Official Title:	**A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin® In 1st Line Treatment for Patients with Advanced/Recurrent Non-Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin AVANA**
NCT Number:	**NCT02810457**
Document Date:	**Protocol Version 5: 22 May 2018**

CONFIDENTIAL AND PROPRIETARY
Information described herein is confidential and may be disclosed
only with the express written permission of Centus Biotherapeutics Limited.
This study will be performed in compliance with Good Clinical Practices.

Title:	A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin® In 1st Line Treatment for Patients with Advanced/Recurrent Non-Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin AVANA
Protocol Number:	FKB238-002
IND Number:	122990
EudraCT Number:	2015-004104-33
Investigational Product:	FKB238
Phase:	III
Sponsor:	Centus Biotherapeutics Limited 1 Francis Crick Avenue Cambridge Biomedical Campus Cambridge CB2 0AA United Kingdom
Sponsor Contact:	[redacted]
Coordinating Investigator:	[redacted]
Contract Research Organization:	PAREXEL International (IRL) Limited 70 Sir John Rogerson's Quay Dublin 2 Ireland
Date of Protocol:	22 May 2018
Version	5

PROTOCOL SYNOPSIS

Study Number:	FKB238-002
Title of Study:	A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin® In 1st Line Treatment for Patients with Advanced/Recurrent Non-Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin Short Title: AVANA
Indication:	Non-squamous non-small cell lung cancer (NS-NSCLC)
Number of Study Centres:	Approximately 200 sites in 31 countries
Development Phase:	III
Study Period	Estimated date of first patient enrolled: June, 2016 Estimated date of last patient last visit: February, 2022
Objectives:	**Primary** • To demonstrate the efficacy equivalence of FKB238 and EU approved-Avastin (EU-Avastin) when used in combination with paclitaxel/carboplatin as measured by overall response rate (ORR) **Secondary** • To compare FKB238 and EU-Avastin through: o ORR at week 19 o Progression-free survival (PFS) o Overall survival (OS) o Duration of response (DOR) o Disease control rate (DCR) • To compare the safety of FKB238 and EU-Avastin • To compare the antidrug antibodies (ADAs) produced by FKB238 and EU-Avastin • To compare the serum trough concentration (C_{trough}) of FKB238 and EU-Avastin
Methodology/ Study Design:	This is a global multi-centre, double-blind, parallel, Phase 3 study designed to compare the efficacy and safety of FKB238 and EU-Avastin when used in combination with paclitaxel and carboplatin in the 1st line treatment of advanced or recurrent NS-NSCLC. Patients aged 18 years or older who have advanced or recurrent NS-NSCLC will be screened for participation up to 28 days before randomisation. Approximately 730 eligible patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups. Randomisation will be stratified according to epidermal growth

	factor receptor (EGFR) mutation and anaplastic lymphoma receptor tyrosine kinase (ALK) gene arrangement status (both are tested and known negative versus status unknown for either), geographical region, prior weight loss over the previous 6 months (< 5% yes versus no), and disease stage (advanced or recurrent). The following treatment groups will be included in this study: • **FKB238 group**: paclitaxel + carboplatin (combination drugs) + FKB238 (investigational product [IP]) • **Avastin group**: paclitaxel + carboplatin (combination drugs) + EU-Avastin (IP) Upon randomisation, patients will enter the Study Treatment Period. Following start of study treatment, patients will attend for study visits every 3 weeks as long as they are receiving study treatment. The combination drugs (paclitaxel + carboplatin) will be administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles is determined by patients' need and the investigator's assessment. FKB238 or EU-Avastin (IP) will also be administrated on Day 1 of each 21-day cycle until objective disease progression (PD) or other criteria for treatment discontinuation are met. Radiological assessment using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 will be performed at screening and every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the remainder of the treatment period, and then every 12 weeks (± 1 week) after the completion of study treatment. Patients who develop toxicity may delay study treatment for up to 3 weeks. In most cases, patients who require the combination drugs and/or IP to be held for more than 3 weeks will discontinue the study treatment. In some cases, should re-start of the study treatment after a delay of more than 3 weeks be required, a discussion should occur between the medical monitor and the investigator. All such decisions need to be appropriately documented. Patients who discontinue study treatment for reasons other than PD will continue to undergo RECIST v1.1 tumour assessments until PD, until death, or until data cut-off (whichever occurs first). Data cut-off is defined as 12 months from randomisation of the last patient enrolled in the study and is expected in January 2019 for the purpose of the primary and secondary endpoint analyses. After discontinuation of the study treatment, further care and treatment will be at the discretion of the investigator. Up to the time of data cut-off, any systemic anti-cancer treatment, radiotherapy or cancer surgery conducted after discontinuation of study treatment will be collected until death, loss to follow-up,

	withdrawal of consent or until end of study. Assessments for survival should be made every 8 weeks (± 1 week) following objective PD. At data cut-off all patients previously discontinued from study treatment and continuing in follow-up will complete the study and no further study assessments will be performed. The Extended Treatment Period is the time after data cut-off to end of study in which patients may continue receiving IP if they are considered by the treating investigator to be gaining clinical benefit.
Number of Patients (planned and analysed):	Assuming a dropout rate of 10%, it is anticipated that approximately 730 patients will be randomised into the study in a 1:1 ratio (365 patients in the FKB238 group and 365 patients in the Avastin group) in order to have a total of 656 patients who complete study treatment. Sample size was determined to meet both the European Medicines Agency (EMA) and Food and Drug Administration (FDA) requirements, which differ in several aspects. To fulfil the EMA requirements, a meta-analysis of available randomised clinical studies of Avastin demonstrated that the risk-difference for the ORR for the control arm compared to the Avastin treatment arm was calculated to be 0.1938 (80% confidence interval [CI]: [0.1564,0.2312]). Based on the result of the meta-analysis, an equivalence margin for the risk-difference was determined to be 0.1221, which preserves over 22% of the treatment effect characterised by the lower 80% CI for the risk-difference of ORR. The NCSS PASS 2005 statistical software was used for the sample size calculation. With the equivalence margin for the risk-difference of 0.1221, an expected response rate of 35% in both treatment arms, the study design employing a two one-sided test (TOST) procedure, and an overall Type I error rate of 2.5%, a sample size of 656 patients (328 per group) was calculated to provide 80% power to demonstrate that the 95% CI about the risk-difference comparing FKB238 and EU-Avastin falls completely within ± 0.1221. A total of approximately 730 NS-NSCLC patients (allowing for a dropout rate of 10%) will be randomised either to the FKB238 group or Avastin group in a 1:1 ratio in a parallel group study. Per the FDA requirements, a meta-analysis was performed on data from relevant clinical trials of Avastin, resulting in an estimate of the risk-ratio of 0.5212 along with a 70% CI, (0.4775, 0.5689). With lower and upper equivalence margins of 0.73 and 1.38, which preserve 50% treatment effects determined by the lower and

