using the fixed-effect method from meta-analysis, or for 80% CI to be [CCI %, CCI %]. The equivalence margin of [-12.5%, 12.5%] will ensure the superiority of SB8 over placebo with a small safety margin retaining around CCI % for 95% CI and CCI % for 80% CI of the effect over the placebo in the difference of best ORR.

With 305 completers in each treatment group, the two-sided 90% CI of the best ORR ratio is expected to lie within [0.737, 1.357] with approximately 80% power, and the two-sided 95% CI of the best ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected best ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.

8.4. Statistical Analysis Timepoints

Safety endpoint will be assessed for DSMB review during the course of the study. Interim safety results will be evaluated by the DSMB, which will be independent of the study conduct. Details will be described in the DSMB charter.

The primary endpoint will be assessed when at least 24 weeks has elapsed since the last subject is randomised. Available efficacy and safety data (a full set of the Induction treatment period data including available data in the maintenance treatment period from a subset of subjects, i.e., those subjects enrolled early) will also be analysed and reported.

A final CSR will be reported once the full set of the maintenance treatment period is obtained, e.g. after EOS.

After at least 24 weeks from the last subject randomised, or its corresponding date, a limited number of individuals of the Sponsor will be unblinded. A formal analysis of the primary efficacy data will then be undertaken. Subjects, Investigators, independent central reviewers and other study personnel will remain blinded throughout the entire treatment period

9. DATA COLLECTION AND MANAGEMENT

9.1. Data Confidentiality

Information about study subjects will be kept confidential. Subject identification information will be labelled with a code number, and will not include the subject's name or other information that could identify them. A list linking the code and the subject's name will be kept in the site files as required by Good Clinical Practice (GCP) to protect the subject's confidentiality.

The coded information will be sent to the Sponsor (or designee) who will analyse it and report the study results both to regulatory and ethical authorities. The Sponsor may also place data on public websites or publish journal articles based upon these results. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes. Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research into lung cancer. Such data sharing practices will be covered by confidentiality agreements. No-one outside the Investigator site will have access to subject-identifiable information.

9.2. Monitoring

The Sponsor has engaged the services of a contract research organisation (CRO) to perform all monitoring functions within this clinical study. The monitors will work in accordance with the CRO SOPs and have the same rights and responsibilities as monitors from the Sponsor organisation. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each Investigator site and inform the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained correctly from all subjects and that data are recorded correctly and completely. Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions. Monitors will verify adherence to the protocol at the Investigator site. All protocol deviations will be reported to the Sponsor via the Monitoring Visit Reports. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted at regular intervals according to GCP. The monitor will provide written reports to the Sponsor on each occasion they make contact with the Investigator regardless of whether it is by phone or in person.

Further details on the monitoring processes and the level of source data verification to be

performed will be outlined in the monitoring plan.

9.3. Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed informed consent forms, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (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 IP or 15 years from completion of the study. These documents should be retained for a longer period if required by the applicable regulatory requirements or the Investigator site, institution or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for the same period of time. These documents may be transferred to another responsible party, deemed acceptable by the Sponsor, and 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 and obtain written permission to do so.

9.4. Database Management and Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). The study eCRF is the primary data collection instrument for the study. Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy.

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the medical records.

Forms should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the eCRF must be carried out by the Investigator or a designated member of staff. These changes may be made either on the initiative of the site staff or in response to monitoring or data queries. Any changes to written data must be made using GCP corrections and any change to electronic data should be made in a system which can provide an audit trail. Monitors and clinical data managers will review the eCRF for accuracy and can generate queries to the investigational staff for resolution. Corrections will be recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. The Investigator must sign and date the eCRF pages as indicated.

Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE). The versions of coding dictionaries used will be stated in the clinical study report.

9.5. Quality Control and Quality Assurance

During the conduct of the study, Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed. The monitors may review source documents to confirm that the data recorded on the eCRFs are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities, sponsor's monitors and auditors direct access to source documents to perform this verification. The study site may be subject to review by the Independent ethics committee (IEC), and/or to quality assurance audits performed by Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that the Investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Institutional Review Board or Independent Ethics Committee

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the institutional review board (IRB)/IEC.

The Investigator must provide the Sponsor with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the Investigator site. The Investigator will supply documentation to the Sponsor relating to the annual renewal of the protocol from the IRB/IEC and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC on a regular basis and in accordance with the timelines required locally. Upon completion of the study, the Investigator will provide the ethics committee with a report on the outcome of the study if required by local regulations.

10.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH guidelines, GCP, the Declaration of Helsinki (2013) and all applicable and current regulatory requirements.

10.3. Informed Consent

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

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP. The Investigator will provide each subject with a copy of the signed and dated ICF and this will be documented in the subject's source notes.

10.4. Investigator Information

10.4.1. Investigator Obligations

This study will be conducted in accordance with the ICH Harmonised Tripartite Guideline for GCP (1997), the ethical principles that have their origin in the Declaration of Helsinki (2013) and local laws and regulations.

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. The Investigator must obtain the informed consent of each subject to whom IP is administered.

10.4.2. Coordinating Investigator

Sponsor will designate a Coordinating Investigator among the Investigators who participate in the study. The roles of the Coordinating Investigator are defined as following:

- Provide scientific and medical advice and/or inputs on current medical practice, protocol development and site selection
- Review ongoing study activities with Interpretation and presentation of final analyses
- Review clinical study reports
- Involved in development of publication strategy
- The designated Coordinating Investigator will sign the signature page of CSR as a

representative of other Investigators.

10.4.3. Training of Investigator Site Personnel

Before the first subject is enrolled into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and will also train them in any study-specific procedures.

The Investigator will ensure that appropriate training relevant to the study is given to all site staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

10.4.4. Protocol Signatures

The Investigator must sign the Investigator Signature Page of this protocol prior to starting recruitment for the study. 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 study in accordance with GCP and applicable regulatory requirements. The study will not be able to start at any Investigator site where the Investigator has not signed the protocol.

10.4.5. Financing and Insurance

Samsung is the Sponsor of this study and will be providing the finances to cover the operation of the study. Details of financial agreements are provided in the Clinical Study Agreements with the Investigator sites and in contracts with other companies involved in the running of the study.

The Sponsor has obtained suitable insurance for this study. The insurance details will be provided to each Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.

11. STUDY DISCONTINUATION

The end of study will occur, when one of the following conditions is met, whichever occurs first;

- Deaths of all the randomised subjects have been reported.
- 12 months after Randomisation of the last subject.
- Discontinuation of IP development.
- Occurrence of previously unknown adverse events that could significantly affect continuation of the study (e.g., at the discretion of DSMB).

- Medical or ethical reasons affecting the continued performance of the study.

After end of study is announced, Sponsor may discontinue supply of IPs and safety follow-up will not be performed.

12. PUBLICATION POLICY

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human subjects. The Sponsor will register and maintain the information of clinical studies on a public registry program such as www.ClinicalTrials.gov. The Sponsor will comply with the guidelines of regulatory authorities with regards to public registration and disclosure of clinical study data.

The clinical study data collected during the study are confidential and proprietary to the Sponsor. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed abstract or presentation.

Any publications from this study should be approved by the Sponsor prior to publication or presentation. The rights of the Investigator with regard to publication of this study are described in the Clinical Study Agreement.

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Sweeney CJ, Miller KD, Sissons SE, et al. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res. 2001; 61: 3369–72.

APPENDIX 1: ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria of The Eastern Cooperative Oncology Group, *Am J Clin Oncol.* 1982; 5(6):649-55.

APPENDIX 2: LUNG CANCER STAGING (AJCC 7TH EDITION)

Definitions for T, N, M

T	Primary tumour
Tx	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)[a]
T1a	Tumour 2 cm or less in greatest dimension
T1b	Tumour more than 2 cm but 3 cm or less in greatest dimension
T2	Tumour more than 3 cm but 7 cm or less or tumour with any of the following features (T2 tumours with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumour more than 5 cm but 7 cm or less in greatest dimension
T3	Tumour more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina1 but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumour nodule(s) in a different ipsilateral lobe
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe, tumour with pleural nodules or malignant pleural (or pericardial) effusion[b]
M1b	Distant metastasis (in extrathoracic organs)

N	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

[a] The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.
[b] Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Anatomic stage/ Prognostic groups

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0

	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Reference:

Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer 2010.

APPENDIX 3: NATIONAL CANCER INSTITUTE-COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 4.03 (NCI-CTCAE v4.03) (IN PART OF)

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

ADL = Activities of Daily Living
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Specific CTCAE Grades for Selected Adverse Events

AE	Grade				
	1	**2**	**3**	**4**	**5**
Neutrophil count decreased	< LLN-1,500/mm^3	< 1,500-1000/mm^3	< 1,000-500/mm^3	< 500/mm^3	-
Platelet count decreased	< LLN-75,000/mm^3	< 75,000-50,000/mm^3	< 50,000-25,000/mm^3	< 25,000/mm^3	-
Febrile neutropenia	-	-	ANC <1,000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
AST/ALT	> ULN–3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20.0 × ULN	-
Blood bilirubin increased	> ULN–1.5 × ULN	> 1.5-3.0 × ULN	> 3.0-10.0 × ULN	> 10.0 × ULN	-
ALP	> ULN-2.5 × ULN	> 2.5-5.0 × ULN	> 5.0-20.0 × ULN	> 20.0 × ULN	-
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only;	Moderate symptoms; limiting instrumental ADL	Sever symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention	Death

AE	Grade				
	1	2	3	4	5
	intervention not indicated			indicated	
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Sever symptoms; limiting self-care ADL		Death
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderated pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	≥ 6 episodes (separated by 5 minutes) in 24hrs; tube feeding, TPN or hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death
ADL = activities of daily living; ANC = absolute neutrophil count TPN = total parenteral nutrition					

Reference:

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. *NCI.* from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

APPENDIX 4: WORLD HEALTH ORGANIZATION HISTOLOGICAL CLASSIFICAION OF TUMOURS OF THE LUNG

Epithelial tumours	
Adenocarcinoma	• Lepidic adenocarcinoma • Acinar adenocarcinoma • Papillary adenocarcinoma • Micropapillary adenocarcinoma • Solid adenocarcinoma • Invasive mucinous adenocarcinoma – mixed invasive mucinous and nonmucinous adenocarcinoma • Colloid adenocarcinoma • Fetal adenocarcinoma • Enteric adenocarcinoma • Minimally invasive adenocarcinoma – nonmucinous, mucinous • Preinvasive lesions – atypical adenomatous hyperplasia, adenocarcinoma in situ (nonmucinous, mucinous)
Squamous cell carcinoma	• Keratinizing squamous cell carcinoma • Nonkeratinizing squamous cell carcinoma • Basaloid squamous cell carcinoma • Preinvasive lesion – squamous cell carcinoma *in situ*
Neuroendocrine tumours	• Small cell carcinoma – combined small cell carcinoma • Large cell neuroendocrine carcinoma – combined large cell neuroendocrine carcinoma • Carcinoid tumours – typical carcinoid tumour, atypical carcinoid tumour • Preinvasive lesion – diffuse idiopathic pulmonary neuroendocrine, cell hyperplasia
Large cell carcinoma	
Adenosquamous carcinoma	
Pleomorphic carcinoma	
Spindle cell carcinoma	

Giant cell carcinoma	
Carcinosarcoma	
Pulmonary blastoma	
Other and unclassified carcinomas	• Lymphoepithelioma-like carcinoma • NUT carcinoma
Salivary gland-type tumours	• Mucoepidermoid carcinoma • Adenoid cystic carcinoma • Epithelial-myoepithelial carcinoma • Pleomorphic adenoma
Papillomas	• Squamous cell papilloma – exophytic, inverted • Glandular papilloma • Mixed squamous and glandular papilloma
Adenomas	• Sclerosing pneumocytoma • Alveolar adenoma • Papillary adenoma • Mucinous cystadenoma • Mucous gland adenoma
Mesenchymal tumours	
Pulmonary hamartoma	
Chondroma	
PEComatous tumours	• Lymphangioleiomyomatosis • PEComa, benign – clear cell tumour • PEComa, malignant
Congenital peribronchial myofibroblastic tumour	
Inflammatory myofibroblastic tumour	
Epithelioid haemangioendothelioma	
Pleuropulmonary blastoma	
Synovial sarcoma	
Pulmonary artery intimal sarcoma	
Pulmonary myxoid sarcoma with *EWSR1–CREB1* translocation	

Myoepithelial tumours	• Myoepithelioma • Myoepithelial carcinoma
Lymphohistiocytic tumours	
Extranodal marginal zone lymphomas of mucosa-associated	• Lymphoid tissue (MALT lymphoma)
Diffuse large cell lymphoma	
Lymphomatoid granulomatosis	
Intravascular large B cell lymphoma	
Pulmonary langerhans cell histiocytosis	
Erdheim– chester disease	
Tumours of ectopic origin	
Germ cell tumours	• Teratoma, mature • Teratoma, immature
Intrapulmonary thymoma	
Melanoma	
Meningioma, NOS	
Metastatic tumours	

Reference:
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart; Volume 7 in 4th Edition.

PROTOCOL SIGNATURE PAGES

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin® in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

Name: PPD SB8 Clinical Research Physician

Institution: Samsung Bioepis Co., Ltd.

Signature: PPD Date: PPD
(Month, Day, Year)

SIGNATURE PAGE

Declaration of the Global Principal/Coordinating Investigator

Protocol Title: A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin® in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer

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Principal/Coordinating Investigator

Name: PPD

Institution: PPD

Signature: _____ Date: PPD
(Month, Day, Year)

SIGNATURE PAGE

Declaration of the Principal/Coordinating Investigator

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Principal/Coordinating Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____
(Month, Day, Year)

AMENDMENT 1: Dec 17, 2015

Section Affected	Original Content	Amended/New Content	Rationale
	Version and Effective Date: **Version 1.0 Oct 05, 2015**	Version and Effective Date: **Amendment 1.0 Dec 17, 2015**	Version control
	Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, **406-840** Republic of Korea	Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, **21987** Republic of Korea	New postal code
Change through text and figure except for AVAiL, E4599 studies' ORR	**ORR**	**Best ORR**	According to US FDA feedback
through text	**AvaiL**	**AVAiL**	To correct typo error
Synopsis-Study Design	**ORR**	**best ORR**	According to US FDA feedback
	Sbjects with metastatic or recurrent non-squamous NSCLC with unknown or without activating EGFR gene mutations or ALK gene translocations will be randomised.	Subjects with metastatic or recurrent non-squamous NSCLC ~~**with unknown or without activating**~~ **without known activating** EGFR gene mutations or ALK gene translocations, will be **randomised**.	According to US FDA feedback
	Approximately 50% of the enrolled subjects will have blood samples collected for PK analysis at pre-dose and post-dose of Cycle 1, 3, 5, and 7.	Approximately 50% of the enrolled subjects will have blood samples collected for PK analysis **of SB8 or Avastin®,** at pre-dose and post-dose of Cycle 1, 3, 5, and 7.	clarification
Synopsis-Target Population	Subjects with metastatic or recurrent non-squamous NSCLC with unknown or without activating EGFR gene	Subjects with metastatic or recurrent non-squamous NSCLC ~~with unknown or without activating~~ **without**	According to US FDA

	mutations or ALK gene translocations	**known activating** EGFR gene mutations or ALK gene translocations	feedback
Synopsis-Eligibility Synopsis-Criteria Inclusion criteria	1. Aged ≥ 18 years	1. Aged ≥ 18 years **(if local regulations are different in this regard, follow the local regulations).**	Different country regulations, e.g., Taiwan
	7.b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion < 1 g or protein/creatinine ratio in spot urine < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	7.b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion **is** < 1 g or protein/creatinine ratio in spot urine **is** < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	To correct typo error
Synopsis-Criteria Exclusion criteria	7. Radiotherapy within 28 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy except for pain relief, are not considered as measurable lesion.).	7. Radiotherapy within 28 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy ~~**except for pain relief,**~~ are not considered as measurable lesion **unless there has been demonstrated progression in the lesion.).**	According to RECIST v1.1
	9. Minor surgical procedure within 7 days prior to Randomisation (requiring local anaesthesia or following procedures: **medianoscopy**, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle biopsy [EBUS & TBNA], pleural biopsy, **thoracenthesis**, pleurodesis, catheter insertions/removal, tooth extraction, superficial incision	9. Minor surgical procedure within 7 days prior to Randomisation (requiring local anaesthesia or following procedures: **mediastinoscopy,** percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle biopsy [EBUS & TBNA], pleural biopsy, **thoracentesis,** pleurodesis, catheter insertions/removal, tooth extraction, superficial incision	To correct typo error
	11. Known or clinically suspected brain metastasis and/or leptomeningeal disease.	11. ~~**Known or clinically suspected**~~ **Symptomatic** brain metastasis and/or leptomeningeal disease.	Investigator's feedback to allow

			incidentaly asymptomatic findings
	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [> 75 mg/day], regular use of aspirin [> 325 mg/day)], dipyridamole, ticlopidine and/or cilostazol);	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [> 75 mg/day], **regular use of aspirin ~~[> 325 mg/day)],~~** dipyridamole, ticlopidine and/or cilostazol);	No lower limit of Aspirin dose
	18.h. Gastrointestinal bleeding, **heamatemesis** or haemoptysis (≥ 1/2 teaspoon of red blood).	18.h. Gastrointestinal bleeding**, haematemesis** or haemoptysis (≥ 1/2 teaspoon of red blood).	To correct typo error
Synopsis-Main Criteria for Evaluation <u>Primary endpoint</u>	• The **ORR** by 24 weeks of chemotherapy (**ORR** is defined as the proportion of subjects whose best overall response is either complete response [CR] or partial response [PR] according to RECIST v1.1) Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles according to RECIST v1.1 and assessed by both Investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review.	• The **best ORR** by 24 weeks of chemotherapy (**best ORR** is defined as the proportion of subjects whose best overall response is either complete response [CR] or partial response [PR] according to RECIST v1.1) Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles according to RECIST v1.1 and **tumour size will be** assessed by both Investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review.	To correct typo error
	For US Food and Drug Administration submission, the primary analysis will be performed for the ratio of the ORR by 24 weeks. For EMA submission, the primary analysis will be performed for the difference of the ORR by 24 weeks.	**~~For US Food and Drug Administration submission, the primary analysis will be performed for the ratio of the ORR by 24 weeks. For EMA submission, the primary analysis will be performed for the difference of the ORR by 24 weeks.~~**	According to US FDA feedback
Synopsis-Main	• Progression free survival (PFS), defined as the time	• Progression free survival (PFS), defined as the time	More

Criteria for Evaluation Secondary endpoints	from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of EOT visit.	from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of EOT visit **or the last tumour assessment date if the date of EOT is not available**.	sophisticated definition of PFS
Synopsis-Statistical Methods Analysis set	Full analysis set (FAS) will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to.	Full analysis set (FAS) will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to **by intention-to-treat principle. However, subjects who do not qualify for randomisation and are inadvertently randomised into the study will be excluded from FAS, provided these subjects do not receive any IP during the study.**	According to US FDA feedback
	Per-protocol set (PPS) will consists of all FAS subjects who complete at least two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. The PPS will be the primary analysis set. Major protocol deviations that will lead to exclusion from the PPS will be pre-specified, and PPS will be determined prior to unblinding the treatment codes.	Per-protocol set (PPS) will consists of all FAS subjects who complete at least two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. ~~**The PPS will be the primary analysis set.**~~ Major protocol deviations that will lead to exclusion from the PPS will be pre-specified, and PPS will be determined prior to unblinding the treatment codes.	According to US FDA feedback
Synopsis-Statistical Methods Efficacy analysis	**For US FDA submission, the primary efficacy analysis for demonstrating the equivalence of SB8 to Avastin® will be done for the ratio of the ORR (SB8 response rate/Avastin® response rate) by 24 weeks. The equivalence will be declared if the two sided 90% confidence interval (CI) of the ORR ratio lies within the pre-defined equivalence margin of [0.742, 1.450].**	**For US FDA submission, the primary efficacy analysis for demonstrating the equivalence of SB8 to Avastin® will be done for the ratio of best ORR (best ORR of SB8/ best ORR of Avastin®) by 24 weeks in the FAS. The equivalence will be declared if the two sided 90% confidence interval (CI) of the best ORR ratio is contained within the pre-defined equivalence**	According to US FDA feedback, recalculate the equivalence margin

	For EMA submission, the primary efficacy analysis will be performed for the difference in ORR between SB8 and Avastin®, and the equivalence will be declared if the two-sided 95% CI lies within the pre-defined equivalence margin of [-12.5%, 12.5%]. The secondary efficacy endpoints (PFS, OS, and DOR) will be analysed using Cox proportional hazard models stratified by age (< 70 and ≥ 70), gender (pooled centre).	**margin of [0.737, 1.357]. The similar analysis will be performed for the PPS to support the primary efficacy result.** **For EMA submission, the primary efficacy analysis will be performed for the difference in best ORR by 24 weeks between SB8 and Avastin® in the PPS, and the equivalence will be declared if the two-sided 95% CI of the best ORR difference in contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The Similar analysis will be performed for the FAS to support the primary efficacy.**	
Synopsis-Statistical Methods Safety analyses	All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the grade of severity will be reported by NCI-CTCAE v4.03. AEs will be summarised descriptively by treatment group. Changes in vital signs and clinical laboratory measurements will be summarised descriptively by treatment group and visit. All other safety variables will be summarised descriptively by treatment group.	All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the grade of severity will be reported by NCI-CTCAE v4.03. AEs will be summarised descriptively by treatment group. Changes in vital signs and clinical laboratory measurements will be summarised descriptively by treatment group. ~~**and visit**~~. All other safety variables will be summarised descriptively by treatment group.	Better term
Synopsis-Statistical Methods Immunogenicity analyses	Incidence of ADAs will be summarised by treatment group and **visit** and listed by treatment group	Incidence of ADAs will be summarised by treatment group and **cycle** and listed by treatment group	Better term
Synopsis-Statistical Methods Sample size calculation	**For the calculation of the equivalence margin, AVAiL [Reck, 2010] and E4599 [Sandler, 2006] studies of Avastin®+ cisplatin/gemcitabine (CG) vs. CG alone and of Avastin® + paclitaxel/carboplatin vs. paclitaxel/carboplatin alone, respectively, were**	**For the calculation of the equivalence margin, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck,**	According to US FDA feedback, more references are cited

	considered. In AVAiL study, ORR rates were 21.6% and 37.8% for placebo and Avastin® + CG groups, respectively. In E4599 study, ORR rates were 15.1% (out of 392) and 34.9% (out of 381) for placebo and Avastin® + paclitaxel/carboplatin groups, respectively. **The overall ratio of ORR and its 95% CI from these two studies are calculated to be 2.0217 [1.6943, 2.4124] using the fixed effect method from meta-analysis. The equivalence margin of [0.742 1.450] will preserve 50% of the effect of Avastin® over the placebo in the lower margin.** **The overall difference in ORR and its 80% CI from these two studies are calculated to be CCI % CCI %, CCI %] using the fixed-effect method from meta-analysis. The equivalence margin of [-12.5%, 12.5%] will preserve at least 20% of the effect of Avastin® over the placebo in the difference of ORR.** **With 305 completers in each treatment group, the two-sided 90% CI of the ORR ratio is expected to lie within [0.742, 1.450] with 90% power, and the two-sided 95% CI of the ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.**	**2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered.** **The overall ratio of best ORR and its 70% CI from above four studies are calculated to be CCI [redacted] using the fixed effect method from meta-analysis. Retaining the CCI % of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks.** **For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] will be used due to the similar derivation.** **With 305 completers in each treatment group, the two-sided 90% CI of the best ORR ratio is expected to lie within [0.737, 1.357] with approximately 80% power, and the two-sided 95% CI of the best ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected best ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.**	

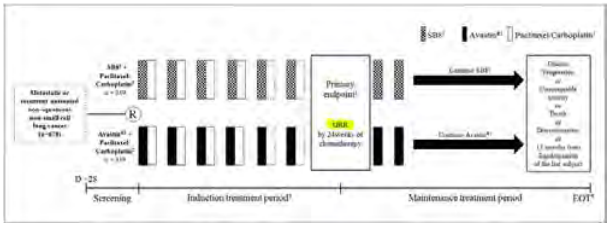
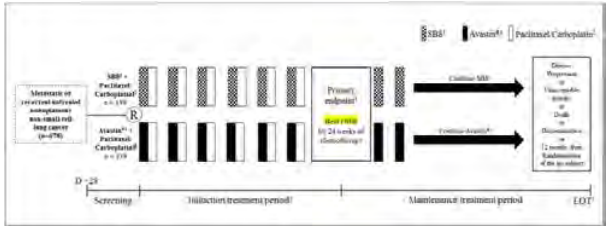
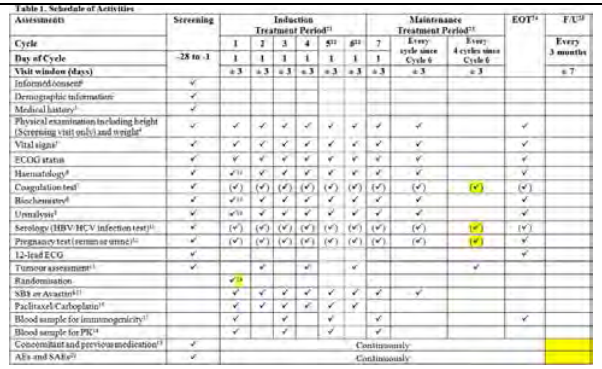
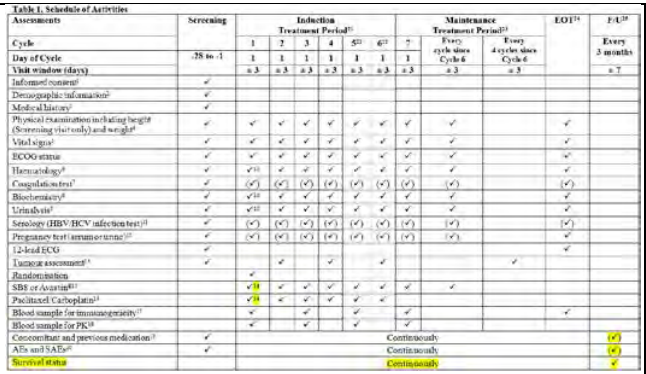
Synopsis-Figure 1	 3 Primary endpoint is the **ORR** by 24 weeks of chemotherapy with SB8 or Avastin®.	 3 Primary endpoint is the **best ORR** by 24 weeks of chemotherapy with SB8 or Avastin®.	According to US FDA feedback
	4 Physical examination, vital sign, ECOG performance status, reviewing the laboratory values including haematology, biochemistry, urinalysis, and reviewing IP compliance will be performed at each cycle. Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles since cycle 6 until disease progression or death or end of study. Tumour response will be assessed using CT or MRI according to local standards.	4 Physical examination, vital sign, ECOG performance status, reviewing the laboratory values including haematology, biochemistry, urinalysis, and reviewing IP compliance will be performed at each cycle. Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles since cycle 6 until disease progression or death or end of study. Tumour response will be assessed using CT or MRI **~~according to local standards~~ following Image Acquisition Guideline that will be provided by Sponsor.**	clarification

Table 1
`

		
	7. Blood coagulation test including prothrombin time/international normalised ratio (PT/INR) will be performed at Screening. Additional blood coagulation test will be performed at the discretion of Investigator if there are any suspicious cases	7. Blood coagulation test including ~~**prothrombin time/**~~international normalised ratio (~~**PT/**~~INR) will be performed at Screening. Additional blood coagulation test will be performed at the discretion of Investigator if there are any suspicious cases	Correct term
	8. Biochemistry tests include creatinine, urea (blood urine nitrogen [BUN]), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), albumin, and electrolytes (sodium, potassium, chloride).	8. Biochemistry tests include creatinine, urea (blood ~~**urine**~~ **urea** nitrogen [BUN]), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), albumin, and electrolytes (sodium, potassium, chloride).	To correct typo error
	9. If urine dipstick is ≥ 2+ (other ways of urinalysis are also acceptable), 24 hours urine protein excretion < 1 g or protein/creatinine ratio in spot urine < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	9. If urine dipstick is ≥ 2+ (other ways of urinalysis are also acceptable), 24 hours urine protein excretion **is** < 1 g or protein/creatinine ratio in spot urine **is** < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	To correct typo error
	11. Hepatitis B and hepatitis C tests should be performed during Screening period. Known history of HIV infection will be confirmed separately at the discretion	11. Hepatitis B and hepatitis C tests should be performed during Screening period **according to local practice.** Known history of HIV infection will be	clarification

	of Investigator. Additional HBV/HCV tests will be performed at the discretion of Investigator if there are any suspicious cases.	confirmed separately at the discrietion of Investigator. Additional HBV/HCV tests will be performed at the discretion of Investigator if there are any suspicious cases.	
	13. Tumour response will be assessed using CT or MRI according to local standards. The same modality used at Screening will be used throughout the study.	13. Tumour response will be assessed using CT or MRI ~~**according to local standards**~~ **following Image Acquisition Guideline that will be provided by Sponsor.** The same modality used at Screening will be used throughout the study.	clarification
	14. The first dose of **IPs** and non IPs should be administered within 7 days after Randomisation.	14. The first dose of **IP and non-IPs** should be administered within 7 days after Randomisation.	plurality
	18. Blood sampling for PK analysis will be performed at pre-dose and post-dose (within 15 minutes after the end of infusion) of Cycle 1, 3, 5, and 7 in approximately 50% of the enrolled subjects.	18. Blood sampling for PK analysis will be performed at pre-dose and post-dose **of IP** (within 15 minutes after the end of infusion) of Cycle 1, 3, 5, and 7 in approximately 50% of the enrolled subjects.	clarification
	19. Concomitant and previous (within 28 days prior to Screening) medications will be recorded at Screening and concomitant medications are to be monitored continuously during the study treatment.	19. Concomitant and previous (within 28 days prior to Screening) medications will be recorded at Screening and concomitant medications are to be monitored continuously during the study treatment **and after EOT visit, if such information is related to SAEs.**	PV rules
	20. All AEs will be recorded from the time when the informed consent form is signed until the EOT visit (progression of NSCLC and death due to progression of NSCLC are not to be reported as an AE or SAE).	20. All AEs will be ~~**recorded**~~ **reported** in the eCRF from the time when the informed consent form is signed until the EOT visit (progression of NSCLC and death due to progression of NSCLC are not to be reported as an AE or SAE). **After the EOT visit, only SAEs will be reported using the paper SAE report form.**	aligned to 7.1.2.
	22. Induction chemotherapy at Cycle 5 and 6 may be replaced with the maintenance therapy at the	22. Induction chemotherapy at Cycle 5 and 6 may be replaced with the maintenance therapy at the discretion	Easier language

	discretion of Investigator. In this case, the schedule of activities must follow those of the maintenance treatment period.	of Investigator. **In this case, all other activities except for non-IPs infusion must follow originally planned activities at each cycle.**	
	25. After completion of study treatment, subjects will be followed for survival status and whether subsequent therapy is received or not by clinic visit or telephone contact every 3 months until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up), EOS date defined as when deaths of all the randomised subjects have been observed, or 12 months from randomisation of the last subject, whichever occurs first.	25. After completion of study treatment, subjects will be followed for survival status and whether subsequent therapy is received or not by clinic visit or telephone contact every 3 months until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up**, or initiation of subsequent therapy for NSCLC**), EOS date defined as when deaths of all the randomised subjects have been observed, or 12 months from randomisation of the last subject, whichever occurs first.	Clarification
List of Abbreviations	ALP Alkaline Phosphate ANOVA Anlaysis of Variance Cmax Maximum Serum Concentration CP Carboplatin/paclitaxel CRF Case Report Form Ctrough Trough Serum Concentration CV Coefficient of Variation EMA European Medicinal Agency HBsAg Hepatitis B surface antigen HCV-Ab Hepatitis C virus antibody IRF Independent Review Facility Nab Neutralising Antibody PTT Partial Thromboplastin Time	**ALP Alkaline Phosphatase** ~~**ANOVA Anlaysis of Variance**~~ **Cmax Maximum ~~Serum~~ Concentration** ~~**CP Carboplatin/paclitaxel**~~ **eCRF Electronic Case Report Form** **Ctrough Trough ~~Serum~~ Concentration** ~~**CV Coefficient of Variation**~~ **EMA European Medicines Agency** **EOT End of Treatment** **EPAR European Public Assessment Reports** ~~**HBsAg Hepatitis B surface antigen**~~ ~~**HCV-Ab Hepatitis C virus antibody**~~ ~~**IRF Independent Review Facility**~~ **NAb Neutralising Antibody** **PC Paclitaxel/carboplatin** ~~**PTT Partial Thromboplastin Time**~~	To correct typo error : removed un-used terms

	RAN Randomised Set	~~**RAN Randomised Set**~~	
Table of Contents	**6.2.6. Unblinding** **6.2.7. Investigational Product Accountability**	~~**6.2.6. Unblinding**~~ **6.2.6. Investigational Product Accountability**	Editorial change: Migrate "Unblinding" to Section 7.1.6.
	7.1.6. Expectedness Assessment **7.1.7. Withdrawal Due to Adverse Events**	**7.1.6. Emergency Unblinding for Safety Reasons** ~~**7.1.6**~~ **7.1.7. Expectedness Assessment** ~~**7.1.7**~~ **7.1.8. Withdrawal Due to Adverse Events**	Editorial change: Migrate "Unblinding" to Section 7.1.6.
	8.4. Interim Analysis	**8.4.** ~~**Interim Analysis**~~ **Statistical Analysis Timepoints**	Better term
List of Tables	**Table 3. Medications and Therapies of NSCLC Prohibited prior to Randomisation and throughout the Study**	**Table 3. Prohibited Medications and Therapies of NSCLC**	Simplification
List of Study Staff	SPONSOR Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, **406-840**	SPONSOR Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, **21987**	New postal code
1. INTRODUCTION 1.1. Background	**AvaiL**	**AVAiL**	To correct typo error
	This result of OS is not inferior than that from another study with 6 cycles of chemotherapy [Patel, 2013].	This result of OS **is not inferior** ~~**than**~~ **to** that from another study with 6 cycles of chemotherapy [Patel, 2013].	To correct typo error
1.2.2. Non-clinical Data of SB8	In addition, in vivo non-clinical toxicology has been performed in cynomoulgus monkeys with SB8 and	In addition, in vivo non-clinical toxicology has been performed in ~~**cynomoulgus**~~ **cynomolgus monkeys** with	To correct typo error

	Avastin®.	SB8 and Avastin®.	
1.2.3. Clinical Data of SB8	Information on the safety of SB8 based on **the reference product information and non-clinical and work is** presented in the Investigator's Brochure (IB).	Information on the safety of SB8 based on **the product information of Avastin®** is presented in the Investigator's Brochure (IB).	Better term
1.3.2.1. Avastin® in Non-small Cell Lung Cancer	**AvaiL** study [Reck, 2009] Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 IV infusion on Day 1 and gemcitabine 1250 mg/m2 IV infusion on Days 1 and 8 of every 3 week cycle for up to 6 cycles (GC) with placebo or **CG** with Avastin® at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle.	**AVAiL** study [Reck, 2009] Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 IV infusion on Day 1 and gemcitabine 1250 mg/m2 IV infusion on Days 1 and 8 of every 3 week cycle for up to 6 cycles (GC) with placebo or **GC** with Avastin® at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle.	Unify to GC than mixed use of GC and CG
1.4. Rationale for the Study	Two drug chemotherapy **regimen** which combine a platinum agent with paclitaxel, docetaxel, vinorelbine, irinotecan, and gemcitabine are usually accepted as standard of care for the treatment of advanced NSCLC. In **AvaiL study,** median PFS was significantly increased (6.7 months vs. 6.1 months) in high dose bevacizumab group compared with placebo [Reck, 2009].	Two drug chemotherapy **regimens** which combine a platinum agent with paclitaxel, docetaxel, vinorelbine, irinotecan, and gemcitabine are usually accepted as standard of care for the treatment of advanced NSCLC. In **AVAiL study,** median PFS was significantly increased (6.7 months vs. 6.1 months) in high dose bevacizumab group compared with placebo [Reck, 2009].	Plurality
2. STUDY OBJECTIVES 2.1. Primary Objective	**Overall response rate** **ORR**	**Best overall response rate** **best ORR**	According to US FDA feedback
2.3. Exploratory Objective	**ORR**	**best ORR**	According to US FDA feedback
3. STUDY DESIGN 3.1. Overview of	Subjects with metastatic or recurrent non-squamous NSCLC with unknown or without activating epidermal	Subjects with metastatic or recurrent non-squamous NSCLC ~~**with unknown or without**~~ **without known**	According to US FDA