	upper limits respectively of the 70% CI, an expected response rate of 35% in both treatment arms, a TOST procedure for equivalence, and an overall Type I error rate at 5%, a sample size of 656 patients (328 per group) provides 80% power to demonstrate that the 90% CI for the risk-ratio comparing FKB238 and EU-Avastin is entirely enclosed within 0.73 and 1.38. Accounting for potential 10% dropouts, approximately 730 patients will be randomised.
Diagnosis and Main Criteria for Inclusion:	The following are the inclusion criteria: 1. Patients aged 18 years or older 2. Newly diagnosed advanced (stage IV) /recurrent NS-NSCLC for which they had not received any systemic anti-cancer therapy for metastatic disease, including chemotherapy, biologic therapy, immunotherapy, or any investigational drug 3. Histologically or cytologically confirmed diagnosis of predominantly NS-NSCLC 4. Be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin for the treatment of advanced or recurrent NS-NSCLC 5. Existence of at least 1 measurable lesion by response evaluation criteria (RECIST v1.1), defined as; at least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. 6. Eastern Collaborative Oncology Group Performance Status (ECOG PS) 0 or 1 7. Life expectancy longer than 6 months 8. Adequate haematological function: absolute neutrophil count ≥ 1.5 × 109/L; platelets ≥ 100 × 109/L; haemoglobin ≥ 9 g/dL 9. International normalised ratio (INR) ≤ 1.5 and partial thromboplastin time ≤ 1.5 × the upper limit of normal (ULN) within 7 days prior to starting study treatment 10. Adequate liver function: Serum bilirubin ≤ 1.5 × ULN (and in case of documented Gilbert's Syndrome [unconjugated hyperbilirubinaemia] ≤ 3 x ULN); transaminases ≤ 2.5 × ULN (and in case of liver metastases < 5 × ULN) 11. Adequate renal function: a. Creatinine clearance, measured and/or calculated according to the formula of Cockroft and Gault ≥ 60 mL/ min AND b. Urine dipstick or urinalysis for proteinuria < 2+. If the urine dipstick or urinalysis is ≥ 2+, 24-hour urine must

	demonstrate ≤ 1 g of protein in 24 hours 12. Negative serum/urine pregnancy test within 7 days of starting study treatment in premenopausal women and women < 2 years after the onset of menopause 13. Signed informed consent 14. Able to comply with the protocol
Exclusion Criteria:	The following are the exclusion criteria: 1. Small cell lung cancer (SCLC) or combination SCLC and NSCLC. Squamous-cell tumours and mixed adenosquamous carcinomas of predominantly squamous nature 2. Recurrence occurred within 12 months from the last dose of neoadjuvant/adjuvant therapy 3. Any unresolved toxicities from prior systemic therapy (eg, adjuvant chemotherapy) greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study drug with the exception of alopecia 4. Evidence of a tumour that compresses or invades major blood vessels or tumour cavitation that in the opinion of the investigator is likely to bleed 5. Known sensitising EGFR mutations (eg, deletion 19 or L858R) or EML4-ALK translocation positive mutations 6. Previous dosing with vascular endothelial growth factor (VEGF) inhibitor 7. Brain metastasis or spinal cord compression (computed tomography or magnetic resonance imaging of the head is required within 4 weeks prior to randomisation) 8. Malignancy other than NS-NSCLC within 5 years before randomisation, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localised prostate cancer treated surgically with curative intent, or ductal carcinoma in situ of the breast treated surgically with curative intent 9. Known hypersensitivity to active ingredients or any excipients of the IPs and combination chemotherapy 10. Use of aspirin (> 325 mg/day) or treatment with dipyridamole, ticlopidine, clopidogrel, prasugrel, or cilostazol within 14 days before the first dose of IP 11. Use of full-dose oral or parenteral anticoagulants or thrombolytic agents within 6 months before the first dose of IP (use of low dose anticoagulants for venous access device maintenance or prophylactic use of anticoagulants will be allowed) 12. Known Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV) infection 13. Major surgery, significant traumatic injury, or radiotherapy

	(except for palliative intention which requires 14 days wash out period for bone lesions outside the thoracic region) within 28 days before the first dose of IP or anticipation of the need for major surgery during study treatment 14. Fine needle aspirations, indwelling catheter placement, or core biopsy within 7 days of randomisation 15. Non-healing wound, ulcer, or bone fracture 16. Uncontrolled hypertension or systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg 17. Patients with unstable angina, myocardial infarction, coronary artery bypass graft, angioplasty, vascular stenting, or cardiovascular event within 6 months before the first dose of IP; coagulopathy, any bleeding disorders, poorly controlled diabetes, or active gastrointestinal inflammation such as gastric or duodenal ulcer, diverticulitis, inflammatory bowel disease, or cholecystitis 18. History of fistulas or abdominal perforations 19. History of arterial or venous thromboembolic or ischemic events, or congestive heart failure (New York Heart Association class ≥ 2) within 6 months before the first dose of IP 20. History of haemoptysis of ≥ ½ teaspoon of red blood within 28 days before the first dose of IP 21. Fertile men or women of childbearing potential not using adequate contraception. Patients of child bearing potential and their partners, who are sexually active, must agree to the use of at least one highly effective form of contraception throughout their participation in the study and for 6 months after last dose of study treatment 22. Breastfeeding women (unless the patient is willing to discontinue breastfeeding throughout their participation in the study and for 6 months after last dose of study treatment) 23. Treatment with any other investigational agent for any reason within 28 days before the first dose of IP 24. Presence of any other disease, metabolic dysfunction, physical examination finding, or laboratory finding that, in the opinion of the investigator, puts the patient at high risk for treatment-related complications in this study
Study Treatment:	**Concomitant Chemotherapy (Combination Drugs), Dose, and Mode of Administration:** Paclitaxel, 200 mg/m^2, intravenous (IV) infusion over 3 hours should be immediately followed by carboplatin, area under the time curve 6.0, IV infusion over 15 to 60 minutes on Day 1. Paclitaxel and carboplatin will be administered once every 21 days (± 3 days) for at least 4, and no more than 6 cycles. The number of cycles is determined by patients' need and the investigator's

	assessment. **Test Product (IP), Dose, Dosage Form, and Mode of Administration:** FKB238, 15 mg/kg, IV infusion immediately following carboplatin, to be administered once every 21 days (± 3 days) until objective PD or other criteria for treatment discontinuation are met the initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. **Reference therapy (IP), Dose, and Mode of Administration:** EU-Avastin (bevacizumab), 15 mg/kg, IV infusion immediately following carboplatin, to be administered once every 21 days (± 3 days) until objective PD or other criteria for treatment discontinuation are met. The initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Duration of Treatment:	Concomitant chemotherapy will be administered once every 21 days (± 3 days) for at least 4, and no more than 6 cycles. IP treatment will be given until PD or other criteria for treatment discontinuation are met.
Duration of Patient Participation in Study:	This study consists of a Screening Period (up to 28 days), a Study Treatment Period, a study treatment discontinuation visit, a Follow-up Period (up to the data cut-off which occurs with a minimum of 12 months after randomisation of the last patient enrolled), and an Extended Treatment Period. Patients may remain on IP treatment until PD or other criteria for treatment discontinuation are met. Patients who are withdrawn from treatment will continue to be followed in the Follow-up Period until formal withdrawal of consent, until death, or until the data cut-off (whichever occurs first). At data cut-off all patients previously discontinued from study treatment and continuing in follow-up will complete the study and no further study assessments will be performed. Following data cut-off, patients on treatment at that time may continue receiving IP during an Extended Treatment Period if the investigator believes they are gaining clinical benefit from the treatment.
Study Populations:	The Intent-to-Treat (ITT) Population includes all patients randomised to treatment. All efficacy analyses will be performed on the ITT population. These analyses will be treated as the primary analysis for the FDA requirement and as sensitivity