Study Design	growth factor receptor (EGFR) gene mutations or anaplastic lymphoma kinase (ALK) gene translocations will be randomised	**activating** epidermal growth factor receptor (EGFR) gene mutations or anaplastic lymphoma kinase (ALK) gene translocations will be randomised	feedback
3.2. Rationale for Study Design	3.2.1. Rationale for Dose Selection of SB8 or Avastin® **AvaiL**	3.2.1. Rationale for Dose Selection of SB8 or Avastin® **AVAiL**	To correct typo error
4. STUDY POPULATION 4.2. Inclusion Criteria	1. Aged ≥ 18 years	1. Aged ≥ 18 years **(if local regulations are different in this regard, follow the local regulations).**	Different country regulations, e.g. Taiwan
	7.b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion < 1 g or protein/creatinine ratio in spot urine < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	7.b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion **is** < 1 g or protein/creatinine ratio in spot urine **is** < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	To correct typo error
4.3. Exclusion Criteria	7. Radiotherapy within 28 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy except for pain relief, are not considered as measurable lesion.).	7. Radiotherapy within 28 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy ~~except for pain relief,~~ are not considered as measurable lesion **unless there has been demonstrated progression in the lesion.).**	According to RECIST v.1.1
	9. Minor surgical procedure within 7 days prior to Randomisation (requiring local anaesthesia or following procedures: **medianoscopy**, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle biopsy [EBUS & TBNA], pleural biopsy, **thoracenthesis**, pleurodesis, catheter insertions/removal, tooth extraction, superficial incision	9. Minor surgical procedure within 7 days prior to Randomisation (requiring local anaesthesia or following procedures: **mediastinoscopy,** percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle biopsy [EBUS & TBNA], pleural biopsy, **thoracentesis,** pleurodesis, catheter insertions/removal, tooth extraction, superficial incision	To correct typo error

	11. Known or clinically suspected brain metastasis and/or leptomeningeal disease.	11. ~~Known or clinically suspected~~ **Symptomatic** brain metastasis and/or leptomeningeal disease.	Investigator's feedback
	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [> 75 mg/day], regular use of aspirin [> 325 mg/day)], dipyridamole, ticlopidine and/or cilostazol);	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [> 75 mg/day], **regular use of aspirin ~~[> 325 mg/day)],~~** dipyridamole, ticlopidine and/or cilostazol);	No lower limit of Aspirin dose
	18.h. Gastrointestinal bleeding, **heamatemesis** or haemoptysis (≥ 1/2 teaspoon of red blood).	18.h. Gastrointestinal bleeding**, haematemesis** or haemoptysis (≥ 1/2 teaspoon of red blood).	To correct typo error
5. STUDY PROCEDURES AND ASSESSMENT 5.1. Procedures by Study Period 5.1.1. Screening Period	- Blood coagulation test including prothrombin time/international normalised ratio (PT/INR)	- Blood coagulation test including ~~**prothrombin time/**~~international normalised ratio ~~**(PT/**~~INR)	Correct term
	- Urinalysis (dipstick): leukocytes, nitrite, urobilinogen, protein, pH, Hb, specific gravity, ketone, bilirubin, glucose (other ways of urinalysis are also allowed), if urine dipstick is ≥ 2+, 24 hours urine protein excretion < 1 g or protein/creatinine ratio in spot urine < 1 g/g creatinine (or < 226.0 mg/mmol **creatitnine)**	- Urinalysis (dipstick): leukocytes, nitrite, urobilinogen, protein, pH, Hb, specific gravity, ketone, bilirubin, glucose (other ways of urinalysis are also allowed), if urine dipstick is ≥ 2+, 24 hours urine protein excretion **is** < 1 g or protein/creatinine ratio in spot urine **is** < 1 g/g creatinine (or < 226.0 mg/mmol **creatinine)**	Correct term
	- Serology: **Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (HCV-Ab) tests,** known history of HIV infection will be confirmed separately at the discretion of Investigator.	- Serology: **test for Hepatitis B and hepatitis C should be performed during Screening period according to local practice**. Known history of HIV infection will be confirmed separately at the discretion of Investigator.	Remove specific tests
	• Baseline tumour assessment (within a maximum 21 days prior to Randomisation) of lung and locoregional lymph nodes by CT scan or MRI. Upper abdominal cavity including the adrenal glands must be included in imaging study. If the case baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. In case of negative confirmation of	• Baseline tumour assessment (within a maximum 21 days prior to Randomisation) of lung and locoregional lymph nodes by CT scan or MRI. Upper abdominal cavity including the adrenal glands must be included in imaging study. If the case baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. ~~**In case of negative confirmation**~~	Clarification

	measurable lesion(s) by the independent central reviewer before subject Randomisation, the concerned subject will be considered as screen failure.	~~**of measurable lesion(s) by the independent central reviewer before subject Randomisation, the concerned subject will be considered as screen failure**~~. **Baseline tumour assessment should be done after allowed surgical procedure to suspected target or non-target lesions (see Sections 4.3. and 5.2.1.).**	
5.1.3. Induction Treatment Period (Cycle 1 to Cycle 6)	• Haematology, biochemistry, and urinalysis (if urine dipstick is ≥ 2+, see Section 7.3.2.) – **laboratory tests may not need to be repeated** if tests have been performed within 14 days prior to Day 1 of Cycle 1.	• Haematology, biochemistry, and urinalysis (if urine dipstick is ≥ 2+, see Section 7.3.2.) – **Repeated laboratory tests may not be needed** if tests have been performed within 14 days prior to Day 1 of Cycle 1.	To correct typo error
	• Serology: **HBsAg and HCV-Ab tests** will be repeated during the course of the study only when clinically suspected.	• Serology: **tests for HBV or HCV** will be repeated during the course of the study only when clinically suspected.	Remove specific tests
	• Premedication of **IPs and/or Non-IPs** (if necessary, see Section 6.6.1.)	• Premedication of IP and/or Non-IPs (if necessary, see Section 6.6.1.) **• Administration of IP and non-IPs on Day 1 of each cycle for at least 4 cycles and up to 6 cycles**	Plurality
	• Blood sampling for PK (approximately 50% of enrolled subjects) at pre-dose and post-dose (within 15 minutes after the end of infusion) of Cycle 1, 3, and 5	• Blood sampling for PK (approximately 50% of enrolled subjects) at pre-dose and post-dose **of IP** (within 15 minutes after the end of infusion) of Cycle 1, 3, and 5	Editorial change
	In case of early switch to maintenance treatment period, subject blood sampling will be collected **at Cycle 3 and/or 5 in the maintenance period,** if applicable.	In case of early switch to maintenance treatment period, subject blood sampling will be collected **as originally planned at Cycle 3 and/or 5,** if applicable.	Easier language
	IPs and non-IPs will be administered on Day 1 of each cycle for at least 4 cycles and up to 6 cycles	~~IPs and non-IPs will be administered on Day 1 of each cycle for at least 4 cycles and up to 6 cycles~~	Redundant
5.1.4. Maintenance Treatment Period	• Serology: **HBsAg and HCV-Ab tests** will be repeated during the course of the study only when clinically	• Serology: **tests for HBV or HCV** will be repeated during the course of the study only when clinically	Remove specific tests

	suspected.	suspected.	
	• Review of concomitant medication	• Review of concomitant medication **• Administration of IP every 3 weeks on Day 1 of each cycle**	Clarification
	If a treatment is delayed, concerned laboratory tests will be repeated within 3 days before the administration of IPs of each cycle.	If a treatment is delayed, concerned laboratory tests will be repeated within 3 days before the administration of IP~~s~~ of each cycle.	To correct typo error
	• Blood sampling for PK (approximately 50% of enrolled subjects) at pre-dose and post-dose (within 15 minutes after the end of infusion) of Cycle 3, 5, and 7.	• Blood sampling for PK (approximately 50% of enrolled subjects) at pre-dose and post-dose **of IP** (within 15 minutes after the end of infusion) of Cycle 3, 5, and 7.	To correct typo error
	• Administration of IPs every 3 weeks on Day 1 of each cycle	~~**• Administration of IPs every 3 weeks on Day 1 of each cycle**~~	Editorial change
5.2. Efficacy Assessment	**ORR**	**best ORR**	According to US FDA feedback
	• PFS, defined as the time from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of the EOT visit.	• PFS, defined as the time from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of the EOT visit **or the date of last tumour assessment if the EOT visit is not available.**	Clarification of PFS
5.2.1. Measurability of Tumour	All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions	All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions **are non-measurable.**	To correct typo error
5.2.1.2. Criteria for Tumour Response	Evaluation of Measurable Lesions Tumour response will be evaluated according to the	Evaluation of Measurable Lesions Tumour response will be evaluated according to the	To correct typo error and

<table>
<tr><td>Evaluation</td><td>RECIST v1.1 criteria. Subjects should continue to undergo tumour response assessment until PD, acceptable toxicity, death or end of study.
In this study, tumour response will be measured using CT scan or MRI (other methods such as X-ray, ultra sound are not permitted for monitoring target lesions).</td><td>RECIST v1.1 criteria. Subjects should continue to undergo tumour response assessment until PD, unacceptable toxicity, death or end of study.
In this study, tumour response will be measured using CT scan or MRI (other methods such as X-ray, ultra sound are not permitted for monitoring target lesions) following Image Acquisition Guideline that will be provided by Sponsor.</td><td>clarification</td></tr>
<tr><td>Table 2</td><td>
<table>
<tr><th>Target lesions</th><th>Non-target lesions</th><th>New Lesions</th><th>Overall response</th></tr>
<tr><td>CR</td><td>CR</td><td>No</td><td>CR</td></tr>
<tr><td>CR</td><td>Non-CR/Non-PD[a]</td><td>No</td><td>PR</td></tr>
<tr><td>CR</td><td>Not evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>PR</td><td>Non-PD[a] or not all evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>SD</td><td>Non-PD[a] or not all evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>Not all evaluated</td><td>Non-PD[a]</td><td>No</td><td>inevaluable</td></tr>
<tr><td>PD</td><td>Any category</td><td>Yes or No</td><td>PD</td></tr>
<tr><td>Any category</td><td>PD[a]</td><td>Yes or No</td><td>cPD</td></tr>
<tr><td>Any category</td><td>Any category</td><td>Yes</td><td>cPD</td></tr>
</table>
</td><td>
<table>
<tr><th>Target lesions</th><th>Non-target lesions</th><th>New Lesions</th><th>Overall response</th></tr>
<tr><td>CR</td><td>CR</td><td>No</td><td>CR</td></tr>
<tr><td>CR</td><td>Non-CR/Non-PD[a]</td><td>No</td><td>PR</td></tr>
<tr><td>CR</td><td>Not evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>PR</td><td>Non-PD[a] or not all evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>SD</td><td>Non-PD[a] or not all evaluated</td><td>No</td><td><s>PR</s> SD</td></tr>
<tr><td>Not all evaluated</td><td>Non-PD[a]</td><td>No</td><td>inevaluable</td></tr>
<tr><td>PD</td><td>Any category</td><td>Yes or No</td><td>PD</td></tr>
<tr><td>Any category</td><td>PD[a]</td><td>Yes or No</td><td><s>cPD</s> PD</td></tr>
<tr><td>Any category</td><td>Any category</td><td>Yes</td><td><s>cPD</s> PD</td></tr>
</table>
</td><td>To correct typo error</td></tr>
<tr><td>5.2.2. Timing of Overall Response</td><td>The overall response is determined once all the data for the subject is known. Best response determination in the</td><td>The overall response is determined once all the data for the subject is known. For best response determination in</td><td>To correct typo error</td></tr>
</table>

<table>
<tr><td>Rate Evaluation: All Time Points</td><td>study where confirmation of complete or partial response IS NOT required:</td><td>the study, confirmation of complete or partial response is NOT required.</td><td></td></tr>
<tr><td>5.3.1. Clinical Safety Assessment</td><td>Safety of subjects will be monitored by physical examination, performance status and vital sign assessment. Subjects will be assessed for AEs at each clinical visit and as necessary throughout the study. A complete medical history will be performed at Screening.</td><td>Safety of subjects will be monitored by physical examination, performance status and vital sign assessment. Subjects will be assessed for AEs at each clinical visit and as necessary throughout the study. <s>A complete medical history will be performed at Screening.</s></td><td>Meaningless sentence</td></tr>
<tr><td rowspan="2">5.3.2. Laboratory Assessment</td><td>• A coagulation test (PT/INR) will be performed at Screening and during the study if clinically suspected.</td><td>• A coagulation test (<s>PT/</s>INR) will be performed at Screening and during the study if clinically suspected.</td><td>To correct typo error</td></tr>
<tr><td>• Serology tests (HBsAg and HCV-Ab) will be repeated during the course of the study only when clinically suspected.</td><td>• <s>Serology tests (HBsAg and HCV-Ab)</s> Tests for HBV or HCV will be repeated during the course of the study only when clinically suspected.</td><td>Remove specific tests</td></tr>
<tr><td>5.4.1. Pharmacokinetic Assessments</td><td>Approximately 50% of the enrolled subjects will be participating by default in the PK sub-study for PK assessment and those subjects will be defined at the time of randomisation in the IWR system. Once the number of subjects is reached to planned number, all further subjects enrolled will not participate the PK sub-study.
Blood sampling for PK analysis will be performed at pre-dose and post-dose (within 15 minutes after the end of infusion) of Cycle 1, 3, 5 and 7.</td><td>Approximately 50% of the enrolled subjects will be participating by default in the PK sub-study for PK assessment and those subjects will be defined at the time of randomisation in the IWRS. Once the number of subjects is reached to the planned number, all further subjects enrolled will not participate in the PK sub-study.
Blood sampling for PK analysis will be performed at pre-dose and post-dose of IP (within 15 minutes after the end of infusion) of Cycle 1, 3, 5 and 7.</td><td>Unify to IWRS</td></tr>
<tr><td>Table 3</td><td>Table 3. Medications and Therapies of NSCLC Prohibited prior to Randomisation and throughout the Study
<table>
<tr><th>Medication or therapies</th><th>Time to be prohibited</th></tr>
<tr><td>Aspirin or NSAIDs with-<s>antiplatelet activity</s></td><td>From Randomisation to EOT</td></tr>
</table></td><td>Table 3. Prohibited Medications and Therapies of NSCLC
<table>
<tr><th>Medication or therapies</th><th>Time to be prohibited</th></tr>
<tr><td><s>Aspirin or NSAIDs with antiplatelet activity</s></td><td><s>From Randomisation to EOT</s></td></tr>
</table></td><td>Simplification
Clarification of time to prohibited</td></tr>
</table>

Anticoagulants or thrombolytic agent:		
Clopidogrel (> 75 mg/day), regular use of aspirin (> 325 mg/day), dipyridamole, ticlopidine and/or cilostazol	Within 10 days prior to Randomisation	
Warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitors, thrombolytic agents including tissue plasminogen activator, anistreplase, streptokinase, urokinase	Within 28 days prior to Randomisation	
Any drugs (include herbal medications) that has not received regulatory approval for any indications	From Randomisation to EOT	
Anticancer chemotherapy regimen other than paclitaxel/carboplatin[a]	From Randomisation to EOT	
Major surgical procedure (include open lung biopsy)[b]	Within 28 days prior to Randomisation	
Minor surgical procedure[c]	Within 7 days prior to Randomisation	
Live/attenuated vaccine	Within 12 weeks prior to Randomisation	
Intravenous bisphosphonates and/or invasive dental procedure	Within 28 days prior to Randomisation	

Anticoagulants or thrombolytic agent:		
Clopidogrel (> 75 mg/day), regular use of aspirin ~~**(> 325 mg/day)**~~ **or NSAID with antiplatelet activity**, dipyridamole, ticlopidine and/or cilostazol	Within 10 days prior to Randomisation **to EOT**	
Warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitors, thrombolytic agents including tissue plasminogen activator, anistreplase, streptokinase, urokinase	Within 28 days prior to Randomisation **to EOT**	
Any drugs (include herbal medications) that has not received regulatory approval for any indications	From Randomisation to EOT	
Anticancer chemotherapy regimen other than paclitaxel/carboplatin[a]	From Randomisation to EOT	
Major surgical procedure (include open lung biopsy)[b]	Within 28 days prior to Randomisation	
Minor surgical procedure[c]	Within 7 days prior to Randomisation	
Live/attenuated vaccine	Within 12 weeks prior to Randomisation **to Cycle 7 Day 1**	

		Intravenous bisphosphonates and/or invasive dental procedure: Within 28 days prior to Randomisation **to EOT** **Radiotherapy[d]: Within 28 days prior to Randomisation**	
	a Requiring more extensive procedure than local anaesthesia (involving general anaesthesia or respiratory assistance or regional anaesthesia) or open lung biopsy. b Requiring local anaesthesia or following procedures; **medianoscopy**, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle aspiration (EBUS & TBNA), pleural biopsy, thoracentesis, pleurodesis, catheter insertion/removal, tooth extraction, superficial incision.	**a Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study.** ~~a~~**b** Requiring more extensive procedure than local anaesthesia (involving general anaesthesia or respiratory assistance or regional anaesthesia) or open lung biopsy. ~~b~~**c** Requiring local anaesthesia or following procedures; mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle aspiration (EBUS & TBNA), pleural biopsy, thoracentesis, pleurodesis, catheter insertion/removal, tooth extraction, superficial incision. **d Radiotherapy of palliative purpose to non-progressive non-target lesions is allowed during the treatment period. If target lesions are included in irradiated field, then those lesions should not be evaluated as measurable thereafter. It is strongly recommended that the Investigator consult to the Sponsor at the timing of planning radiotherapy. IP and non-IPs should be suspended during radiotherapy and may be resumed at the discretion of the Investigator.**	Investigator's feedback about palliative RT during the study
6. TREATMENT	**6.2.6. Unblinding**	**7.1.6. Emergency Unblinding for Safety Reasons**	The title of

AND INVESTIGATION-AL PRODUCT	Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's **care** by their Investigator or a regulatory body. In general, unblinding of subjects during the conduct of the clinical study is not allowed unless there are compelling medical or safety reasons to do so. The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual. If the blind is broken, it may be broken only for the subject in question. The Sponsor must be notified immediately if a subject and/or Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information.	Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's **~~care~~ safety** by their Investigator or a regulatory body. In general, unblinding of subjects during the conduct of the clinical study is not allowed unless there are compelling medical or safety reasons to do so. The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual. If the blind is broken, it may be broken only for the subject in question. The Sponsor must be notified before or immediately after a subject and/or Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information.	section 6.2.6. is changed to "Emergency Unbliding for Safety Reasons" and the section is inserted between Section 7.1.5. and 7.1.6.
	6.2.7. Investigational Product Accountability	**6.2.6.** Investigational Product Accountability	Editorial change
6.3.1.1. Preparation and Storage of Paclitaxel	Refer to the prescribing information in paclitaxel for the formulation, preparation, and storage of paclitaxel.	Refer to the prescribing information in paclitaxel for the formulation, preparation, and storage of paclitaxel. **Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study.**	
6.4.2. Schedule Modification of SB8 or Avastin®	• **Gastointestinal** perforations (gastrointestinal perforation, fistulae formation in the gastrointestinal tract, intra-abdominal abscess), fistulae formation involving an internal organ	• **Gastrointestinal** perforations (gastrointestinal perforation, fistulae formation in the gastrointestinal tract, intra-abdominal abscess), fistulae formation involving an internal organ	To correct typo error

Table 6

Non-Haematological AE			
Nausea/vomiting	Grade ≥ 3	1st event	• Maintain the same dose.
		2nd event	• Reduce dose by one level.
Diarrhea lasting > 24 hours despite maximum anti-diarrheal management	Grade ≥ 3	1st event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.
		2nd event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.
Mucositis	Grade ≥ 3	1st event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.
		2nd event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.

Non-Haematological AE			
Nausea/vomiting	Grade ≥ 3	1st event	• Maintain the same dose.
		2nd event	• Reduce dose by one level.
		3rd event or later	• **Maintain the reduced dose**
Diarrhea lasting > 24 hours despite maximum anti-diarrheal management	Grade ≥ 3	1st event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.
		2nd event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.
		3rd event or later	• **Hold until recovery to ≤ grade 1 or baseline. Once recovers, maintain the reduced dose.**
Mucositis	Grade ≥ 3	1st event	• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.
		2nd event	• Hold until

More sophistication

							recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.	
						3rd event or later	• **Hold until recovery to ≤ grade 1 or baseline.** • **Once recovers, maintain the reduced dose.**	
	Hepatic dysfunction	Increased AST or ALT Grade ≥ 2 and Increased total bilirubin Grade 1	• Hold until AST/ALT have recovery to ≤ grade 1 or baseline. • Once recovers, - Maintain the same dose if bilirubin within normal limit. - If bilirubin is still increased to grade 1, Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.	**Biochemistry**	Increased AST or ALT Grade ≥ 2 and Increased total bilirubin Grade 1	• Hold until AST/ALT ~~have~~ recovery to ≤ grade 1 or baseline. • Once **AST/ALT** recovers, - Maintain the same dose if bilirubin within normal limit. - If bilirubin is still **increased** to grade 1, Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.		
		Grade ≥ 3 AST or ALT or Grade ≥ 2 total bilirubin	• Hold until AST/ALT and bilirubin have returned to ≤ grade 1 or baseline. • Once recover, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.		Grade ≥ 3 AST or ALT or Grade ≥ 2 total bilirubin	• Hold until AST/ALT and bilirubin ~~have returned~~ **recovery to** ≤ grade 1 or baseline. • Once **AST/ALT and bilirubin recover**, - Paclitaxel: reduce		

		dose by one level. Carboplatin: maintain the same dose.	
6.6. General Concomitant Medication and Supportive Care Guidelines	In addition, any diagnostic, therapeutic or surgical procedure performed during the study period (from Screening to end of study), must be recorded.	In addition, any diagnostic, therapeutic or surgical procedure performed during the ~~study~~ **treatment** period (from Screening to end of ~~study~~ **treatment**), must be recorded.	Clarify time frame
6.6.5. Other Supportive Care	Subjects with anemia can be treated according to the local practice. Subjects using bisphosphonate therapy for their approved labeled indication is not permitted during the study (see Section 6.2.5.).	Subjects with anemia can be treated according to the local practice**.** ~~Subjects using~~ **Intravenous** bisphosphonate therapy for their approved labeled indication is not permitted during the study (see Section 6.2.5.).	To correct typo error
7. SAFETY MONITORING AND REPORTING 7.1.1.2. Clinically Significant Abnormalities	**Any clinically significant abnormality** discovered during the laboratory test, physical examination, vital signs and/or other safety assessments should be reported as an AE.	**If there are any abnormalities** discovered during the laboratory test, physical examination, vital signs and/or other safety assessments ~~**should be reported as an AE.**~~ **and the abnormality is assessed clinically significant by the Investigator, it should be reported as an AE**.	Broader definition of AE
	Laboratory Test Abnormalities If the Investigator determines a laboratory abnormality or out of range result to be clinically significant, it will be reported as an AE however, if the laboratory test abnormality is consistent with a current diagnosis or pre-existing conditions, it should be documented accordingly and will not be recorded as an AE. Vital Signs, Physical Examinations and Other Safety Assessments If a vital sign result is outside the expected range for the subject's age, gender and race then it should be repeated	~~**Laboratory Test Abnormalities**~~ ~~**If the Investigator determines a laboratory abnormality or out of range result to be clinically significant, it will be reported as an AE however, if the laboratory test abnormality is consistent with a current diagnosis or pre-existing conditions, it should be documented accordingly and will not be recorded as an AE.**~~ ~~**Vital Signs, Physical Examinations and Other Safety Assessments**~~ ~~**If a vital sign result is outside the expected range for**~~	Simplification

	after 5 minutes' rest. If the repeat result is outside the expected range and clinically significant then it should be reported as an AE. Any clinically significant abnormality discovered during the physical examination or other safety assessment should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening.	~~**the subject's age, gender and race then it should be repeated after 5 minutes' rest. If the repeat result is outside the expected range and clinically significant then it should be reported as an AE.**~~ ~~**Any clinically significant abnormality discovered during the physical examination or other safety assessment should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening.**~~	
7.1.2. Period of Observation for Adverse Events	AEs will be **recorded** from the time the informed consent form (ICF) is signed until the EOT visit. **During the follow-up period after the EOT visit, SAEs that are considered to be related to the IP will be recorded.**	AEs will be **reported** from the time the informed consent form (ICF) is signed until the EOT visit. **After the EOT visit, only SAEs will be reported.** **The Investigator does not need to actively monitor subjects for AEs once the clinical study has ended. However, SAEs that occurred after the EOS should be reported to the Sponsor if the Investigator becomes aware of the SAEs.**	Clarification about post-EOT PV rules
	SAEs that are considered to be related to the IP can be collected regardless of planned clinical study period. If the Investigator detects an SAE in a subject after the EOS, and considers the event to be related to the IP, the Investigator should contact Sponsor to determine how the SAE should be documented and reported.	~~**SAEs that are considered to be related to the IP can be collected regardless of planned clinical study period. If the Investigator detects an SAE in a subject after the EOS, and considers the event to be related to the IP, the Investigator should contact Sponsor to determine how the SAE should be documented and reported.**~~	Clarification about post-EOT PV rules
	Unresolved AEs during the study period should be followed up until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up), or EOS date,	Unresolved AEs until **the ~~Study~~ EOT** should be followed up until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up**, or initiation of subsequent therapy for NSCLC**),	Clarification about post-EOT PV rules

		or EOS date,	
	6.2.6. Unblinding Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's care by their Investigator or a regulatory body. In general, unblinding of subjects during the conduct of the clinical study is not allowed unless there are compelling medical or safety reasons to do so. The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual. If the blind is broken, it may be broken only for the subject in question. The Sponsor must be notified immediately if a subject and/or Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information.	**7.1.6. Emergency Unblinding for Safety Reasons** Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the subject's ~~**care**~~ **safety** by their Investigator or a regulatory body. In general, unblinding of subjects during the conduct of the clinical study is not allowed unless there are compelling medical or safety reasons to do so. The IWRS will be used to break the blind and details on how to do this are provided in the IWRS manual. If the blind is broken, it may be broken only for the subject in question. The Sponsor must be notified before or immediately after a subject and/or **the** Investigator is unblinded during the course of the study along with the reason for breaking the blind. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents. This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the date of the unblinding and the relevant IP information.	The title of section 6.2.6. is changed to "Emergency Unbliding for Safety Reasons" and the section is migrated to between Section 7.1.5. and 7.1.6.
	7.1.6. Expectedness Assessment	**7.1.7.** Expectedness Assessment	Editorial change
	7.1.7. Withdrawal Due to Adverse Events Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons. Subjects withdrawn due to an AE should be followed up until the time point specified in the protocol. **Subjects who discontinue the administration of IPs**	**7.1.8.** Withdrawal Due to Adverse Events Subject withdrawal from the study due to an AE should be distinguished from withdrawal due to personal reasons. Subjects withdrawn due to an AE should be followed up until the time point specified in the protocol. **When a subject withdraws from the study**	Editorial change

	because of serious or significant safety issues should be followed closely until the AEs are resolved or stabilised. **When a subject withdraws from the study due to an SAE, the SAE must be reported in accordance with the requirements outlined in Section 7.2.2.**	**due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 7.2.2.** **Subjects who discontinue the administration of IPs because of serious or significant safety issues should be followed closely until the events are fully and permanently resolved or stabilised.**	
7.2.2. Reporting Serious Adverse Event	SAEs must be immediately reported at least within 24 h of the Investigator becoming aware of the event to Sponsor or its designated representative using the SAE report form provided by the Sponsor.	SAEs **before EOT visit** must be immediately reported at least within 24 h of the Investigator becoming aware of the event to Sponsor or its designated representative using the **SAE report form in the eCRF.** ~~**provided by the Sponsor.**~~ **SAEs that occurred after the EOT visit must be reported at least within 24 h of the Investigator becoming aware of the event to Sponsor or its designated representative using the paper SAE report form. Contact information for SAE reporting will be provided in SAE Report Completion Instruction.**	Clarification to report SAE
	The Investigator is obligated to pursue and provide information to Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured.	The Investigator is obligated to pursue and provide information to Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured **in the SAE report form.**	Clarification to report SAE
7.3.2. Proteinuria	If subject is discovered to have ≥ 2+ proteinuria on urine dipstick (or other ways of urinalysis) and demonstrate 24 hours urine protein excretion < 1 g or protein/creatinine ratio in spot urine < 1 g/g creatinine (or < 226.0	If subject is discovered to have ≥ 2+ proteinuria on urine dipstick (or other ways of urinalysis) and demonstrate 24 hours urine protein excretion ≥ 1 g or protein/creatinine ratio in spot urine ≥ 1 g/g creatinine	To correct typo error

	mg/mmol creatinine), should be classified as AESI.	(or ≥ 226.0 mg/mmol creatinine), should be classified as AESI.	
7.4. Pregnancy	Although pregnancy is not an AE, all pregnancies must be followed up every 2 months until 6-8 weeks after the outcome of the pregnancy becomes available, unless the subject is lost to follow-up.	Although pregnancy is not an AE, all pregnancies must be followed up ~~**every 2 months**~~ until 6-8 weeks after the outcome of the pregnancy becomes available, unless the subject is lost to follow-up.	More feasible to conduct
8. STATISTICAL CONSIDERATION AND ANALYTICAL PLAN 8.1. Analysis Sets	• Full analysis set (FAS): FAS will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to.	• Full analysis set (FAS): FAS will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to **by intention-to-treat principle. However, subjects who do not qualify for randomisation and are inadvertently randomised into the study will be excluded from FAS, provided these subjects do not receive any IP during the study.**	According to US FDA feedback
	• Per-protocol set (PPS): PPS will consists of all FAS subjects who complete at least two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. The PPS will be the primary efficacy analysis set.	• Per-protocol set (PPS): PPS will ~~**consists**~~ **consist** of all FAS subjects who complete at least two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. ~~**The PPS will be the primary efficacy analysis set.**~~	Editorial change
8.2.2.1. Primary Efficacy Analysis	The primary efficacy endpoint is the **ORR** by 24 weeks of chemotherapy. The **ORR** is defined as the proportion of subjects whose best overall response is either CR or PR according to RECIST v1.1 during the induction treatment period. If a subject has either CR or PR at least once during the induction treatment period, the subject will be considered as the responder. Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and	The primary efficacy endpoint is the **best ORR** by 24 weeks of chemotherapy. The **best ORR** is defined as the proportion of subjects whose best overall response is either CR or PR according to RECIST v1.1 during the induction treatment period. If a subject has either CR or PR at least once during the induction treatment period, the subject will be considered as the responder. Tumour assessment will be performed after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3,	According to US FDA feedback

	will be performed every 4 cycles according to RECIST v1.1 and assessed by both investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review. The primary efficacy analysis will aim to demonstrate equivalence in the **ORR** between SB8 and Avastin® in the PPS. The null hypothesis tested for the primary efficacy analysis will be either (1) SB8 is inferior to Avastin® or (2) SB8 is superior to Avastin® based on a pre-specified equivalence margin. For US Food and Drug Administration submission, the primary efficacy analysis will be performed **for the response ratio (SB8 response rate/ Avastin® response rate), and the equivalence will be declared if the 90% C.I. is contained within the proposed equivalence margin of [0.742, 1.450].** For EMA submission, the primary efficacy analysis will be performed for the difference in the ORR, and the equivalence between the two treatment groups will be declared if the 95% confidence interval (CI) is entirely contained within the pre-justified equivalence margin of [-12.5%, 12.5%]. **The analysis method in detail will be described in the SAP, and the SAP will be finalised prior to the first database lock.** **The same analysis planned for the primary efficacy analysis will be repeated for the FAS to explore the robustness of the results. In this analysis, subjects who withdraw early without any tumour assessment**	5, and 7 and will be performed every 4 cycles according to RECIST v1.1. **Tumour size will be** assessed by both investigators and independent central reviewer. The primary efficacy analysis will be based on the data from the independent central review. The primary efficacy analysis will aim to demonstrate equivalence in the **best ORR** between SB8 and Avastin® ~~**in the PPS**~~. The null hypothesis tested for the primary efficacy analysis will be either (1) SB8 is inferior to Avastin® or (2) SB8 is superior to Avastin® based on a ~~**pre-specified**~~ **pre-defined** equivalence margin. For US Food and Drug Administration submission, the primary efficacy analysis will be performed **in the FAS for the ratio of best ORR by 24 weeks (best ORR of SB8/ best ORR of Avastin®), and the equivalence will be declared if the 90% confidence interval(CI) of the best ORR ratio is contained within the pre-defined equivalence margin of [0.737, 1.357].** The similar analysis will be performed for the PPS to support the primary analysis. For EMA submission, the primary efficacy analysis will be performed **in the PPS** for the difference in the **best** ORR **by 24 weeks**, and the equivalence between the two treatment groups will be declared if the 95% ~~**confidence interval (CI)**~~ **CI of the difference** is entirely contained within the ~~**pre-justified**~~ **pre-defined** equivalence margin of [-12.5%, 12.5%]. **The similar analysis will be performed for the FAS to**	

	will be considered as non-responders.	**support the primary analysis.** **The statistical method to get the CI for primary analysis will be described in the Statistical Analysis Plan (SAP), and the SAP will be finalised prior to the first database lock.**	
8.2.2.2. Secondary Efficacy Analyses	The secondary efficacy endpoints are as following: • Progression free survival (PFS): PFS is defined as the time from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of the EOT visit. • Overall Survival (OS): OS is defined as the time from the date of Randomisation to the date of death regardless of the cause of death. Subjects who are alive at the time of analysis will be censored at the date of last known alive. • Duration of response (DOR): DOR is defined as the time from documented tumour response (CR or PR) until documented disease progression. Only the subjects who have the tumour response will be included in the analysis. The secondary efficacy endpoints will be analyzed using Cox proportional hazard model stratified by ECOG performance status, gender and region (pooled centres) for PPS and FAS	The secondary efficacy endpoints **of PFS, OS and DOR will be analysed for PPS and FAS and described in the SAP.** ~~**are as following:**~~ ~~**• Progression free survival (PFS): PFS is defined as the time from the date of Randomisation to the date of disease progression or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the date of the EOT visit.**~~ ~~**• Overall Survival (OS): OS is defined as the time from the date of Randomisation to the date of death regardless of the cause of death. Subjects who are alive at the time of analysis will be censored at the date of last known alive.**~~ ~~**• Duration of response (DOR): DOR is defined as the time from documented tumour response (CR or PR) until documented disease progression. Only the subjects who have the tumour response will be included in the analysis.**~~ ~~**The secondary efficacy endpoints will be analyzed using Cox proportional hazard model stratified by ECOG performance status, gender and region (pooled centres) for PPS and FAS**~~	According to US FDA feedback
8.2.2.3. Exploratory	The exploratory efficacy endpoint is the tumour response	The exploratory efficacy endpoint is the best ORR by 11	According to