	analysis otherwise. The Per-Protocol Set (PPS) includes all ITT patients who received at least 1 dose of IP with no important protocol violations or deviations. All efficacy analyses will be performed on the PPS population. These analyses will be treated as the primary analysis for the EMA requirement and as sensitivity analysis otherwise. The Safety Population includes all ITT patients who received at least 1 dose of IP. All safety analyses will be performed on the Safety Population. The Pharmacokinetic (PK) Population includes all PPS patients who have at least 1 serum drug concentration data, which is defined in the study protocol, after IP administration.
Evaluation: Efficacy	Primary Endpoints: • ORR (by RECIST v1.1) assessed as the rate of the best response (complete response [CR] or partial response [PR]). Primary efficacy assessment will be presented based on the investigators' assessment results as well as the independent central radiological assessment results, but primary efficacy assessment based on the independent central radiological assessment results will be used as a pivotal result of the study. Secondary Endpoints: • ORR (by RECIST v1.1) at week 19, defined as the rate of the best response of CR or PR assessed at week 19 • PFS, defined as the time from randomisation to the first documented PD or death, whichever occurs first • OS, defined as the time from randomisation to death from any cause • DOR, defined as the time from the first documented PR or CR (by RECIST v1.1) to the first documented PD or death, whichever occurs first • DCR, defined as the rate of CR, PR, SD (≥ 6 weeks) Data from efficacy assessments during the Extended Access Period will not be collected.
Evaluation: Safety	Safety will be evaluated through adverse events (AEs), vital signs, haematology, clinical chemistry, urinalysis, electrocardiogram, ECOG PS, and physical examination. Only serious adverse events, pregnancies, overdoses, and AEs that lead to treatment discontinuation or death will be collected during the Extended Treatment Period.

Evaluation: Other	• Pharmacokinetics: C_{trough} • Immunogenicity: presence of ADAs Samples for pharmacokinetics and immunogenicity will not be collected during the Extended Treatment Period.
Statistical Methods:	The TOST procedure will be used for testing the null hypothesis of non-equivalence against the alternative hypothesis of equivalence. To fulfil the EMA's requirement, the TOST procedure will be carried out using PPS by comparing a 95% confidence interval (CI) for the ORR difference between FKB238 and EU-Avastin to the margin [± 0.1221], which is deemed to represent a clinically acceptable difference with respect to ORR. If the true CI is within the interval [± 0.1221], an equivalence between FKB238 and EU-Avastin, with respect to the ORR, is confirmed. To meet the FDA's requirements, the TOST procedure will be performed based on ITT population by comparing a 90% CI for the ORR ratio between FKB238 and EU-Avastin to the margin [0.73, 1.38], which is deemed to represent a clinically acceptable difference with respect to ORR. If the CI is within the interval [0.73, 1.38], an equivalence between FKB238 and EU-Avastin, with respect to the ORR, is confirmed. The logistic regression model will be fitted for the overall response and treatment adjusted for the covariates. The adjusted odds ratio and corresponding 95% CI will be presented. Kaplan-Meier curves for PFS, OS, and DOR, medians, and corresponding 95% CI based on Kaplan-Meier estimator per treatment arm will be presented. The multiple Cox proportional hazards model will be fitted for all time to event endpoints, including treatment group adjusted for the covariates. The hazard ratios and corresponding 95% CI for treatment effect and the covariates will be presented. PFS and OS will be compared between treatment groups and descriptive statistics will be provided. DCR and ORR at week19 will be estimated and compared between treatment groups, using descriptive statistics. C_{trough} will be compared between treatment groups and descriptive statistics will be provided. The ADA rates of FKB238 and EU-Avastin at each time point will be summarised.

LIST OF STUDY PERSONNEL

Sponsor	Centus Biotherapeutics Limited 1 Francis Crick Avenue Cambridge Biomedical Campus Cambridge CB2 0AA United Kingdom
Sponsor Contact	[redacted]
Coordinating Investigator	[redacted]
Contract Research Organization	PAREXEL International (IRL) Limited 70 Sir John Rogerson's Quay Dublin 2 Ireland Phone: +35 314 739500 Fax: +35 314 739501

Contact details of other study participants (eg, central laboratory, medical monitor for safety reporting, study drug logistics) are provided in the study manual.

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A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin® In 1st Line Treatment for Patients with Advanced/Recurrent Non-Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Centus Biotherapeutics Limited representatives below:

[redacted]
Signature

04-June-2018
Date

[redacted]
Head of Medical, Centus
UK

[redacted]
Signature

06-June-2018
Date

[redacted]
Head of Statistics, Centus
Gaithersburg, MD, USA

2. INVESTIGATOR AGREEMENT

2.1 Coordinating Investigator

A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin® In 1st Line Treatment for Patients with Advanced/Recurrent Non-Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin

I understand that all information concerning FKB238 supplied to me by Centus Biotherapeutics Limited (hereafter referred to as Centus) and the Contract Research Organization, in connection with this study and not previously published is confidential and should not be disclosed, other than to those directly involved in the execution or ethical review of this study. This information includes the Investigator's Brochure, protocol, case report forms, assay methods, technical methodology, and basic scientific data.

As the Coordinating Investigator I agree to act as a signatory to the Clinical Study Report (CSR) for the referenced clinical study, thereby acknowledging that to the best of my knowledge the CSR accurately describes the conduct and results of the study. In reporting the results of this multi-centre study, I am expressing an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

[redacted]

Coordinating Investigator's Signature

08 JUN 2018

Date

[redacted]

Coordinating Investigator's Name

[redacted]

AVANA International Principal Investigator

2.2 Investigator Agreement

I understand that all information concerning FKB238 supplied to me by Centus and the Contract Research Organization, in connection with this study and not previously published is confidential and should not be disclosed, other than to those directly involved in the execution or ethical review of this study. This information includes the Investigator's Brochure, protocol, case report forms, assay methods, technical methodology, and basic scientific data.

I agree to conduct this study according to this protocol and in keeping with the principles of the Declaration of Helsinki, Good Clinical Practice, and the laws and regulations of the country where the study is to be conducted. I understand that any substantial changes to the protocol must be approved in writing by Centus, Regulatory Authorities, and the Institutional Review Board/Independent Ethics Committee before implementation as applicable, except where necessary to eliminate apparent immediate hazards to the patients.

I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor and as described in the guidelines for Good Clinical Practice.

I confirm that I will report all adverse events following the regulations laid down in the protocol.

I agree to make available to Centus personnel, their representatives, and relevant regulatory authorities, my patients' study records in order to verify the data that I have entered into the case report forms. I confirm that I am informed of the need for record retention and that no data can be destroyed without the written consent of Centus.

I understand that Centus may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Centus.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this version of the protocol.

Investigator's Signature	Date
Investigator's Name (printed)	

3. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma receptor tyrosine kinase
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the curve
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CBDCA	carboplatin
CDDP	cisplatin
CFR	US Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
Combination drugs	paclitaxel and carboplatin
CR	complete response
CRO	contract research organization
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	serum trough concentration
CYP	cytochrome P450
DCR	disease control rate
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Collaborative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
Flt-1	Fms-like tyrosine kinase-1
FOLFOX	fluorouracil + leucovorin + oxaliplatin
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GEM	gemcitabine

Abbreviation	Definition
GGT	gamma glutamyl transferase
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFL	irinotecan + fluorouracil + leucovorin
INR	international normalised ratio
IP	investigational product; FKB238 and EU-Avastin
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
KDR	kinase insert domain receptor
LDH	lactate dehydrogenase
LS	least square
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mBC	metastatic breast cancer
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
mL	millilitre
mmHg	millimeter of mercury
mRCC	metastatic renal cell cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
N	number
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NS-NSCLC	non-squamous non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	disease progression (progression of disease)
PET	positron emission tomography
PFS	progression-free survival
PHL	potential Hy's Law
PK	pharmacokinetics
PPS	per-protocol set
PR	partial response
PTT	partial thromboplastin time
PTX	paclitaxel
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation	Definition
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TOST	two one-sided test
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE	venous thromboembolism
XELOX	capecitabine + oxaliplatin

4. ETHICAL AND REGULATORY REQUIREMENTS

4.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

4.2 Patient Data Protection

The informed consent forms (ICFs) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study. The ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by the Sponsor will be identified by an "individual treatment code" and study code. The Sponsor will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by the law.