Efficacy Analysis	rate by 11 and 17 weeks. The tumour response rate will be computed by the number of subjects with either CR or PR by each timepoint divided by the total number of patients in the analysis population. The tumour response rate will be analyzed for PPS and FAS.	and 17 weeks **and will be analysed with the similar manner of the primary endpoint analysis.** ~~**The tumour response rate will be computed by the number of subjects with either CR or PR by each timepoint divided by the total number of patients in the analysis population.**~~ ~~**The tumour response rate will be analyzed for PPS and FAS.**~~	US FDA feedback
8.2.3. Safety	All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MEDDRA). No statistical testing will be performed for AEs.	All reported terms for AEs will be coded **using** ~~**the Medical Dictionary for Regulatory Activities (MEDDRA)**~~ **MedDRA.** No statistical testing will be performed for AEs.	Follow the official name
	Changes in vital signs and clinical laboratory measurements will be summarised descriptively by treatment group and visit. Other safety variables (e.g., infusion reaction) will be summarised and listed.	Changes in vital signs and clinical laboratory measurements will be summarised descriptively by treatment group ~~**and visit**~~. Other safety variables (e.g., infusion reaction) will be summarised and listed.	Editorial change
8.2.5. Immunogenicity	The incidence of anti-rug antibodies and neutralising antibodies will be summarised by treatment group and visit for SAF	The incidence of anti-**d**rug antibodies and neutralising antibodies will be summarised by treatment group and ~~**visit**~~ **cycle** for SAF	To correct typo error
8.3. Determination of Sample Size	**For the calculation of the equivalence margin, AVAiL [Reck, 2010] and E4599 [Sandler, 2006] studies of Avastin® + cisplatin/gemcitabine (CG) vs. CG alone and of Avastin® + paclitaxel/carboplatin vs. paclitaxel/carboplatin alone, respectively, were considered. In AVAiL study, ORR rates were 21.6% and 37.8% for placebo and Avastin® + CG groups, respectively. In E4599 study, ORR rates were 15.1% (out of 392) and 34.9% (out of 381) for placebo and Avastin® + paclitaxel/carboplatin groups,**	**For the calculation of the equivalence margin, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered.** **The overall ratio of best ORR and the 70% CI from above four studies are calculated to be** CCI [redacted] **using the fixed effect method from**	According to US FDA feedback, more references are cited

	respectively. **The overall ratio of ORR and its 95% CI from these two studies are calculated to be 2.0217 [1.6943, 2.4124] using the fixed effect method from meta-analysis. The equivalence margin of [0.742 1.450] will preserve 50% of the effect of Avastin® over the placebo in the lower margin.** **The overall difference in ORR and its 80% CI from these two studies are calculated to be CCI % [CCI %, CCI %] using the fixed-effect method from meta-analysis. The equivalence margin of [-12.5%, 12.5%] will preserve at least 20% of the effect of Avastin® over the placebo in the difference of ORR.** **With 305 completers in each treatment group, the two-sided 90% CI of the ORR ratio is expected to lie within [0.742, 1.450] with 90% power, and the two-sided 95% CI of the ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.**	**meta-analysis. Retaining the CCI % of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks.** **For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] will be used due to the similar derivation.** **With 305 completers in each treatment group, the two-sided 90% CI of the best ORR ratio is expected to lie within [0.737, 1.357] with approximately 80% power, and the two-sided 95% CI of the best ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected best ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.**	
8.4. Statistical Analysis Timepoints	**8.4. Interim Analysis** **The primary endpoint will be assessed after the last subject completes the Induction treatment period. Available efficacy and safety data (a full set of the Induction treatment period data including available data in the maintenance treatment period from a**	**8.4. Statistical Analysis Timepoints** **Safety endpoint will be assessed for DSMB review during the course of the study. Interim safety results will be evaluated by the DSMB, which will be independent of the study conduct. Details will be described in the DSMB charter.**	The title of section 8.4. is changed and all the statement is changed

	subset of subjects, i.e., those subjects enrolled early) will also be analysed and reported. A final CSR will be reported once the full set of the maintenance treatment period is obtained. **Interim analyses for DSMB review will be performed during the course of the study. Interim results will be evaluated by the DSMB, which will be independent of the study conduct. Details will be described in the DSMB charter.** **Subjects, Investigators, independent central reviewers and other study personnel will remain blinded throughout the entire treatment period. After the last subject completes the induction treatment period, or its corresponding visit, a limited number of prospectively identified individuals of the Sponsor will be unblinded. A formal analysis of the primary efficacy data will then be undertaken.**	**The primary endpoint will be assessed when at least 24 weeks has elapsed since the last subject is randomised. Available efficacy and safety data (a full set of the Induction treatment period data including available data in the maintenance treatment period from a subset of subjects, i.e., those subjects enrolled early) will also be analysed and reported.** **A final CSR will be reported once the full set of the maintenance treatment period is obtained, e.g. after EOS.** **After at least 24 weeks from the last subject randomised, or its corresponding date, a limited number of individuals of the Sponsor will be unblinded. A formal analysis of the primary efficacy data will then be undertaken. Subjects, Investigators, independent central reviewers and other study personnel will remain blinded throughout the entire treatment period.**	
9. DATA COLLECTION AND MANAGEMENT 9.1. Data Confidentiality	Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research into breast cancer.	Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research into ~~**breast cancer**~~ **lung cancer.**	To correct typo error
9.4. Database Management and Coding	Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MEDDRA).	Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities ~~**(MEDDRA)**~~**(MedDRA).**	To correct typo error
10. ETHICAL CONSIDERATIONS	10.4.5. Financing and Insurance A copy of the insurance details will be provided to each	10.4.5. Financing and Insurance ~~**A copy of**~~ The insurance details will be provided to each	Some countries do not mandate

AND ADMINISTRATIVE PROCEDURES 10.4. Investigator Information	Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.	Investigator who will be responsible for providing the IRB/IEC with these details according to local requirements.	submission of Insurance documents
13. REFERENCES	**Avastin® Summary of Product Characteristics (EMEA/H/C/000582 -II/0072). *EMEA.* (May 27, 2015). Retrieved Aug 07, 2015 from** http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf.	**Avastin® Summary of Product Characteristics (EMEA/H/C/000582 -II/0082). *EMEA* (Oct 29, 2015). Retrieved on Nov 04, 2015 from** http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf **Botrel TEA, Clark O, Clark L, et al. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): Systematic review and meta-analysis. *Lung Cancer*. 2011; 74:89-97** **Johnson DH, Fehrenbacher L, Novotny WF, 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: 2184-2191.** **Niho S, Kunitoh H, Nokihara H, 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**	Updated

<table>
<tr><td></td><td></td><td>cancer. Lung Cancer. 2012; 362-367</td><td></td></tr>
<tr><td>APPENDIX 1: ECOG PERFORMANCE STATUS</td><td>Referece:</td><td>Reference:</td><td>To correct typo error</td></tr>
<tr><td>APPENDIX 2: LUNG CANCER STAGING</td><td><table><tr><td>T1a</td><td>Tumour 2 cm or less in greatest dimension</td></tr><tr><td>T1b</td><td>Tumour more than 2 cm but 3 cm or less in greatest dimension</td></tr></table></td><td><table><tr><td>T1a</td><td>Tumour 2 cm or less in greatest dimension</td></tr><tr><td><s>T2b</s>
T1b</td><td>Tumour more than 2 cm but 3 cm or less in greatest dimension</td></tr></table></td><td>To correct typo error</td></tr>
<tr><td>APPENDIX 4: WORLD HEALTH ORGANIZATION HISTOLOGICAL CLASSIFICAION OF TUMOURS OF THE LUNG</td><td>Epithelioid hemangioendothelioma</td><td>Epithelioid haemangioendothelioma</td><td>To correct typo error</td></tr>
</table>

AMENDMENT 2: Aug 18, 2016

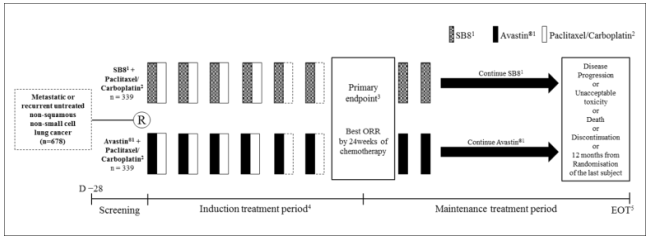
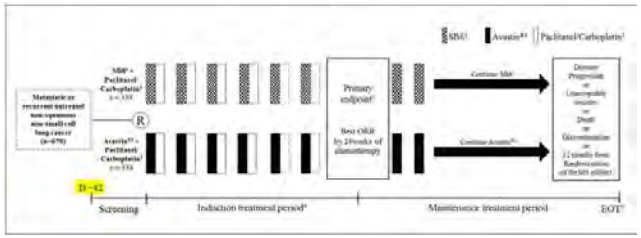
Section Affected	Original Content	Amended/New Content	Rationale
Synopsis-Eligibility Criteria Inclusion criteria	3. Histologically and/or cytologically confirmed metastatic (TNM stage IV) or recurrent adenocarcinoma of the lung or large cell carcinoma of the lung or NSCLC-not otherwise specified (NOS).	3. Histologically and/or cytologically confirmed metastatic (**AJCC 7th edition** TNM stage IV) or recurrent ~~**adenocarcinoma of the lung or large cell carcinoma of the lung**~~ **non-squamous NSCLC** or NSCLC-not otherwise specified (NOS).	Clarification
	7. b Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion is < 1 g or protein/creatinine ratio in spot urine is < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	7. b Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion ~~**is**~~ **should be** < 1 g or protein/creatinine ratio in spot urine ~~**is**~~ **should be** < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	Grammatical change
	8. Subjects and their partners of childbearing potential (female or male) who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 6 months after the last administration of investigational product (IP). A pregnancy test result is required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. True abstinence will be considered sufficient for subjects who do not have a partner.	8. Subjects and their partners of childbearing potential (female or male**) including those with history of elective sterilisation (e.g. fallopian tube ligation)** who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 6 months after the last administration of investigational product (IP). A pregnancy test result is required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. True abstinence will be considered sufficient for subjects who do not have a	German agency's comments. "some patients may decide to reverse elective sterilisation"

		partner.	
Synopsis-Eligibility Criteria Exclusion criteria	1. Diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung (mixed tumour should be categorised according to predominant histology).	1. Diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. **For mixed tumour with the component of squamous cell carcinoma, it** should be categorised according to predominant histology. **Any component of small cell carcinoma of the lung is to be excluded.**	Clarification on mixed histology.
	4. History of systemic chemotherapy administered in the first-line setting for metastatic or recurrent disease of NSCLC.	4. History of systemic ~~**chemotherapy**~~ **anti-cancer therapy** administered in the first-line setting for metastatic or recurrent disease of NSCLC.	Change to include chemotherapy, immunotherapy, targeted agents, etc.
	5. Neoadjuvant or adjuvant chemotherapy for administered for NSCLC and completed less than 12 months prior to Randomisation.	5. **Any systemic anti-cancer therapy including** neoadjuvant or adjuvant chemotherapy ~~**for**~~ administered for NSCLC and completed less than 12 months prior to Randomisation.	Clarification to exclude any history of anti-cancer therapy within 12 months from randomisation
	7. Radiotherapy within 28 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered as measurable lesion unless there has been demonstrated progression in the lesion.).	7. Radiotherapy within ~~**28**~~ **14** days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered as measurable lesion unless there has been demonstrated progression in the	Change made to reduce delay in systemic therapy

		lesion.).	
	8. Major surgical procedure within 28 days prior to Randomisation (requiring more extensive procedure than local anaesthesia [involving general anaesthesia or respiratory assistance or regional anaesthesia] or open lung biopsy).	8. Major surgical procedure within 28 days prior to Randomisation (**e.g.,** requiring more extensive procedure than local anaesthesia [involving general anaesthesia or respiratory assistance or regional anaesthesia] or open lung biopsy) **or expected major surgical procedure during the study**.	Additional clarification
Synopsis-Eligibility Criteria Exclusion criteria	11. Symptomatic brain metastasis and/or leptomeningeal disease.	11. Symptomatic brain metastasis and/or leptomeningeal disease. **Baseline brain imaging is strongly recommended to evaluate for presence of brain metastases. If brain metastases are found, they can be treated according to local practice at the discretion of investigator. Treatment options for brain metastases may include whole brain radiation, radiosurgery, craniotomy, etc. as deemed medically appropriate by the investigator. Subjects should have no neurologic symptoms off corticosteroids for at least 1 day to ensure that subjects do not have symptomatic brain metastasis. If subjects initially developed symptomatic brain metastases that resolved after treatment, they could be considered 'asymptomatic' and eligible for the study if they have no residual neurological dysfunction off corticosteroids for at least 1 day.**	Additional clarification. Off-steroid requirements to determine asymptomatic brain mets
	12. Previous malignancy other than NSCLC in the last 5 years except for locally curable cancers that have been	12. Previous malignancy other than NSCLC in the last 5 years except for locally curable cancers that have been	Better terminology

	complete response and need no subsequent therapy, such as basal or squamous cell cancer of the skin, carcinoma *in situ* of the cervix or breast, or superficial bladder cancer.	**in complete ~~response~~ remission** and need no subsequent therapy, such as basal or squamous cell cancer of the skin, carcinoma in situ of the cervix or breast, or superficial bladder cancer.	
	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [> 75 mg/day], regular use of aspirin, dipyridamole, ticlopidine and/or cilostazol); anticoagulant therapy within 28 days prior to Randomisation (e.g., with warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitor, and thrombolytic agent including tissue plasminogen activator, anistreplase, streptokinase, urokinase).	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel **[≥ 75 mg/day],** regular use of aspirin, dipyridamole, ticlopidine and/or cilostazol); anticoagulant therapy within 28 days prior to Randomisation (e.g., with warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitor, and thrombolytic agent including tissue plasminogen activator, anistreplase, streptokinase, urokinase).	A typo error
Synopsis-Eligibility Criteria <u>Exclusion criteria</u>	18. h. Gastrointestinal bleeding, haematemesis or haemoptysis (≥ 1/2 teaspoon of red blood).	18. h. Gastrointestinal bleeding, haematemesis or haemoptysis (≥ 1/2 teaspoon of red blood) **or any other major bleeding events.**	Additional clarification
	20. Serologically confirmed active or chronic hepatitis B or hepatitis C	20. Serologically confirmed active or chronic hepatitis B or hepatitis C **(asymptomatic inactive carriers are allowed at investigator's discretion per local standards)**	Additional clarification to allow asymptomatic hepatitis carrier
	29. Currently enrolled in another clinical study.	29. Currently enrolled in another **interventional** clinical study.	Additional clarification
Synopsis-Planned	Subjects will be followed for survival status and whether	Subjects will be followed for survival status and	Additional

Study Period	subsequent therapy is received or not by clinic visit or telephone contact every 3 months until withdrawal of consent or death or 12 months from Randomisation of the last subject.	whether subsequent **systemic anti-cancer** therapy is received or not by clinic visit or telephone contact every 3 months until withdrawal of consent or death or 12 months from Randomisation of the last subject.	Clarification
Synopsis-Statistical Methods Analysis set		**Randomised set (RAN) will consist of all subjects who receive a randomisation number at the Randomisation.**	Clarification
Synopsis-Statistical Methods Efficacy analysis	For US FDA submission, the primary efficacy analysis for demonstrating the equivalence of SB8 to Avastin® will be done for the ratio of the best ORR (best ORR of SB8/best ORR of Avastin®) by 24 weeks in the FAS.	For US FDA ~~submission~~ **or other regulatory agency submissions for those who are in favour of risk ratio,** the primary efficacy analysis for demonstrating the equivalence of SB8 to Avastin® will be done for the ratio of the best ORR (best ORR of SB8/best ORR of Avastin®) by 24 weeks in the FAS.	Submission to different agencies
	For EMA submission, the primary efficacy analysis will be performed for the difference in best ORR by 24 weeks between SB8 and Avastin® in the PPS, and the equivalence will be declared if the two-sided 95% CI of the best ORR difference in contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The Similar analysis will be performed for the FAS to support the primary efficacy.	For EMA ~~submission,~~ **MFDS or other regulatory agency submissions for those who are in favour of risk difference,** the primary efficacy analysis will be performed for the difference ~~in~~ **of** the best **ORR (best ORR of SB8 – best ORR of Avastin®)** by 24 weeks between SB8 and Avastin® in the PPS, and the equivalence will be declared if the two-sided 95% CI of the best ORR difference ~~in~~ **is** contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The Similarsimilar analysis will be performed for the FAS to support the primary efficacy **result.**	Submission to different agencies Clarification
Synopsis-Statistical Methods	For the calculation of the equivalence margin, a meta-analysis published by Botrel et al. using all of the four	~~For~~ **Regarding** the calculation of the equivalence margin **for the ratio of the best ORR by 24 weeks**, a	Editorial

Sample size calculation	published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered.	meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered.	change
Synopsis-Figure 1			Increase screening period to 42 days to allow some study-required procedures
	[5]EOT is defined as discontinuation of treatment due to disease progression, unacceptable toxicity, death, or last administration of IP before end of study. After completion of study treatment, subjects will be followed for survival status and whether subsequent therapy is received or not by clinic visit or telephone contact every 3 months until withdrawal of consent, death, or 12 months from Randomisation of the last subject. EOT visit will be performed at least 21 days after last IP administration and prior to subsequent therapy.	[5]EOT is defined as discontinuation of treatment due to disease progression, unacceptable toxicity, death, or last administration of IP before end of study. **EOT visit will be performed at least 21 days after last IP administration and prior to subsequent therapy.** ~~**After completion of study treatment,**~~Subjects will be followed for survival status and whether subsequent **systemic anti-cancer** therapy is received or not by clinic visit or telephone contact every 3 months ~~**until**~~ **from EOT until discontinuation of the subject from the study (e.g., death,** withdrawal of consent, ~~**death**~~, **lost to follow-up or initiation of subsequent therapy for NSCLC) or EOS date,**	Additional clarification