4.3 Ethics and Regulatory Review

An Independent Ethics Committee (IEC) or Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICFs and any other written information and/or materials to be provided to the patients. The investigator or Contract Research Organization (CRO) will ensure the distribution of these documents to the applicable IEC/IRB, and to the study site staff. The opinion of the IEC/IRB should be given in writing. The investigator or CRO should submit the written approval to the Sponsor before enrolment of any patient into the study. The IEC/IRB should approve all advertising used to recruit patients for the study. The Sponsor should approve any modifications to the ICF that are needed to meet local requirements. If required by local regulations, the protocol should be re-approved by the IEC/IRB.

Before enrolment of any patient into the study, the final study protocol is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. The Sponsor or its representative will handle the distribution of any of these documents to the national regulatory authorities. The Sponsor or its representative will provide regulatory authorities, IECs/IRBs, and investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

4.4 Informed Consent

The investigator at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study, including the following: collection of study blood samples and biopsies, specifically to fulfil study inclusion requirements
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IEC/IRB

4.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Coordinating Investigator and the Sponsor. If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (revised clinical study protocol). The amendment is to be approved by the relevant IEC/IRB and, if applicable, also the national regulatory authority before implementation. Local requirements are to be followed for revised protocols. The Sponsor or its representative will distribute any subsequent amendments and new versions of the protocol to each investigator. For distribution to IECs/IRBs see Section 4.3.

If a protocol amendment requires a change to a centre's ICF, the Sponsor (or its representative) and the centre's IEC/IRB are to approve the revised ICF before the revised form is used. If local regulations require, any administrative change will be communicated to or approved by each IEC/IRB.

4.6 Audits and Inspections

Authorised representatives of the Sponsor, a regulatory authority, or an IEC/IRB may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study

related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the centre.

5. INTRODUCTION

Bevacizumab is a recombinant humanised monoclonal antibody (mAb) expressed in Chinese Hamster Ovary (CHO) cells. Bevacizumab binds vascular endothelial growth factor (VEGF)-A and prevents the interaction of VEGF-A with its receptors, Fms-like tyrosine kinase-1 (Flt-1; vascular endothelial growth factor receptor-1 [VEGFR-1]) and kinase insert domain receptor (KDR; VEGFR-2), which are present in varying degrees on endothelial cells. VEGF-A is overexpressed in a variety of tumours and is known to be a cytokine involved in tumour growth. This is mediated by interaction of VEGF-A with its receptors (primarily KDR), which has been observed to cause endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis, a key factor in the growth of many tumour types. Bevacizumab was first approved for the treatment of metastatic carcinoma of the colon or rectum (mCRC) in February 2004 in the United States (US) and in January 2005 in the European Union (EU), and was subsequently launched globally under the brand name Avastin®. Avastin is currently indicated for the treatment of mCRC and non-small cell lung cancer (NSCLC) in the EU, US, and Japan, ovarian cancer in the EU and Japan, metastatic renal cell cancer (mRCC) in the EU and US, metastatic breast cancer (mBC) in the EU and Japan, glioblastoma in the US and Japan, and persistent, recurrent, or metastatic carcinoma of the cervix in the US. Approved doses and treatment regimens are tumour- and region-specific and generally range between 5 and 15 mg/kg. Avastin is a solution for intravenous (IV) infusion and is presented as 100 mg in a 4 mL or 400 mg in a 16 mL vial.[1]

FKB238 is being developed as a proposed biosimilar biological product to Avastin. FKB238 is a recombinant humanised mAb expressed in the CHO cell line. The similarity between FKB238 and Avastin has been assessed in a range of initial characterisation studies and no significant differences have been observed. In addition, preliminary nonclinical studies demonstrate similarity between FKB238 and EU-Avastin in terms of pharmacological activity.

5.1 Summary of Nonclinical and Clinical Studies

5.1.1 Nonclinical Studies

With respect to nonclinical development, the EU and US guidance documents recommend a risk-based approach to evaluation of biosimilar mAbs and in determining the choice and extent of *in vitro* and *in vivo* studies to be conducted.

Fujifilm Kyowa Kirin Biologics Co., Ltd. has conducted *in vitro* and *in vivo* studies to evaluate the following:

- Binding to the target antigen
- Binding to the Fcγ receptors and FcRn
- Fab-associated functions (neutralisation activity)
- Fc-associated functions (binding to C1q)

- Pharmacological effects on xenograft model mice
- Single dose pharmacokinetic (PK) study in rats
- 2-week repeated dose toxicology study in rats

In vitro studies have shown that FKB238 and Avastin are similar in terms of binding to the target antigen (recombinant human VEGF isoforms), binding to Fcγ receptors and FcRn, neutralisation of VEGF mediated activities, and binding to C1q. An *in vivo* study using a severe combined immunodeficient mouse model bearing human colorectal adenocarcinoma DLD-1 cells showed that the mean increase in tumour volume observed for the study was suppressed to a similar extent by FKB238 and Avastin. A PK study in Crl:CD(SD) rats revealed that the PK concentration-time curves for FKB238 and Avastin were similar. A Good Laboratory Practice-compliant, repeat-dose, nonspecific toxicity study in 20 Crl:CD(SD) rats was conducted to evaluate the toxicity of FKB238 15 mg/kg or 75 mg/kg when repeatedly administered by IV twice weekly for 2 weeks. No animals died or were euthanized due to moribundity in the FKB238 group. No toxic changes were observed in clinical signs, body weight, food consumption, water consumption, ophthalmology, urinalysis, haematology, blood chemistry, bone marrow examination, organ weights, gross pathology, and histopathology in the FKB238 group. Toxicokinetics showed no differences in systemic exposure between male and female groups. It was concluded from these results that under the conditions of this study, there were no toxicities seen with the FKB238 treatments.

Additional details on nonclinical studies can be found in the FKB238 Investigator's Brochure.[1]

5.1.2 Clinical Studies

Avastin has been studied in over 5200 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials. The most frequently observed adverse reactions across clinical trials in patients receiving Avastin, according to the Summary of Product Characteristics (SmPC), were hypertension, fatigue or asthenia, diarrhoea, and abdominal pain. The occurrence of hypertension and proteinuria with Avastin therapy appears to be dose-dependent. According to the Avastin US Product Label, the most common adverse reactions (>10% and at least twice the control arm rate) were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal haemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis.

The first human study of FKB238, a randomised, double-blind, active-control study to compare the safety and PK of FKB238 and Avastin after single doses, by IV infusion, in healthy male volunteers has completed study enrolment in March 2015. Initially, a total of 120 healthy male subjects were expected to be enrolled in the study. But after a pre-planned interim analysis conducted at the time when PK data from 46 subjects became available, study enrolment was terminated following the pre-specified criteria. As a result, a total of 99 subjects were randomly assigned to receive a single 5 mg/kg IV

infusion of EU-approved Avastin (EU-Avastin), US-licensed Avastin (US-Avastin), or FKB238, in a 1:1:1 ratio. Similarity between FKB238 and EU-Avastin, FKB238 and US-Avastin, EU-Avastin and US-Avastin was all confirmed in all 2 primary PK parameters analysed ($AUC_{0-\infty}$, AUC_{0-t}). Two secondary PK parameters (C_{max} and $t_{1/2}$) also met pre-specified equivalence criteria. A summary of similarity analysis is shown in Table 1 and Table 2.

Table 1 Summary of Similarity Analysis of Primary Endpoints

	Geometric Least Square (LS) Mean [1]		
	FKB238	**EU-Avastin**	**US-Avastin**
$AUC_{0-\infty}$ (h*µg/mL)	52,300	49,400	53,500
AUC_{0-t} (h*µg/mL)	50,800	49,300	51,800
	Ratio of Geometric LS Means (90% Confidence Interval [CI])		
	FKB238 / EU-Avastin	**FKB238 / US-Avastin**	**EU-Avastin / US-Avastin**
$AUC_{0-\infty}$ (h*µg/mL)	1.06 (0.99, 1.13)	0.98 (0.92, 1.04)	0.92 (0.87, 0.98)
AUC_{0-t} (h*µg/mL)	1.03 (0.97, 1.09)	0.98 (0.93, 1.04)	0.95 (0.90, 1.01)

[1] Similarity is achieved if the 90% CI falls within pre-specified acceptance range (0.80, 1.25)

Table 2 Summary of Similarity Analysis of Secondary Endpoints

	Geometric Least Square (LS) Mean [1]		
	FKB238	**EU-Avastin**	**US-Avastin**
C_{max} (µg/mL)	139	142	138
$t_{1/2}$ (h)	439	412	463
	Ratio of Geometric LS Means (90% Confidence Interval [CI])		
	FKB238 / EU-Avastin	**FKB238 / US-Avastin**	**EU-Avastin / US-Avastin**
C_{max} (µg/mL)	0.97 (0.91, 1.04)	1.01 (0.94, 1.07)	1.03 (0.97, 1.10)
$t_{1/2}$ (h)	1.06 (0.98, 1.16)	0.95 (0.87, 1.03)	0.89 (0.82, 0.97)

[1] Similarity is achieved if the 90% CI falls within pre-specified acceptance range (0.80, 1.25)

There were no deaths nor serious adverse events (SAEs) observed in the PK comparison study. Numerically, a greater percentage of subjects on FKB238 arm had treatment-emergent adverse events (TEAEs) when compared to either EU-Avastin or US-Avastin (97%, 76%, 72% respectively). Similarly, treatment-emergent adverse drug reactions were experienced by a greater numerical percentage of subjects receiving FKB238 compared to either EU-Avastin or US-Avastin (45%, 32%, 38%, respectively).

All the observed treatment-emergent adverse drug reactions were mild or moderate. A single subject had a TEAE which was a grade 3 or above (grade 3 tooth infection) but causality to study drug was assessed as not related. The most common adverse event (AE) was headache, experienced in 48.5% of the subjects who received FKB238. Similarly the most common adverse drug reaction was headache.

Four out of overall 99 enrolled subjects were positive for antidrug antibody (ADA). ADA positive subjects were equally distributed in 3 arms (1 in FKB238 arm, 2 in EU-Avastin arm, and 1 in US-Avastin arm).

Additional details on clinical studies can be found in the FKB238 Investigator's Brochure.[1]

5.2 Potential Risks and Benefits

5.2.1 Established Safety Profile for Avastin

The safety and immunogenicity data for Avastin are mostly from clinical studies and postmarketing experience in patients with cancers such as mCRC, NS-NSCLC, mBC, glioblastoma, or mRCC, treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. Many of the adverse effects observed are considered to be influenced by the underlying disease state of the patients; eg, as described in the SmPC for Avastin, in clinical studies, the incidence of gastrointestinal perforation/fistula in each cancer type was different, suggesting that these events are related to underlying disease related conditions such as tumour necrosis, chemotherapy related colitis, bowel surgery, and peritoneal metastasis. Also, as SmPC suggested, haemorrhagic reactions observed in clinical studies of Avastin were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (eg, epistaxis).

While bevacizumab is not a cytotoxic agent, its use is associated with a number of mechanism based AEs. Gastrointestinal perforations, haemorrhage, and arterial thromboembolism are specified as the most serious adverse reactions of the drug. In addition, fistulas, wound-healing complications, hypertension, congestive heart failure, posterior reversible encephalopathy syndrome, proteinuria, hypersensitivity reactions/infusion reactions, and laboratory test abnormalities are also listed as serious adverse reactions. Of these, as described in the SmPC for Avastin, hypertension and proteinuria have been noted to be likely dose-dependent.

5.2.1 Potential Safety Profile for FKB238

From the first in human clinical study of FKB238, no SAEs were observed. All the observed treatment-emergent adverse drug reactions were mild or moderate. FKB238 is intended to be developed as a biosimilar product to bevacizumab. Data obtained during a range of initial characterisation and nonclinical studies with FKB238 to date do not indicate an additional potential impact on patient safety. Therefore, it could be expected that similar class effects and a safety profile to Avastin (bevacizumab) will be observed. However, due to the very limited patient exposure to FKB238, it should be noted that unexpected safety issues may arise during clinical development.

Additional details are available in the Investigator's Brochure.[1]

5.3 Study Rationale

The FKB238-002 study is designed to confirm equivalence of efficacy for FKB238 and EU-Avastin.

The current European Medicines Agency (EMA) "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1)" describes that "in the absence of surrogate markers for efficacy, it is usually necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, by using efficacy endpoints." Due to the lack of a validated surrogate serum biomarker for the evaluation of efficacy of bevacizumab in any indications approved, the current study will directly compare the efficacy of FKB238 to EU-Avastin.

Choice of Patient Population

The development program for FKB238 is designed to obtain the data necessary to support the approval of FKB238 as a biosimilar to Avastin in the EU, US, and Japan. Among the approved indications of Avastin, NSCLC and mCRC are the only 2 that are common to all 3 regions. On this basis, patients with these conditions were considered to represent the most appropriate populations for inclusion in this study.

In the scientific literature, there are 2 randomised Phase 3 studies of Avastin in combination with chemotherapy that have been conducted in 1st line NS-NSCLC and 2 Phase 3 studies in 1st line mCRC (Table 3). In each of the 2 randomised studies in 1st line NS-NSCLC, there was a statistically significant treatment benefit of Avastin as assessed by overall response rate (ORR) and progression-free survival (PFS).[2,3,4] In 1 of the 2 studies in 1st line mCRC, a statistically significant treatment effect was also noted in both ORR and PFS,[5] while in the other, the effect was only observed in relation to PFS.[6] A statistically significant overall survival (OS) benefit was observed in 1 of 2 studies conducted in each population. Thus, based on the available data, while Avastin was clearly effective in both cancer types, the efficacy was more consistently observed across the study endpoints in patients with NS-NSCLC. Therefore, NS-NSCLC was considered as the most sensitive population to assess clinical efficacy of bevacizumab. During the health authority meetings with FDA and EMA, both agencies agreed that the proposed patient population is considered to be most sensitive for the proposed study.