<table>
<tr><td></td><td></td><td>defined as when deaths of all the randomised subjects have been observed. or 12 months from Randomisation of the last subject. <s>EOT visit will be performed at least 21 days after last IP administration and prior to subsequent therapy.</s> whichever occurs first</td><td></td></tr>
<tr><td>Table 1</td><td><table>
<tr><td>Assessments</td><td>Screening</td><td colspan="8">Induction Treatment Period[11]</td><td colspan="2">Maintenance Treatment Period[13]</td><td>EOT[14]</td><td>F/U[15]</td></tr>
<tr><td>Cycle</td><td></td><td>1</td><td>2</td><td>3</td><td>4</td><td>5[12]</td><td>6[12]</td><td>7</td><td>Every cycle since Cycle 6</td><td>Every 4 cycles since Cycle 6</td><td></td><td>Every 3 months</td></tr>
<tr><td>Day of Cycle</td><td>-28 to -1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Visit window (days)</td><td></td><td>±3</td><td>±3</td><td>±3</td><td>±3</td><td>±3</td><td>±3</td><td>±3</td><td>±3</td><td>±3</td><td></td><td>±7</td></tr>
<tr><td>Informed consent[1]</td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Demographic information[2]</td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Medical history[3]</td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Physical examination including height (Screening visit only) and weight[4]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td></td></tr>
<tr><td>Vital signs[5]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>ECOG status</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Haematology[6]</td><td>✓</td><td>✓[16]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Coagulation test[7]</td><td>✓</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td></td><td></td><td>(✓)</td><td></td></tr>
<tr><td>Biochemistry[8]</td><td>✓</td><td>✓[10]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Urinalysis[9]</td><td>✓</td><td>✓[10]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Serology (HBV/HCV infection test)[11]</td><td>✓</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td></td><td></td><td>(✓)</td><td></td></tr>
<tr><td>Pregnancy test (serum or urine)[12]</td><td>✓</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>12-lead ECG</td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Tumour assessment[17]</td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td></td><td>✓</td><td></td><td></td></tr>
<tr><td>Randomisation</td><td></td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SB8 or Avastin®[18]</td><td></td><td>✓[16]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>Paclitaxel/Carboplatin[19]</td><td></td><td>✓[16]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Blood sample for immunogenicity[1]</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Blood sample for PK[18]</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Concomitant and previous medication[20]</td><td>✓</td><td colspan="9">Continuously</td><td></td><td>(✓)</td></tr>
</table></td><td><table>
<tr><td>Assessments</td><td>Screening</td><td colspan="8">Induction Treatment Period[11]</td><td colspan="2">Maintenance Treatment Period[13]</td><td>EOT[14]</td><td>F/U[15]</td></tr>
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<tr><td>Day of Cycle</td><td>Within 42 days prior to Randomisation</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td></td><td></td><td></td><td></td></tr>
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<tr><td>Demographic information[2]</td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td>Physical examination including height (Screening visit only) and weight[4]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td></td></tr>
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<tr><td>ECOG status</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td></td></tr>
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<tr><td>Coagulation test[7]</td><td>✓</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td></td><td>(✓)</td><td></td></tr>
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<tr><td>Urinalysis[9]</td><td>✓</td><td>✓[16]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td></td></tr>
<tr><td>Serology (HBV/HCV infection test)[11]</td><td>✓</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td></td><td>(✓)</td><td></td></tr>
<tr><td>Pregnancy test (serum or urine)[12]</td><td>✓</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td>(✓)</td><td></td><td>✓</td><td></td></tr>
<tr><td>12-lead ECG</td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Tumour assessment[17]</td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td></td><td>✓</td><td></td><td></td></tr>
<tr><td>Randomisation</td><td></td><td>✓[18]</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SB8 or Avastin®[18]</td><td></td><td>✓[16]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>Paclitaxel/Carboplatin[19]</td><td></td><td>✓[16]</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Blood sample for immunogenicity[1]</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Blood sample for PK[18]</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Concomitant and previous medication[20]</td><td>✓</td><td colspan="9">Continuously</td><td></td><td>(✓)</td></tr>
<tr><td>AEs and SAEs[21]</td><td>✓</td><td colspan="9">Continuously</td><td></td><td>(✓)</td></tr>
<tr><td>Survival status</td><td></td><td colspan="9">Continuously</td><td></td><td>✓</td></tr>
</table></td><td>Increase screening period to 42 days to allow some study-required procedures</td></tr>
<tr><td></td><td>7. Blood coagulation test including international normalised ratio (INR) will be performed at Screening. Additional blood coagulation test will be performed at the discretion of Investigator if there are any suspicious cases.</td><td>7. Blood coagulation test<s>, including</s> international normalised ratio (INR) will be performed at Screening. Additional blood coagulation test will be performed at the discretion of Investigator if there are any suspicious cases.</td><td>Additional clarification</td></tr>
<tr><td></td><td>10. Haematology, biochemistry, urinalysis may not need to be repeated on Day 1 of Cycle 1 if the tests have been performed within 14 days prior to administration of IPs.</td><td>10. Haematology, biochemistry and urinalysis need to be completed within 28 days prior to Randomisation. They may not need to be repeated on Day 1 of Cycle 1 if the tests have been performed within 14 days prior to</td><td>Additional clarification</td></tr>
</table>

		administration of IPs.	
	13. Tumour assessments should be performed at Screening (within a maximum 21 days prior to Randomisation) and after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles until disease progression, unacceptable toxicity, death, or end of study. At least one measurable lesion should be confirmed. If the case baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. Tumour response will be assessed using CT or MRI following Image Acquisition Guideline that will be provided by Sponsor. The same modality used at Screening will be used throughout the study.	13. Tumour assessments should be performed at Screening (within a maximum **of** 21 days prior to Randomisation) and after IP administration of Cycle 2, 4, and 6, and before planned Day 1 of Cycle 3, 5, and 7 and then will be performed every 4 cycles until disease progression, unacceptable toxicity, death, or end of study. **If tumour assessment was already performed according to the schedule but next IP administration needs to be delayed due to any reasons, tumour assessment does not need to be repeated.** At least one measurable lesion should be confirmed **prior to Randomisation.** If the ~~**case**~~ baseline tumour assessment ~~**is**~~ **was** not performed within 21 days prior to Randomisation, it should be repeated. Tumour response will be assessed using CT or MRI following Image Acquisition Guideline that will be provided by Sponsor. The same modality used at Screening will be used throughout the study.	Additional clarification
		14. All screening procedures must be completed and reviewed within 42 days prior to Randomisation. All eligibility criteria must be reviewed and confirmed prior to Rrandomisation	Additional clarification
	25. After completion of study treatment, subjects will be followed for survival status and whether subsequent therapy is received or not by clinic visit or telephone	~~**25.**~~ **26.** ~~**After completion of study treatment,**~~ Subjects will be followed for survival status and whether subsequent **systemic anti-cancer** therapy is received or	Additional clarification

	contact every 3 months until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up, or initiation of subsequent therapy for NSCLC), EOS date defined as when deaths of all the randomised subjects have been observed, or 12 months from randomisation of the last subject, whichever occurs first	not by clinic visit or telephone contact every 3 months **from EOT** until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up, or initiation of subsequent therapy for NSCLC) **or EOS date,** defined as when deaths of all the randomised subjects have been observed, or 12 months from randomisation of the last subject, whichever occurs first.	
List of Abbreviations		**AJCC American Joint Committee on Cancer** **CCr Creatinine Clearance** **DOR Duration of Response** **MFDS Ministry of Food and Drug Safety**	Addition of abbreviations
List of Study Staff	Clinical Research Physician PPD Medical Write PPD Statistician PPD Project Safety Lead PPD	Clinical Research Physician PPD Medical Writer PPD Statistician PPD Project Safety Lead PPD	Change in personnel

	PPD	PPD	
4. STUDY POPULATION 4.2. Inclusion Criteria	3.Histologically and/or cytologically confirmed metastatic (TNM stage IV) or recurrent adenocarcinoma of the lung or large cell carcinoma of the lung or NSCLC-not otherwise specified (NOS).	3.Histologically and/or cytologically confirmed metastatic (**AJCC 7th edition** TNM stage IV) or recurrent ~~**adenocarcinoma of the lung or large cell carcinoma of the lung**~~ **non-squamous NSCLC** or NSCLC-not otherwise specified (NOS).	Additional clarification
	7.b. Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion is < 1 g or protein/creatinine ratio in spot urine is < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	7. b Urine dipstick for proteinuria of less than 2+ (other ways of urinalysis are also acceptable); if urine dipstick is ≥ 2+, 24 hours urine protein excretion ~~**is**~~ **should be** < 1 g or protein/creatinine ratio in spot urine ~~**is**~~ **should be** < 1 g/g creatinine (or < 226.0 mg/mmol creatinine).	Grammatical
	8. Subjects and their partners of childbearing potential (female or male) who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 6 months after the last administration of IP. A pregnancy test result is required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. True abstinence will be considered sufficient for subjects who do not have a partner.	8. Subjects and their partners of childbearing potential (female or male**) including those with history of elective sterilisation (e.g. fallopian tube ligation)** who agree to use at least two forms of appropriate contraception (e.g., established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilisation or true abstinence) from Screening until 6 months after the last administration of investigational product (IP). A pregnancy test result is required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. True abstinence will be considered sufficient for subjects who do not have a	German agency's comments. "some patients may decide to reverse elective sterilisation"

		partner.	
4.3. Exclusion Criteria	1.Diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung (mixed tumour should be categorised according to predominant histology).	1. Diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. **For mixed tumour with the component of squamous cell carcinoma, it** should be categorised according to predominant histology. **Any component of small cell carcinoma of the lung is to be excluded.**	Clarification on mixed histology.
	4.History of systemic chemotherapy for metastatic administered in the first-line setting or recurrent disease of NSCLC.	4.History of systemic ~~**chemotherapy for metastatic**~~ **anti-cancer therapy** administered in the first-line setting **for metastatic** or recurrent disease of NSCLC.	Change to include chemotherapy, immunotherapy, targeted agents, etc.
	5.Neoadjuvant or adjuvant chemotherapy administered for NSCLC and completed less than 12 months prior to Randomisation.	5. **Any systemic anti-cancer therapy including** neoadjuvant or adjuvant chemotherapy for administered for NSCLC and completed less than 12 months prior to Randomisation.	Clarification to exclude any history of anti-cancer therapy within 12 months from randomisation
	7.Radiotherapy within 28 days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered as measurable lesion unless there has been demonstrated progression in the lesion.).	7. Radiotherapy within ~~**28**~~ **14** days prior to Randomisation (tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered as measurable lesion unless there has been demonstrated progression in the	Change made to reduce delay in systemic therapy

		lesion.).	
4.3. Exclusion Criteria	8. Major surgical procedure within 28 days prior to Randomisation (requiring more extensive procedure than local anaesthesia [involving general anaesthesia or respiratory assistance or regional anaesthesia] or open lung biopsy)	8. Major surgical procedure within 28 days prior to Randomisation (**e.g.,** requiring more extensive procedure than local anaesthesia [involving general anaesthesia or respiratory assistance or regional anaesthesia] or open lung biopsy) **or expected major surgical procedure during the study**.	Additional clarification
	11.Symptomatic brain metastasis and/or leptomeningeal disease.	11. Symptomatic brain metastasis and/or leptomeningeal disease. **Baseline brain imaging is strongly recommended to evaluate for presence of brain metastases. If brain metastases are found, they can be treated according to local practice at the discretion of investigator. Treatment options for brain metastases may include whole brain radiation, radiosurgery, craniotomy, etc. as deemed medically appropriate by the investigator. Subjects should have no neurologic symptoms off corticosteroids for at least 1 day to ensure that subjects do not have symptomatic brain metastasis. If subjects initially developed symptomatic brain metastases that resolved after treatment, they could be considered 'asymptomatic' and eligible for the study if they have no residual neurological dysfunction off corticosteroids for at least 1 day.**	Additional clarification. Off-steroid requirements to determine asymptomatic brain mets
	12. Previous malignancy other than NSCLC in the last 5 years except for locally curable cancers that have been	12. Previous malignancy other than NSCLC in the last 5 years except for locally curable cancers that have been	Better terminology

	complete response and need no subsequent therapy, such as basal or squamous cell cancer of the skin, carcinoma in situ of the cervix or breast, or superficial bladder cancer.	**in complete ~~response~~ remission** and need no subsequent therapy, such as basal or squamous cell cancer of the skin, carcinoma in situ of the cervix or breast, or superficial bladder cancer.	
4.3. Exclusion Criteria	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel [> 75 mg/day], regular use of aspirin, dipyridamole, ticlopidine and/or cilostazol); anticoagulant therapy within 28 days prior to Randomisation (e.g., with warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitor, and thrombolytic agent including tissue plasminogen activator, anistreplase, streptokinase, urokinase).	15. Subjects treated with anticoagulant therapy within 10 days prior to Randomisation (e.g., clopidogrel **[≥ 75 mg/day],** regular use of aspirin, dipyridamole, ticlopidine and/or cilostazol); anticoagulant therapy within 28 days prior to Randomisation (e.g., with warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitor, and thrombolytic agent including tissue plasminogen activator, anistreplase, streptokinase, urokinase).	A typo error
	18. h. Gastrointestinal bleeding, haematemesis or haemoptysis (≥ 1/2 teaspoon of red blood).	18. h. Gastrointestinal bleeding, haematemesis or haemoptysis (≥ 1/2 teaspoon of red blood) **or any other major bleeding events.**	Additional clarification
	20. Serologically confirmed active or chronic hepatitis B or hepatitis C	20. Serologically confirmed active or chronic hepatitis B or hepatitis C **(asymptomatic inactive carriers are allowed at investigator's discretion per local standards).**	Additional clarification to allow asymptomatic hepatitis carrier
	29. Currently enrolled in another clinical study.	29. Currently enrolled in another **interventional** clinical study.	Additional clarification

4.4 Subject Withdrawal		• AEs requiring permanent discontinuation of IP (see Section 6.4.2) • Unblinding (except unblinding for the purpose of regulatory reporting)	Additional guidelines
	All the subjects who withdraw alive from the study will be asked to return to the Investigational site for the EOT visit procedures to be performed (see Section 5.1.5.) and to have a follow-up telephone contact or clinic visit.	All the subjects who withdraw ~~**alive**~~ from the study will be asked to return to the Investigational site for the EOT visit procedures to be performed (see Section 5.1.5.) and to have a follow-up telephone contact or clinic visit.	Grammatical
5. STUDY PROCEDURES AND ASSESSMENT 5.1. Procedures by Study Period 5.1.1. Screening Period	Screening should be performed within 28 days before Randomisation. All subjects must provide written informed consent prior to any study related procedures being performed.	Screening should be performed within ~~**28**~~ **42** days before Randomisation. All subjects must provide written informed consent prior to any study related procedures being performed.	Increase screening period to 42 days to allow some study-required procedures
	The following procedures and assessments should be performed within 28 days before Randomisation.	The following procedures and assessments should be performed within ~~**28**~~ **42** days before Randomisation. **Retesting or re-evaluation is allowed within the screening period, but the latest assessment will be used to determine the eligibility. Re-screening or re-consenting after 42 day screening period has elapsed is not allowed.**	Increase screening period to 42 days to allow some study-required procedures
	• Review of previous or concomitant medication (within 28 days prior to informed consent; within 12 weeks in case of vaccines)	• Review of previous or concomitant medication (within 28 days **prior to informed consent;** within 12 weeks prior to informed consent in case of vaccines)	Grammatical/Clarification

	• Haematology, biochemistry, urinalysis, and serology (retesting is allowed within the Screening period within 28 days prior to Randomisation.) (…) - Blood coagulation test including international normalised ratio (INR) (…) - Urinalysis (dipstick): leukocytes, nitrite, urobilinogen, protein, pH, Hb, specific gravity, ketone, bilirubin, glucose (other ways of urinalysis are also allowed), if urine dipstick is ≥ 2+, 24 hours urine protein excretion is < 1 g or protein/creatinine ratio in spot urine is < 1 g/g creatinine (or < 226.0 mg/mmol creatinine)	• Haematology, biochemistry, urinalysis, and serology (retesting is allowed during the Screening period). **Haematology, biochemistry and urinalysis need to be completed within 28 days before Randomisation.** (…) - Blood coagulation test**: ~~including~~** international normalised ratio (INR). **If there is significant deviation in the value (i.e., INR > 1.5), it is highly recommended that the investigator determine the cause (i.e., warfarin – which would be excluded) and reversibility. If the Investigator determines that the subject is at a high risk of bleeding as a result of abnormal INR, subject should be excluded according to section 4.3 (exclusion criterion 14).** (…) - Urinalysis (dipstick): leukocytes, nitrite, urobilinogen, protein, pH, Hb, specific gravity, ketone, bilirubin, glucose (other ways of urinalysis are also allowed), if urine dipstick is ≥ 2+, 24 hours urine protein excretion **~~is~~ should be** < 1 g or protein/creatinine ratio in spot urine **~~is~~ should be** < 1 g/g creatinine (or < 226.0 mg/mmol creatinine) (…) - **If other laboratory tests not listed above are checked by local practice and found to be abnormal, it is recommended that Investigator use the best clinical judgement to determine if the abnormal values would**	Clarification on timing of laboratory tests Additional guidelines on INR value and other laboratory tests

		affect patient safety while participating in the study.	
5.1.2. Randomisation	If the subject meets all the criteria of eligibility and signs off the ICF, the Investigator should check the whole eligibility criteria of the subjects prior to Randomisation.	If the subject ~~**meets all the criteria of eligibility and**~~ signs ~~**off**~~ the ICF, the Investigator should check the whole eligibility criteria of the subjects prior to Randomisation.	Grammatical/ Simpler
5.1.2.2. Stratification Factors	• Age: < 70 vs. ≥ 70	• Age **at randomisation**: < 70 vs. ≥ 70	Clarification
5.1.3. Induction Treatment Period (Cycle 1 to Cycle 6)	• Imaging tumour assessment of target and non-target lesion by CT scan or MRI will be performed after IP administration of Cycle 2, 4, and 6 and before planned Day 1 of Cycle 3, 5, and 7 (upper abdominal cavity including the adrenal glands must be included in imaging study.).	• Imaging tumour assessment of target and non-target lesion by CT scan or MRI will be performed after IP administration of Cycle 2, 4, and 6 and before planned Day 1 of Cycle 3, 5, and 7 (upper abdominal cavity including the adrenal glands must be included in imaging study.). **Tumour assessment does not need to be repeated if IP is delayed due to any reasons.**	Additional clarification
5.1.6. Follow-up Period	After completion of study treatment, subjects will be followed for survival status and whether subsequent therapy is received or not by clinic visit or telephone contact every 3 months (± 7 days) until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up) or EOS date, defined as when deaths of all the randomised subjects have been observed, or 12 months from Randomisation of the last subject, whichever occurs first. SAEs that are considered to be related to the IP should	~~**After completion of study treatment,**~~ Subjects will be followed for survival status and whether subsequent therapy is received or not by clinic visit or telephone contact every 3 months (± 7 days) **from EOT** until discontinuation of the subject from the study (e.g., death, withdrawal of consent, lost to follow-up **or initiation of subsequent therapy for NSCLC**) or EOS date, defined as when deaths of all the randomised subjects have been observed, or 12 months from Randomisation of the last subject, whichever occurs	Additional clarification

	continue to be reported to Sponsor during the follow-up period.	first. SAEs ~~**that are considered to be related to the IP should**~~ will continue to be reported to Sponsor during the follow-up period. **(see Section 7.2.2)**	
5.2.1.1. Definition of Target and Non-target Lesions	During the baseline assessment before IP administrations, all lesions detected in the lung are classified as either target lesions or non-target lesions on CT/MRI scan	During the baseline assessment before IP administrations, all lesions detected ~~**in the lung**~~ are classified as either target lesions or non-target lesions on CT/MRI scan • **Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions total, representative of all involved organs should be identified as target lesions and recorded at baseline. Target lesions should be selected based on their size and their suitability for accurate repeated measurements by imagaing.** • **Non-target lesions: All other lesions including small lesions and other non-measurable lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up.** **For detailed instructions, please refer to Completion Guide for Tumour Assessment Worksheet.**	Added more details
5.2.1.2. Criteria for	The use of oral and IV contrast, etc., should be consistent	The use of oral and IV contrast, etc., ~~**should be**~~	Clarification

Tumour Response Evaluation	unless contraindication exists. Tumour evaluations should be made by the same Investigator or radiologist for each subject during the study, if possible. Baseline total tumour burden must be assessed no more than 21 days prior to Randomisation. If the case baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. Baseline tumour assessment will include the adrenal glands and the entire liver. If case of contrast contraindication, MRI will be performed. Additional PET-scan, or bone scan will be performed at the discretion of the Investigator (optional), if there are symptoms or clinical suspicion of distant metastasis. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion	~~consistent~~ **is highly recommended and should be used consistently** unless contraindication exists. Tumour evaluations should be made by the same Investigator or radiologist for each subject during the study, if possible. Baseline total tumour burden must be assessed no more than 21 days prior to Randomisation. If the ~~case~~ baseline tumour assessment is not performed within 21 days prior to Randomisation, it should be repeated. Baseline tumour assessment will include the adrenal glands and the entire liver. ~~If~~ **In** case of contrast contraindication, MRI ~~will~~ **or non-contrast CT scans can** be performed. Additional PET-scan, or bone scan will be performed at the discretion of the Investigator (optional), if there are symptoms or clinical suspicion of distant metastasis. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion. **For baseline brain imaging, MRI with contrast is preferred but CT scan with IV contrast is acceptable if MRI cannot be obtained (Ex. pacemaker, unavailable MRI facility, etc). If brain metastases are found but not treated (asymptomatic), they could be potentially listed as target and/or non-target lesions at discretion of investigators. However, all target**	on imaging modality Clarification on imaging for brain metastases

		and/or non-target lesions should be followed using the same imaging modality throughout the study. If brain metastases are found and treated, those should be listed as "non-target" lesions for tumour response evaluation according to RECIST 1.1. If brain mets are treated and patients are asymptomatic, follow -up brain imaging is not required unless clinically suspected.	
6.2.4.1. Preparation and Administration of SB8 or Avastin®	• Volume (mL) = dose amount (mg) ÷ concentration of bevacizumab (mg/mL)	• $\text{Volume (mL)} = \frac{\text{dose amount (mg)}}{\text{concentration of bevacizumab (mg/mL)}}$	Graphical
6.2.5. Prohibited Concomitant Medications or Therapies	Medication and therapies are prohibited prior to Randomisation and throughout the study are presented in Table 3.	Medication and therapies **that** are prohibited prior to Randomisation and/**or** throughout the study are presented in Table 3.	Grammar

Table 3

Table 3. Prohibited Medications and Therapies of NSCLC

Medication or therapies	Time to be prohibited
Anticoagulants or thrombolytic agent:	
Clopidogrel (> 75 mg/day), regular use of aspirin or NSAIDs with antiplatelet activity, dipyridamole, ticlopidine and/or cilostazol	Within 10 days prior to Randomisation to EOT
Warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitors, thrombolytic agents including tissue plasminogen activator, anistreplase, streptokinase, urokinase	Within 28 days prior to Randomisation to EOT
Any drugs (include herbal medications) that has not received regulatory approval for any indications	From Randomisation to EOT
Anticancer chemotherapy regimen other than paclitaxel/carboplatin[a]	From Randomisation to EOT
Major surgical procedure (include open lung biopsy)[b]	Within 28 days prior to Randomisation
Minor surgical procedure[c]	Within 7 days prior to Randomisation
Live/attenuated vaccine	Within 12 weeks prior to Randomisation to Cycle 7 Day 1
Intravenous bisphosphonates and/or invasive dental procedure	Within 28 days prior to Randomisation to EOT
Radiotherapy[d]	Within 28 days prior to Randomisation to EOT

[a] Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study.

[b] Requiring more extensive procedure than local anaesthesia (involving general anaesthesia or respiratory assistance or regional anaesthesia) or open lung biopsy.

[c] Requiring local anaesthesia or following procedures; mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device,

Table 3. Prohibited Medications and Therapies of NSCLC

Medication or therapies	Time to be prohibited
Anticoagulants or thrombolytic agent:	
Regular use of aspirin	**Prior to Randomisation**
Aspirin (≥325 mg daily)[a] ****After randomisation, low dose aspirin (< 325mg daily) is allowed if medically indicated at the discretion of Investigator.***	**From Ranomisation to EOT**
Antiplatelet agents such as Clopidogrel (≥ 75 mg/day), ~~**regular use of aspirin or NSAIDs with antiplatelet activity,**~~ dipyridamole, ticlopidine and/or cilostazol[b]	Within 10 days prior to Randomisation to EOT
Warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitors, thrombolytic agents including tissue plasminogen activator, anistreplase, streptokinase, urokinase[c] ****After randomisation, anticoagulation is allowed if medically indicated***	Within 28 days prior to Randomisation to EOT
Any drugs (include herbal medications) that has not received regulatory approval for any indications	From Randomisation to EOT
Anticancer ~~**chemotherapy regimen**~~ **systemic therapy** other than paclitaxel/carboplatin/**Avastin®/SB8[d]**	From Randomisation to EOT
Major surgical procedure (include open lung biopsy)[e] ****If a major surgical procedure is indicated after randomisation, treatment needs to be held for at least 28 days after surgery and subject needs to completely recover from surgery. The maximum allowed delay is 6 weeks from the last IP infusion.***	Within 28 days prior to Randomisation
Minor surgical procedure[f] ****If a minor surgical procedure is indicated after randomisation, treatment needs to be held for at least 7 days after surgery and subject needs to completely recover from surgery. The maximum allowed delay is 6 weeks from the last IP infusion.***	Within 7 days prior to Randomisation
Live/attenuated vaccine	Within 12 weeks prior to Randomisation to Cycle 7 Day 1
Intravenous bisphosphonates and/or invasive dental procedure ****Allowed after randomisation if determined by investigator as clinically necessary (ex. Bone metastases related to NSCLC or tooth abscess requiring extraction, etc.)***	Within 28 days prior to Randomisation ~~**to EOT**~~
Radiotherapy[g]	Within ~~**28**~~**14** days prior to Randomisation to EOT

[a] After randomisation, low dose aspirin < 325mg daily is allowed if medically indicated (cardiac prophylaxis, etc.) and there is no bleeding diathesis that would increase the risk of therapy at the discretion of Investigator.

[b] Non-chronic use of NSAIDS (not including aspirin) for symptom management are permitted if there is no bleeding diathesis that would increase the risk of

Allowing certain anticoagulants at discretion of Investigator

	endobronchoscopy ultra sono & transbronchial needle aspiration (EBUS & TBNA), pleural biopsy, thoracentesis, pleurodesis, catheter insertion/removal, tooth extraction, superficial incision. [d] Radiotherapy of palliative purpose to non-progressive non-target lesions is allowed during the treatment period. If target lesions are included in irradiated field, then those lesions should not be evaluated as measurable thereafter. It is strongly recommended that the Investigator consult to the Sponsor at the timing of planning radiotherapy. IP and non-IPs should be suspended during radiotherapy and may be resumed at the discretion of the Investigator.	**therapy at the discretion of Investigator.** **[c]After randomisation, therapeutic anticoagulation (heparin, warfarin, etc.) is allowed if medically indicated in case of new thromboembolic events (i.e., deep venous thrombosis) at the discretion of Investigator. Refer to section 6.4.2 Table 4 for specific guidelines. Non-systemic use of anticoagulants (ex. heparin flush) to maintain patency of intravenous injection devices is allowed** [d] Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study. [e] Requiring more extensive procedure than local anaesthesia (involving general anaesthesia or respiratory assistance or regional anaesthesia) or open lung biopsy. [f] Requiring local anaesthesia or following procedures; mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle aspiration (EBUS & TBNA), pleural biopsy, thoracentesis, pleurodesis, catheter insertion/removal, tooth extraction, superficial incision. [g] Radiotherapy of palliative purpose to non-progressive non-target lesions is allowed during the treatment period. If target lesions are included in irradiated field, then those lesions should not be evaluated as	

		measurable thereafter. It is strongly recommended that the Investigator consult to the Sponsor at the timing of planning radiotherapy. IP and non-IPs should be suspended during radiotherapy and may be resumed at the discretion of the Investigator.	
6.3.1.2. Dose and Schedule of Paclitaxel	Paclitaxel will be administered as IV infusion over 3 hours after the completion of SB8 or Avastin® administration. Dose and schedule modification for toxicity are permitted (see Section 6.4.).	Paclitaxel will be administered as IV infusion over **approximately** 3 hours after the completion of SB8 or Avastin® administration. Dose and schedule modification for toxicity are permitted (see Section 6.4.).	Clarification
6.3.2.2. Dose and Schedule of Carboplatin	Carboplatin will be administered as IV infusion over 30 minutes (± 10) after the completion of paclitaxel. Dose modification and delays for toxicity are permitted (see Section 6.4.).	Carboplatin will be administered as IV infusion over **approximately** 30 minutes ~~**(± 10)**~~ after the completion of paclitaxel. Dose modification and delays for toxicity are permitted (see Section 6.4.).	Clarification

6.3.2.2. Dose and Schedule of Carboplatin	Calvert formula = target AUC × (CCr + 25) mg/day CCr must be calculated prior to every dosage of carboplatin based on below the formula (Cockcroft-Gault equation): CCr = ([140 – Age[y]] × body weight)/(72 × serum creatinine [mg/dL]) × 0.85 (if women)	• **Carboplatin dose (mg)** = target AUC × (CCr + 25) ~~**mg/day**~~ CCr must be calculated prior to every dosage of carboplatin ~~**based on**~~ **using** below ~~**the**~~ formula (Cockcroft-Gault equation) **and it should NOT exceed 125 ml/min:** **Male:** $$\mathbf{CCr} = \frac{\mathbf{(140 - Age[y]) \times body\ weight\ [kg]}}{\mathbf{72 \times serum\ creatinine[mg/dL]}}$$ **Female:** $$\mathbf{CCr} = \frac{\mathbf{(140 - \boldsymbol{Age}[y]) \times \boldsymbol{body\ weight}\ [kg]}}{\mathbf{72 \times \boldsymbol{serum\ creatinine}[mg/dL]}} \times \mathbf{0.85}$$	Typo CCr cap based on US FDA recommenda-tion
6.4.1. General Consideration	1. Dose modifications must be based on the dose level changes in Table 5 and Table 6 and not in other ways. (…) 5. Subjects may only be re-treated if all related toxicities have resolved to baseline or ≤ grade 1.	1. Dose modifications must be based on the dose level changes in Table 5 and Table 6 ~~**and not in other ways**~~ (…) 5. Subjects may only be re-treated if all related toxicities have resolved to baseline or ≤ grade 1 **at the discretion of Investigator.**	Clarification

6.4.2. Schedule Modification of SB8 or Avastin® Table 4	**Table 4. Schedule modification of SB8 or Avastin®** **Adverse Event** / **CTCAE Grade[a]** / **Action to be taken** Haemoptysis — 1 — • If no source was found, and the bleeding resolved within 1 week, reinitiate with same dose. • If a source of bleeding was discovered, it will be treated according to current medical practice. ≥2 — • Discontinue Hypertension — ≥2 — • Hold SB8 or Avastin® until recovery to grade ≤ 1, and then reinitiate with same dose. Proteinuria — ≥2 — • Hold SB8 or Avastin® until recovery to grade ≤ 1, and then reinitiate with same dose. AST or ALT — ≥ 3 — • Hold SB8 or Avastin® until recovery to grade ≤ 2, and then continue SB8 or Avastin®. Other clinically significant AEs — ≥ 3 — • Hold SB8 or Avastin® until recovery to grade ≤ 2, and then continue SB8 or Avastin®. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase a NCI-CTCAE v4.03 will be used (see APPENDIX 3).	**Table 4. Schedule modification of SB8 or Avastin®** **Adverse Event** / **CTCAE Grade[a]** / **Action to be taken** Haemoptysis — 1 — • If no source was found, and the bleeding resolved within 1 week, reinitiate with **the** same dose. • If a source of bleeding was discovered, it will be treated according to current medical practice. ≥2 — • Discontinue Hypertension — ≥2 — • **Hold SB8 or Avastin® until recovery to resting BP of < 150/100 mmHg and then reinitiate with the same dose. Anti-hypertensive medications are allowed and recommended for blood pressure control at the discretion of Investigator.** **4** — • **Discontinue** **Congestive heart failure (left ventricular systolic dysfunction)** — **3** — • **Hold until resolution to Grade ≤ 1** **4** — • **Discontinue** Proteinuria — ≥2 — • Hold SB8 or Avastin® until recovery to grade ≤ 1, and then reinitiate with **the** same dose. **Arterial thromboembolism (New onset or worsening CVAs, TIAs, MIs, etc.)** — **Any** — • **Discontinue** **Venous thromboembolism** — **≤ 3** — • **Closely monitor. Anticoagulation (heparin, warfarin, etc.) is recommended and allowed per local practice at the discretion of Investigator and patients should not have any grade of pulmonary/CNS haemorrhage or grade ≥ 2 haemorrhagic event while on anticoagulation.** **4** — • **Discontinue** **Increased** AST or ALT — ≥ 3 — • Hold SB8 or Avastin® until recovery to grade ≤ 2, and then continue SB8 or Avastin®. Other clinically significant AEs[b] — ≥ 3 — • Hold SB8 or Avastin® until recovery to grade ≤ 2, and then continue SB8 or Avastin®. **CVA=cerebrovascular accident; TIA=transient ischemic attack; MI=myocardial infarction; CNS=central nervous system;** ALT= alanine aminotransferase; AST = aspartate aminotransferase; AE = adverse event **[a] NCI-CTCAE v4.03 will be used (see APPENDIX 3)** **[b] Other clinically significant AEs will be determined**	Additional details on IP schedule modification Allowing anticoagulation for certain thrombo-embolic events

		at the discretion of Investigator	
6.4.2. Schedule Modification of SB8 or Avastin®	In any subject who experienced one of the events listed below, the Investigator should consider to discontinue administration of IP permanently, according to the approved label of Avastin®: (...) • Severe arterial thromboembolic events (grade ≥ 3) • Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism • Grade 4 hypertension (hypertensive crisis or hypertensive encephalopathy) • Nephrotic syndrome (grade ≥ 3 proteinuria or ≥ 3.5 g/24 h) • Posterior Reversible Encephalopathy Syndrome (PRES)	~~**In any subject who experienced one of the events listed below,**~~ The investigator should ~~**consider to**~~ discontinue administration of IP permanently, ~~**according to the approved label of Avastin®**~~ **and remove subjects from the study if experiencing one of the events specified below:** (...) • ~~**Severe**~~ Arterial thromboembolic events (~~**grade ≥ 3**~~ **any grade**) • Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism • Grade 4 hypertension (hypertensive crisis or hypertensive encephalopathy) • **Grade 4 congestive heart failure (left ventricular systolic dysfunction)** • Nephrotic syndrome (grade ≥ 3 proteinuria or ≥ 3.5 g/24 h) • Posterior Reversible Encephalopathy Syndrome (PRES) • **If the investigator determines that situations not listed above but could jeopardise safety of subjects with continuation of IP, IP should be permanently discontinued.**	Change to mandate discontinuation of IP in case of certain serious events.
6.4.3.1. Paclitaxel and Carboplatin	All dose modifications for paclitaxel and carboplatin are based on the dose level changes in Table 5. A stepwise dose reduction is permitted. If a reduction to dose level 3	All dose modifications for paclitaxel and carboplatin are based on the dose level changes in Table 5. A stepwise dose reduction is permitted. If a reduction to dose level -	Additional clarification

<table>
<tr><td></td><td>is required then subjects must be discontinued from paclitaxel and carboplatin treatment. If paclitaxel and carboplatin are discontinued due to toxicity, continuation of SB8 or Avastin® as monotherapy is allowed at the discretion of Investigator.</td><td>3 is required then subjects must be discontinued from paclitaxel and/or carboplatin treatment. If more than one AE requiring dose-reduction is found (e.g. Grade 4 neutrophil count decreased and Grade 3 platelet count decreased) during the same evaluation period, one dose level reduction is indicated according to Table 6. If both paclitaxel and carboplatin are discontinued due to toxicity, continuation of SB8 or Avastin® as monotherapy is allowed at the discretion of Investigator.</td><td></td></tr>
<tr><td>Table 5</td><td>Table 5. Dose Levels for Paclitaxel and Carboplatin
<table><tr><th></th><th>Dose level 0</th><th>Dose level 1</th><th>Dose level 2</th><th>Dose level 3</th></tr><tr><td>Paclitaxel</td><td>200 mg/m^2</td><td>150 mg/m^2</td><td>100 mg/m^2</td><td>Discontinue</td></tr><tr><td>Carboplatin</td><td>AUC 6</td><td>AUC 4.5</td><td>AUC 3</td><td>Discontinue</td></tr></table></td><td>Table 5. Dose Levels for Paclitaxel and Carboplatin
<table><tr><th></th><th>Dose level 0</th><th>Dose level -1</th><th>Dose level -2</th><th>Dose level -3</th></tr><tr><td>Paclitaxel</td><td>200 mg/m^2</td><td>150 mg/m^2</td><td>100 mg/m^2</td><td>Discontinue</td></tr><tr><td>Carboplatin</td><td>AUC 6</td><td>AUC 4.5</td><td>AUC 3</td><td>Discontinue</td></tr></table></td><td>Change to conventional terms.</td></tr>
</table>

Table 6

Neutrophil count decreased	Grade 4 ≥ 7 days or Febrile neutropenia with ANC < 1.0 × 10^9/L	1st event	• Hold until ≥ 1.5 × 10^9/L and body temperature < 38°C • Once recovers, reduce dose by one level.
		2nd event despite dose reduction	• Hold until ≥ 1.5 × 10^9/L and body temperature < 38°C • Once recovers, reduce dose by one level.
		3rd event	• Discontinue
Platelets count decreased	Grade 1 or 2	≥ 50 × 10^9/L to < 100 × 10^9/L	• Hold until ≥ 100 × 10^9/L. • Once recovers, maintain the same dose.
	Grade ≥ 3	1st event: ≥ 25 × 10^9/L to < 50 × 10^9/L	• Hold until ≥ 100 × 10^9/L. • Once recovers, reduce dose by one level.
		2nd event: ≥ 25 × 10^9/L to < 50 × 10^9/L	• Hold until ≥ 100 × 10^9/L. • Once recovers, reduce dose by one level.
		Despite previous dose reduction: < 50 × 10^9/L	• Discontinue.
	Grade 4 or Grade 3 with bleeding	< 25 × 10^9/L or < 50 × 10^9/L with bleeding	• Hold until > 100 × 10^9/L. • Once recovers, reduce dose by one level.
		Despite previous dose reduction for platelet count decrease : < 25 × 10^9/L	• Discontinue.