Table 3 Phase 3 Results of Avastin in 1st Line NS-NSCLC and 1st Line mCRC

Study	Target	Treatment Arm	N	ORR (%)	PFS (months)	OS (months)
Sandler et al., 2006[2]	1st line NS-NSCLC	PTX + CBDCA	433	15	4.5	10.3
		PTX + CBDCA + Avastin 15 mg/kg	417	35 (p<0.001)	6.2 (p<0.001)	12.3 (p=0.003)
Reck et al., 2009,[3] Reck et al., 2010[4]	1st line NS-NSCLC	GEM + CDDP	347	21.6	6.1	13.1
		GEM + CDDP + Avastin 7.5 mg/kg	345	37.8 (p=0.0001)	6.7 (p=0.003)	13.6 (p=0.42)
		GEM + CDDP + Avastin 15 mg/kg	351	34.6 (p=0.0002)	6.5 (p=0.03)	13.4 (p=0.76)
Hurwitz et al., 2004[5]	1st line mCRC	IFL	411	34.8	6.2	15.6
		IFL + Avastin	402	44.8 (p=0.004)	10.6 (p<0.001)	20.3 (p<0.001)
Saltz et al., 2008[6]	1st line mCRC	FOLFOX4/XELOX	701	38	8	19.9
		FOLFOX4/XELOX + Avastin	699	38 (p=0.99)	9.4 (p=0.0023)	21.3 (p=0.77)

Abbreviations: NS-NSCLC = non-squamous non-small cell lung cancer; mCRC = metastatic colorectal cancer; ORR = overall response rate; PFS = progression-free survival; OS = overall survival; CBDCA = carboplatin; CDDP = cisplatin; GEM = gemcitabine; FOLFOX = fluorouracil + leucovorin + oxaliplatin; IFL = irinotecan + fluorouracil + leucovorin; PTX = paclitaxel; XELOX = capecitabine + oxaliplatin.

Choice of Dose Regime

Patients will receive either FKB238 or EU-Avastin 15mg/kg every 3weeks (investigational products [IPs]) in combination with paclitaxel and carboplatin (combination drugs) in line with the approved regiment for Avastin outlined in the Package Insert and the SmPC.

Choice of Primary Endpoint

Among the conventional clinical efficacy endpoints in oncology studies, ORR is considered as the most sensitive parameter for evaluation of the similarity of efficacy of FKB238 versus EU-Avastin. In the draft FDA guidance 'Scientific Considerations in Demonstrating Biosimilarity to a Reference Product February 2012," the FDA recommends that a Sponsor use endpoints that are clinically relevant and sufficiently sensitive to detect clinically meaningful differences in safety and effectiveness between the proposed product and the reference product. In addition, the draft guidance states that a Sponsor can use endpoints that are different from those used in the pivotal trial for the reference product. A similar position was given in the 'EMA Guideline on similar biological medicinal products containing monoclonal antibodies - nonclinical and clinical issues (EMA/CHMP/BMWP/403543/2010)." This guideline suggests that conventional clinical efficacy endpoints other than ORR, such as PFS and OS, may not be feasible or sensitive enough for establishing similarity of an anti-cancer biosimilar mAb to a reference mAb. This perspective comes from one of the core concepts of biosimilarity which is that the focus of the similarity exercise is to demonstrate similar efficacy and safety and not patient benefit *per se*. In fact, PFS and OS will be influenced by factors not attributable to efficacy differences between the products, but by factors such as tumour

burden, performance status, previous lines of treatment, underlying clinical conditions, and subsequent lines of treatment (for OS). Given the above considerations, ORR was considered as the most appropriate primary endpoint for this efficacy equivalence study. However, ORR at week 19, PFS, OS, DOR, and DCR data representing patient benefit will also be collected and evaluated as secondary endpoints.

The results of this efficacy equivalence study, together with completed PK comparison study, will fully support the global biosimilar product applications and that the planned trials are consistent with the US biosimilar guidance as well as EU guidelines for biosimilars.

Choice of PK Endpoint

Sparse PK sampling (8 samples per subject) will be gathered during the study. A single dose PK study in healthy subjects has already established the PK similarity of FKB238 and EU-Avastin. The sparse sampling in this study will further help evaluate the multiple dose PK comparison of the two compounds in the target patient population. Samples will also be drawn for ADA assessment of the two compounds.

6. STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of this study is:

- To demonstrate the efficacy equivalence of FKB238 and EU-Avastin when used in combination with paclitaxel/carboplatin as measured by ORR

6.2 Secondary Objectives

Secondary objectives of this study are:

- To compare FKB238 and EU-Avastin through:
    - ORR at week 19
    - PFS
    - OS
    - Duration of response (DOR)
    - Disease control rate (DCR)
- To compare the safety of FKB238 and EU-Avastin
- To compare the ADAs produced by FKB238 and EU-Avastin

- To compare the serum trough concentration (C_{trough}) of FKB238 and EU-Avastin

6.3 Study Endpoints

The primary endpoint is:

- ORR (by Response Evaluation Criteria [RECIST] v1.1) assessed as the rate of the best response (complete response [CR] or partial response [PR])

The secondary efficacy endpoints are:

- ORR (by RECIST v1.1) at week 19, defined as the rate of the best response of CR or PR assessed at week 19
- PFS, defined as the time from randomisation to the first documented disease progression (PD) or death, whichever occurs first
- OS, defined as the time from randomisation to death from any cause
- DOR, defined as the time from the first documented PR or CR (by RECIST v1.1) to the first documented objective PD or death, whichever occurs first
- DCR, defined as the rate of CR, PR, SD (≥ 6 weeks)

Other endpoints are:

- Safety as evaluated through AEs, vital signs, haematology, clinical chemistry, urinalysis, electrocardiogram (ECG), Eastern Collaborative Oncology Group Performance Status (ECOG PS), and physical examination
- Immunogenicity (presence of ADAs)
- Pharmacokinetics (C_{trough})

7. INVESTIGATION PLAN

7.1 Overall Study Design and Plan Description

This is a global multi-centre, double-blind, parallel comparative, Phase 3 study designed to compare the efficacy and safety of FKB238 and EU-Avastin when used in combination with paclitaxel and carboplatin in the 1st line treatment of advanced or recurrent NS-NSCLC.

Patients aged 18 years or older who have advanced or recurrent NS-NSCLC will be screened for participation up to 28 days before randomisation. Approximately 730 eligible patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups. Randomisation will be stratified according to epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma receptor tyrosine kinase (ALK) gene arrangement

status (both are tested and known negative versus status unknown for either), geographical region, prior weight loss over the previous 6 months (< 5% yes versus no), and disease stage (advanced or recurrent). The following treatment groups will be included in this study:

- **FKB238 group**: paclitaxel + carboplatin (combination drugs) + FKB238 (IP)
- **Avastin group**: paclitaxel + carboplatin (combination drugs) + EU-Avastin (IP)

Upon randomisation, patients will enter the Study Treatment Period. Following start of study treatment, patients will attend for study visits every 3 weeks as long as they are receiving study treatment. The combination drugs (paclitaxel + carboplatin) will be administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles is determined by patients' need and the investigator's assessment. FKB238 or EU-Avastin (IP) will also be administrated on Day 1 of each 21-day cycle until objective PD or other criteria for treatment discontinuation are met.

Radiological assessment using RECIST v1.1 will be performed at screening until PD and every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the treatment period up to data cut-off, and then every 12 weeks (± 1 week) after the completion of study treatment up to data cut-off. Following data cut-off, study-specific radiological assessments will not be performed for patients in the Extended Treatment Period. The investigator may elect to perform radiological assessments according to locally defined standard of care practices. However, no efficacy data will be collected by the sponsor during the Extended Treatment Period.