Neutrophil count decreased	Grade 4 ≥ 7 days or Febrile neutropenia with ANC < 1.0 × 10^9/L ***G-CSF is allowed at the discretion of Investigator**	1st event	• Hold until ≥ 1.5 × 10^9/L and body temperature < 38°C • Once recovers, reduce dose by one level.
		2nd event despite dose reduction	• Hold until ≥ 1.5 × 10^9/L and body temperature < 38°C • Once recovers, reduce dose by one level.
		3rd event	• Discontinue
Platelets count decreased	Grade 1 or 2	≥ 50 × 10^9/L to < 100 × 10^9/L	• Hold until ≥ 100 × 10^9/L. • Once recovers, maintain the same dose.
	Grade 3 **without bleeding**	1st event: ≥ 25 × 10^9/L to < 50 × 10^9/L	• Hold until ≥ 100 × 10^9/L. • Once recovers, reduce dose by one level.
		2nd event: ≥ 25 × 10^9/L to < 50 × 10^9/L	• Hold until ≥ 100 × 10^9/L. • Once recovers, reduce dose by one level.
		Despite ~~previous dose reduction~~ **two dose reductions**: < 50 × 10^9/L	• Discontinue.
	Grade 4 or Grade 3 with bleeding	**1st event** < 25 × 10^9/L or < 50 × 10^9/L with bleeding	• Hold until > 100 × 10^9/L. • Once recovers, reduce dose by one level.
		Despite previous dose reduction for platelet count decrease : < 25 × 10^9/L	• Discontinue.

Clarification to allow G-CSF

Clarification on Grade 3 platelets count decreased

Change in dose reduction for neurotoxicity

Table 6	<table><tr><td rowspan="2">Neurosensory toxicity</td><td>Grade 2</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.</td></tr><tr><td>Grade 3 or 4</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, - Paclitaxel: reduce dose by two levels. Carboplatin: maintain the same dose.</td></tr><tr><td rowspan="2">Biochemistry</td><td>Increased AST or ALT Grade ≥ 2 and Increased total bilirubin Grade 1</td><td>• Hold until AST/ALT recovery to ≤ grade 1 or baseline. • Once AST/ALT recovers, - Maintain the same dose if bilirubin within normal limit. - If bilirubin is still increased to grade 1, Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.</td></tr><tr><td>Grade ≥ 3 AST or ALT or Grade ≥ 2 total bilirubin</td><td>• Hold until AST/ALT and bilirubin recovery to ≤ grade 1 or baseline. • Once AST/ALT and bilirubin recover, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.</td></tr><tr><td rowspan="2">Other clinically significant AEs</td><td>Grade 2</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.</td></tr><tr><td>Grade 3 or 4</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.</td></tr></table>	<table><tr><td rowspan="2">Neurosensory toxicity</td><td>Grade 2</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.</td></tr><tr><td>Grade 3 or 4</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, - Paclitaxel: discontinue Carboplatin: reduce dose by one level.</td></tr><tr><td rowspan="2"><s>Biochemistry</s>AST or ALT or blood bilirubin increased</td><td>Increased AST or ALT Grade ≥ 2 and Increased total bilirubin Grade 1</td><td>• Hold until AST/ALT recovery to ≤ grade 1 or baseline. • Once AST/ALT recovers, - Maintain the same dose if bilirubin within normal limit. - If bilirubin is still increased to grade 1, Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.</td></tr><tr><td>Grade ≥ 3 AST or ALT or Grade ≥ 2 total bilirubin</td><td>• Hold until AST/ALT and bilirubin recovery to ≤ grade 1 or baseline. • Once AST/ALT and bilirubin recover, - Paclitaxel: reduce dose by one level. Carboplatin: maintain the same dose.</td></tr><tr><td rowspan="2">Other clinically significant AEs[b]</td><td>Grade 2</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, maintain the same dose.</td></tr><tr><td>Grade 3 or 4</td><td>• Hold until recovery to ≤ grade 1 or baseline. • Once recovers, reduce dose by one level.</td></tr></table>	
Table 6	AE = adverse event; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine transaminase; NCI-CTCAE = national cancer institute common terminology criteria for adverse events [a] NCI-CTCAE v4.03 will be used (see APPENDIX 3).	AE = adverse event; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine transaminase; G-CSF= Granulocyte Colony-stimulating Factor; NCI-CTCAE = national cancer institute common terminology criteria for adverse events [a] NCI-CTCAE v4.03 will be used (see APPENDIX 3) **[b] Other clinically significant AEs will be determined at the discretion of Investigator**	Additional clarifications
6.6.3. Granulocyte Colony-stimulating Factor (G-CSF) Use	Therapeutic or secondary prophylactic use of G-CSF may be given at the discretion of Investigator and should follow NCCN Guidelines of Myeloid Growth Factors Version 1, 2015. In subjects with risk factor developing	**~~Therapeutic or secondary prophylactic use of~~** G-CSF may be given at the discretion of Investigator and **~~should follow~~ recommend** following NCCN Guidelines of Myeloid Growth Factors **~~Version 1, 2015~~**.	Clarification to allow general use of G-CSF NCCN is a

	febrile neutropenia (sepsis syndrome, aged ≥ 65, severe neutropenia [ANC < 0.1 × 109/L], neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalisation at the time of fever, prior episode of febrile neutropenia) prophylaxis with G-GSF will be permitted.	In subjects with risk factor**s for** developing febrile neutropenia (sepsis syndrome, aged ≥ 65, severe neutropenia [ANC < 0.1 × 109/L], neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalisation at the time of fever, prior episode of febrile neutropenia) prophylaxis with G-~~**GSF**~~ **CSF**-will be permitted.	guide that continuously gets updated.
6.6.4. Antibiotics Use	At the discretion of Investigator, antibiotics may be administered according to NCCN Guidelines of Cancer-related Infections Version 2, 2015 or ASCO Guidelines [Flowers, 2013] in febrile neutropenia cases.	At the discretion of Investigator, antibiotics may be administered according to NCCN Guidelines of Cancer-related Infections ~~**Version 2, 2015**~~ or ASCO Guidelines ~~**[Flowers, 2013]**~~ in febrile neutropenia cases.	These guidelines continue to get updated.
6.6.5. Other Supportive Care	Subjects with anemia can be treated according to the local practice. Intravenous bisphosphonate therapy for their approved labeled indication is not permitted during the study (see Section 6.2.5.).	Subjects with anemia can be treated according to the local practice. Intravenous bisphosphonate therapy ~~**for their approved labeled indication**~~ is ~~**not**~~ permitted during the study **if clinically indicated (e.g., bone metastases for NSCLC)** (see Section 6.2.5.).	Allow IV bisphosphonate therapy if clinically indicated
7.1.1.2. Clinically Significant Abnormalities	If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be collected as an AE. If the abnormality can be characterised by a precise clinical term, the clinical term should be recorded as the AE. (…)	**All laboratory abnormalities that require intervention (e.g., transfusion, IV infusion) should be reported as clinically significant AEs according to NCI-CTCAE v4.03.** If the clinically significant laboratory or other abnormality from safety assessment is not a sign of a disease or syndrome, the abnormality itself should be collected as an AE. (…)	Additional clarification
7.1.6. Emergency Unblinding for	(…) This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the	(…) This includes who performed the unblinding, the subject(s) affected, the reason for the unblinding, the	Clarification

Safety Reasons	date of the unblinding and the relevant IP information.	date of the unblinding and the relevant IP information. **After unblinding (except unblinding for the purpose of regulatory reporting), subjects will be discontinued from the study.**	on unblinding
8.1. Analysis Sets	The following sets will be used for the analyses performed in the study:	following sets will be used for the analyses performed in the study: • **Randomised set (RAN): RAN will consist of all subjects who receive a randomisation number at the randomisation.**	Clarification
8.2.1. Demographics and Baseline Characteristics	The Baseline value is defined as that recorded at the Randomisation visit (Day 1) for all analyses. If the Baseline value is missing at the Randomisation visit, the last measurement prior to the time of first IP administration will be used. Subject demographics and baseline characteristics will be summarised by treatment group for the FAS. (…) Relevant medical history and continuing medical conditions will be summarised by treatment group for the FAS.	The Baseline value **~~is~~ will be** defined as **~~that recorded at the Randomisation visit (Day 1) for all analyses. If the Baseline value is missing at the Randomisation visit,~~** the last **available** measurement **value** prior to the time of first IP administration **~~will be used~~**. Subject demographics and baseline characteristics will be summarised by treatment group for the **~~FAS~~ RAN**. (…) Relevant medical history and continuing medical conditions will be summarised by treatment group for the **~~FAS~~ RAN**	Clarification
8.2.2.1. Primary Efficacy Analysis	For US Food and Drug Administration submission, the primary efficacy analysis will be performed in the FAS for the ratio of best ORR by 24 weeks (best ORR of SB8/ best ORR of Avastin®), and the equivalence will be declared if the 90% confidence interval (CI) of the best	For US Food and Drug Administration **~~submission~~ or other regulatory agency submissions for those who are in favour of risk ratio,** the primary efficacy analysis will be performed in the FAS for the ratio of best ORR **~~by 24 weeks~~** (best ORR of SB8/ best ORR of	Submission to different agencies

	ORR ratio is contained within the pre-defined equivalence margin of [0.737, 1.357]. The similar analysis will be performed for the PPS to support the primary analysis. For EMA submission, the primary efficacy analysis will be performed in the PPS for the difference in the best ORR by 24 weeks, and the equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The similar analysis will be performed for the FAS to support the primary analysis. The statistical method to get the CI for primary analysis will be described in the Statistical Analysis Plan (SAP), and the SAP will be finalised prior to the first database lock.	Avastin®) **by 24 weeks**, and the equivalence will be declared if the 90% confidence interval (CI) of the best ORR ratio is contained within the pre-defined equivalence margin of [0.737, 1.357]. The similar analysis will be performed for the PPS to support the primary analysis. For EMA ~~**submission**~~, **MFDS or other regulatory agency submissions for those who are in favour of risk difference,** the primary efficacy analysis will be performed in the PPS for the difference ~~**in**~~ **of** the best ORR **(best ORR of SB8 – best ORR of Avastin®)** by 24 weeks, and the equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The similar analysis will be performed for the FAS to support the primary analysis. ~~**The statistical method to get the CI for primary analysis will be described in the Statistical Analysis Plan (SAP), and the SAP will be finalised prior to the first database lock.**~~ **The primary efficacy analysis will be performed using the log binomial model with treatment. The sensitivity analysis will be performed using the log binomial model with the covariates of age (< 70, ≥ 70 years), sex (female, male), region (country or pooled centres) and treatment to explore the robustness of**	Clarification

		the primary efficacy results. **In the primary efficacy analysis for FAS, the response of the patients without any post-baseline tumour assessment will be imputed as following:** • **Missing data from patients who withdrew the study due to progression disease (PD), lack of efficacy and AEs without any tumour assessment will be considered as non-responder.** • **Missing data from patients who withdrew the study with reasons other than PD, lack of efficacy and AEs without any tumour assessment will be imputed using multiple imputation method.** • **Missing data from patients who remained in the study but do not have any valid tumour assessment will be imputed using multiple imputation method.** **In the primary efficacy analysis for the PPS, missing data will not be imputed.**	
8.2.2.2. Secondary Efficacy Analyses	The secondary efficacy endpoints of PFS, OS and DOR will be analysed for PPS and FAS and described in the SAP.	The secondary efficacy endpoints of PFS, OS and DOR will be analysed for PPS and FAS ~~**and described in the SAP.**~~ **PFS and OS will be analysed using the Kaplan-Meier method with median survival time and its 95% CI by treatment. The analysis using the stratified Cox proportional hazard model will be additionally performed to adjust the covariates used in the sensitivity analysis. DOR will be summarised**	Clarification

		using descriptive statistics by treatment.	
8.3. Determination of Sample Size	For the calculation of the equivalence margin, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered.	~~**For**~~ **Regarding** the calculation of the equivalence margin **for the ratio of the best ORR by 24 weeks**, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704) [Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho, 2012]) was considered. **The overall response rate for Avastin® was reported as 34.9% (133 of 381 patients), 34.7% (114 of 329 patients), 32.4% (11 of 34 patients) and 56.2% (68 of 121 patients) compared to the overall response rate of 15.1% (59 of 392 patients), 21.7% (71 of 327 patients), 18.8% (6 of 32 patients) and 33.9% (20 of 59 patients) for chemotherapy, in E4599, AVAiL, AVF0757 and JO19907 respectively.**	Clarification
	The overall ratio of best ORR and the 70% CI from above four studies are calculated to be [redacted] using the fixed effect method from meta-analysis. Retaining the [redacted]% of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks. For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%,	The overall ratio of **the** best ORR and the 70% CI from above four studies are calculated to be [redacted] using the fixed effect method from meta-analysis. Retaining the [redacted]% of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks. **For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] will be used due to the similar**	Clarification

	12.5%] will be used due to the similar derivation.	**derivation.** **For the calculation of the equivalence margin for the difference of the best ORR by 24 weeks, E4599 [Sandler, 2006] and AVAiL [Reck, 2010] studies were considered. The overall response rate for Avastin® was reported as 34.9% (133 of 381 patients) and 37.8% (130 of 344 patients), compared to the overall response rate of 15.1% (59 of 392 patients) and 21.6% (75 of 347 patients) for chemotherapy, in E4599 and AVAiL, respectively.** **The overall difference in the best ORR and its 95% CI from these two studies are calculated to be [CCI % [CCI %, CCI %] using the fixed-effect method from meta-analysis, or for 80% CI to be [CCI %, CCI %]. The equivalence margin of [-12.5%, 12.5%] will ensure the superiority of SB8 over placebo with a small safety margin retaining around CCI % for 95% CI and C CI % for 80% CI of the effect over the placebo in the difference of best ORR.**	
13. REFERENCES APPENDIX 1: ECOG PERFORMANCE STATUS	Avastin® Summary of Product Characteristics (EMEA/H/C/000582 -II/0082). EMEA (Oct 29, 2015). Retrieved on Nov 04, 2015 from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf	Avastin® Summary of Product Characteristics (EMEA/H/C/000582 -II/0082). EMEA (Oct 29, 2015). Retrieved on ~~**Nov 04**~~ **Dec 21**, 2015 from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf	Updated

<table>
<tr><td></td><td></td><td>Reck M, von Pwel J, Zatloukal P, et al. Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Annals of Oncology. 2010; 21: 1804–1809</td><td></td></tr>
<tr><td>APPENDIX 2: LUNG CANCER STAGING</td><td>APPENDIX 2: LUNG CANCER STAGING</td><td>APPENDIX 2: LUNG CANCER STAGING (AJCC 7TH EDITION)</td><td>Updated</td></tr>
<tr><td>APPENDIX 3: NATIONAL CANCER INSTITUTE-COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 4.03 (NCI-CTCAE v4.03) (IN PART OF)</td><td>
<table>
<tr><th rowspan="2">AE</th><th colspan="5">Grade</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Neutrophil count decreased</td><td>< LLN-1,500/mm³</td><td>< 1,500-1000/mm³</td><td>< 1,000-500/mm³</td><td>< 500/mm³</td><td>-</td></tr>
<tr><td>Platelet count decreased</td><td>< LLN-75,000/mm³</td><td>< 75,000-50,000/mm³</td><td>< 50,000-25,000/mm³</td><td>< 25,000/mm³</td><td>-</td></tr>
<tr><td>Febrile neutropenia</td><td>-</td><td>-</td><td>ANC <1,000/mm³ with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour.</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></tr>
<tr><td>AST/ALT</td><td>> ULN–3.0 × ULN</td><td>> 3.0-5.0 × ULN</td><td>> 5.0-20.0 × ULN</td><td>> 20.0 × ULN</td><td>-</td></tr>
<tr><td>Blood bilirubin increased</td><td>> ULN–1.5 × ULN</td><td>> 1.5-3.0 × ULN</td><td>> 3.0-10.0 × ULN</td><td>> 10.0 × ULN</td><td>-</td></tr>
<tr><td>ALP</td><td>> ULN-2.5 × ULN</td><td>> 2.5-5.0 × ULN</td><td>> 5.0-20.0 × ULN</td><td>> 20.0 × ULN</td><td>-</td></tr>
</table>
</td><td>
Specific CTCAE Grades for Selected Adverse Events
<table>
<tr><th rowspan="2">AE</th><th colspan="5">Grade</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Neutrophil count decreased</td><td>< LLN-1,500/mm³</td><td>< 1,500-1000/mm³</td><td>< 1,000-500/mm³</td><td>< 500/mm³</td><td>-</td></tr>
<tr><td>Platelet count decreased</td><td>< LLN-75,000/mm³</td><td>< 75,000-50,000/mm³</td><td>< 50,000-25,000/mm³</td><td>< 25,000/mm³</td><td>-</td></tr>
<tr><td>Febrile neutropenia</td><td>-</td><td>-</td><td>ANC <1,000/mm³ with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour.</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></tr>
<tr><td>AST/ALT</td><td>> ULN–3.0 × ULN</td><td>> 3.0-5.0 × ULN</td><td>> 5.0-20.0 × ULN</td><td>> 20.0 × ULN</td><td>-</td></tr>
<tr><td>Blood bilirubin increased</td><td>> ULN–1.5 × ULN</td><td>> 1.5-3.0 × ULN</td><td>> 3.0-10.0 × ULN</td><td>> 10.0 × ULN</td><td>-</td></tr>
<tr><td>ALP</td><td>> ULN-2.5 × ULN</td><td>> 2.5-5.0 × ULN</td><td>> 5.0-20.0 × ULN</td><td>> 20.0 × ULN</td><td>-</td></tr>
</table>
</td><td>Added a title for the table</td></tr>
<tr><td>PROTOCOL SIGNATURE PAGES</td><td></td><td>Declaration of the Global Principal/Coordinating Investigator</td><td>Insert signature page for global PI</td></tr>
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