Patients who develop toxicity may delay study treatment for up to 3 weeks. In most cases, patients who require the combination drugs and/or IP to be held for more than 3 weeks will discontinue the study treatment. In some cases, should re-start of the study treatment after a delay of more than 3weeks be required, a discussion should occur between the medical monitor and the investigator. All such decisions need to be appropriately documented. Patients who discontinue IP treatment for reasons other than PD will continue to undergo RECIST v1.1 tumour assessments until PD, until death, or until data cut-off (whichever occurs first).

After the discontinuation of the study treatment, further care and treatment will be at the discretion of the investigator. Any systemic anti-cancer treatment, radiotherapy or cancer surgery conducted after discontinuation of study treatment will be collected until death, loss to follow-up, withdrawal of consent or until end of study. Assessments for survival should be made every 8 weeks (± 1 week) following objective PD until data cut-off.

At data cut-off, all patients previously discontinued from study treatment and continuing in follow-up will complete the study and no further study assessments will be performed.

The end of the study is defined as the last patient last visit. The endpoint analyses occur after data cut-off, which is a minimum of 12 months after randomisation of the last patient enrolled. The Extended Treatment Period is the time after data cut-off to end of

study in which patients may continue receiving IP if they are considered to be gaining clinical benefit. These patients may receive treatment until withdrawal, PD, or death. See Section 7.7.5 for information regarding patient management and reporting after data cut-off.

Prior to data cut-off, AEs will be collected from time of signature of informed consent, throughout the treatment period and up to and including 30 calendar days after the last study treatment. All ongoing and any new AEs/SAEs identified at data cut-off and during the 30 calendar days after last dose of study treatment must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

The Schedule of Assessments prior to Data Cut-Off (Table 13) indicates the timing of the planned visits including visit window for the study visits. The investigator/sub-investigator should adhere to the Schedule of Assessment procedures and perform tests/observations according to the protocol. Assessments after start of Study Treatment should be performed within a window of ± 3 days of the scheduled visit date. Computed tomography (CT) or magnetic resonance imaging (MRI) assessments should be done within a window of ± 7 days of the scheduled date according to the RECIST v1.1 criteria, but every effort should be made to adhere as closely as possible to the original schedule of scans.

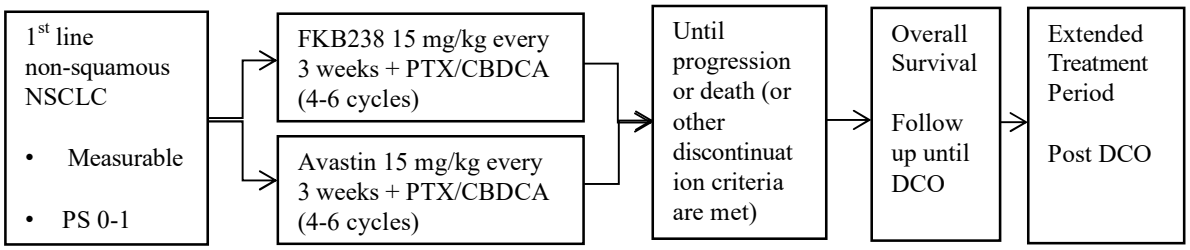
Baseline RECIST v1.1 assessment will be performed using CT (or MRI scans where CT is clinically contra-indicated) at screening no more than 28 days prior to start of study treatment (Cycle 1 Day 1) and ideally should be performed as close as possible to the start of the study treatment. Baseline radiological assessments should cover the chest and the upper abdomen (including liver and the adrenal glands). Brain CT/MRI is required within 4 weeks prior to randomization. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients.

After start of study treatment, RECIST v1.1 assessment using CT (or MRI scans where CT is clinically contra-indicated) will be performed every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the remainder of the treatment period, until objective PD or data cut-off. The methods of assessment of tumour burden used at baseline CT or MRI scans of chest and upper abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

No further radiological tumour assessments will be done after objective PD is documented. Patients who discontinue study treatment for reasons other than PD will continue to undergo RECIST v1.1 tumour assessments every 12 weeks (± 1 week) until PD, death or the data cut-off (whichever occurs first).

Every effort should be made to adhere to the original schedule of RECIST v1.1 scans.

Figure 1 presents a graphic description of the study design.



Abbreviations: CBDCA=carboplatin; NSCLC=non-small cell lung cancer; PS=performance status; PTX=paclitaxel; DCO=data cut-off.

Figure 1: Study Design

7.2 Discussion of Study Design, Including the Choice of Control Groups

FKB238 is a recombinant humanised mAb expressed in CHO cell line to be developed as a proposed biosimilar product to the Avastin (bevacizumab) product currently marketed and available to the public in the EU, US, and Japan. This efficacy equivalence study is designed to compare the efficacy and safety of FKB238 to EU-Avastin. Similarity between FKB238 and EU-Avastin, FKB238 and US-Avastin, EU-Avastin and US-Avastin were all confirmed in all 2 primary PK parameters analysed ($AUC_{0-\infty}$, AUC_{0-t}) in the first human study of FKB238, a randomised, double-blind, parallel study to compare PK and safety of FKB238 and Avastin after single dose IV infusion, in healthy male volunteers. Two secondary PK parameters (C_{max} and $t_{1/2}$) also met pre-specified equivalence criteria. As such, EU-Avastin has been selected as the active comparator in a randomised, double-blind study.

Paclitaxel and carboplatin were selected as the concomitant chemotherapy for both treatment groups as a widely accepted and approved standard regimen, where the efficacy and drug-drug interaction of these chemotherapy agents with Avastin have been well established.

Efficacy equivalence will be evaluated based on ORR. In the draft FDA guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product February 2012," the FDA recommends that a Sponsor use endpoints that are clinically relevant and sufficiently sensitive to detect clinically meaningful differences in safety and effectiveness between the proposed product and the reference product. In addition, the draft guidance states that a Sponsor can use endpoints that are different from those used in the pivotal trial for the reference product. A similar position was given in the "EMA Guideline on similar biological medicinal products containing monoclonal antibodies-nonclinical and clinical issues (EMA/CHMP/BMWP/403543/2010)." This guideline suggests that conventional clinical efficacy endpoints other than ORR, such as PFS and OS, may not be feasible or sensitive enough for establishing similarity of an anti-cancer biosimilar mAb to a reference mAb. This perspective comes from one of the core concepts of biosimilarity which is that the focus of the similarity exercise is to

demonstrate similar efficacy and safety and not patient benefit per se. PFS and OS will be influenced by factors not attributable to efficacy differences between the products, but by factors such as tumour burden, performance status, previous lines of treatment, underlying clinical conditions, and subsequent lines of treatment (for OS). Given the above considerations and further discussions with health authorities, ORR was considered and agreed to be the most appropriate primary endpoint for this study.

Safety will be compared based on the frequency/severity of all AEs, clinical laboratory assessments, ECG, ECOG PS, and physical examination results. Immunogenicity will be determined by the presence of ADAs.

7.3 Selection of Study Population

7.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet all of the following criteria:

1. Patients aged 18 years or older
2. Newly diagnosed advanced (stage IV) /recurrent NS-NSCLC for which they had not received any systemic anti-cancer therapy for metastatic disease, including chemotherapy, biologic therapy, immunotherapy, or any investigational drug
3. Histologically or cytologically confirmed diagnosis of predominantly NS-NSCLC
4. Be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin for the treatment of advanced or recurrent NS-NSCLC
5. Existence of at least 1 measurable lesion by response evaluation criteria (RECIST v1.1; APPENDIX C) defined as; at least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. For additional information, refer to Section 7.8.1.3.
6. ECOG PS 0 or 1 (APPENDIX B – Eastern Collective Oncology Group Performance Status)
7. Life expectancy longer than 6 months
8. Adequate haematological function: absolute neutrophil count (ANC) ≥ 1.5×10^9/L; platelets ≥ 100×10^9/L; haemoglobin ≥ 9 g/dL
9. International normalised ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 1.5 × the upper limit of normal (ULN) within 7 days prior to starting study treatment

10. Adequate liver function: Serum bilirubin ≤ 1.5 × ULN (and in case of documented Gilbert's Syndrome [unconjugated hyperbilirubinaemia] ≤ 3 x ULN); transaminases ≤ 2.5 × ULN (and in case of liver metastases < 5 × ULN)

11. Adequate renal function:

    a. Creatinine clearance, measured and/or calculated according to the formula of Cockroft and Gault ≥ 60 mL/min AND

    b. Urine dipstick or urinalysis for proteinuria < 2+. If the urine dipstick or urinalysis is ≥ 2+, 24-hour urine must demonstrate ≤ 1 g of protein in 24 hours.

12. Negative serum/urine pregnancy test within 7 days of starting study treatment in premenopausal women and women < 2 years after the onset of menopause

13. Signed informed consent

14. Able to comply with the protocol

7.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Small cell lung cancer (SCLC) or combination SCLC and NSCLC. Squamous-cell tumours and mixed adenosquamous carcinomas of predominantly squamous nature

2. Recurrence occurred within 12 months from the last dose of neoadjuvant/adjuvant therapy

3. Any unresolved toxicities from prior systemic therapy (eg, adjuvant chemotherapy) greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study drug with the exception of alopecia

4. Evidence of a tumour that compresses or invades major blood vessels or tumour cavitation that in the opinion of the investigator is likely to bleed

5. Known sensitising EGFR mutations (eg, deletion 19 or L858R) or EML4-ALK translocation positive mutations

6. Previous dosing with VEGF inhibitor

7. Brain metastasis or spinal cord compression (computed tomography [CT] or magnetic resonance imaging [MRI] of the head is required within 4 weeks prior to randomisation)

8. Malignancy other than NS-NSCLC within 5 years before randomisation, except for

adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localised prostate cancer treated surgically with curative intent, or ductal carcinoma in situ of the breast treated surgically with curative intent

9. Known hypersensitivity to active ingredients or any excipients of the IPs (APPENDIX D – Excipients of the IPs) and combination chemotherapy

10. Use of aspirin (> 325 mg/day) or treatment with dipyridamole, ticlopidine, clopidogrel, prasugrel, or cilostazol within 14 days before the first dose of IP

11. Use of full-dose oral or parenteral anticoagulants or thrombolytic agents within 6 months before the first dose of IP (use of low dose anticoagulants for venous access device maintenance or prophylactic use of anticoagulants will be allowed)

12. Known Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV) infection

13. Major surgery, significant traumatic injury, or radiotherapy (except for palliative intention which requires 14 days wash out period for bone lesions outside the thoracic region) within 28 days before the first dose of IP or anticipation of the need for major surgery during study treatment

14. Fine needle aspirations, indwelling catheter placement, or core biopsy within 7 days of randomisation

15. Non-healing wound, ulcer, or bone fracture

16. Uncontrolled hypertension or systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg

17. Patients with unstable angina, myocardial infarction, coronary artery bypass graft, angioplasty, vascular stenting, or cardiovascular event within 6 months before the first dose of IP; coagulopathy, any bleeding disorders, poorly controlled diabetes, or active gastrointestinal inflammation such as gastric or duodenal ulcer, diverticulitis, inflammatory bowel disease, or cholecystitis

18. History of fistulas or abdominal perforations

19. History of arterial or venous thromboembolic or ischemic events, or congestive heart failure (New York Heart Association class ≥ 2) within 6 months before the first dose of IP

20. History of haemoptysis of ≥ ½ teaspoon of red blood within 28 days before the first dose of IP

21. Fertile men or women of childbearing potential not using adequate contraception. Patients of child bearing potential and their partners, who are sexually active, must agree to the use of at least one highly effective form of contraception throughout their participation in the study and for 6 months after last dose of study treatment

22. Breastfeeding women (unless the patient is willing to discontinue breastfeeding throughout their participation in the study and for 6 months after last dose of study treatment)

23. Treatment with any other investigational agent for any reason within 28 days before the first dose of IP

24. Presence of any other disease, metabolic dysfunction, physical examination finding, or laboratory finding that, in the opinion of the investigator, puts the patient at high risk for treatment-related complications in this study

7.4 Patient Enrolment

Investigators should keep a record, the patient screening log, of patients who entered pre-study screening. The investigators will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed

2. Assign potential patient a unique 7-digit enrolment number obtained through the interactive voice response system (IVRS) in the following format ECCNNXXX: CC being the country code, NN being the centre number and XXX being the patient enrolment code at the centre

3. Determine patient eligibility (see Section 7.3)

At Cycle 1 Day 1, once the patient is confirmed to be eligible, the investigator or suitably trained delegate will:

4. Perform a drug dispensing call in IVRS

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused.

7.4.1 Procedures for Handling Patients Incorrectly Enrolled or Initiated on Study Treatment

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled in this clinical study. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where patients who do not meet the selection criteria are started on treatment in error, the investigator should inform the medical monitor immediately, and a discussion should occur between the medical monitor and the investigator regarding whether to continue or discontinue the patient from treatment. The medical monitor is to ensure that all such decisions are appropriately documented.

7.4.2 Discontinuation of Study Treatment

Patients may voluntarily withdraw from study treatment at any time and for any reason. At the time of withdrawal from study treatment, patients will be asked to provide a primary reason for discontinuation. Reasons for withdrawal from study treatment may include:

- Objective PD assessed by RECIST v1.1
- Intolerable AE
- Unable to initiate a new cycle of study treatment with a delay of more than 3 weeks. Should re-start of the study treatment after a delay of more than 3 weeks be required, a discussion should occur between the medical monitor and the investigator. All such decisions are to be appropriately documented.
- Pregnancy
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing the study data
- Development of an intercurrent illness or situation which would, in the opinion of the investigator, affect assessments of clinical status and study endpoints to a significant degree
- The patient is unwilling or unable to adhere to the protocol
- Patient withdrawal of consent
- Patient is lost to follow-up. A patient should be considered lost to follow-up only after multiple efforts have been made to contact the patient to assess his/her health status. If after 2 documented phone calls the study site is still unable to contact the patient, a certified letter should be sent to his/her home for immediate response. If there is still no response, the patient is to be considered lost to follow-up. A record of the patient being lost to follow-up should be noted in the source documents along with the phone contacts and the returned certified mail (if sent back)
- Investigator discretion
- Sponsor terminates the study

Withdrawal from study treatment does not constitute withdrawal from study. All patients who discontinue study treatment prior to data cut-off, regardless of reason for discontinuation, should complete the study treatment discontinuation visit and should be encouraged to remain on the study for follow-up of primary and secondary endpoints,

according to Table 13. In all cases, the reason for withdrawal from the study treatment must be recorded in the eCRF and in the patient's medical records. After data cut-off, once the patient withdraws from treatment, they will also withdraw from the study and the investigator will be required to submit a paper Subject Disposition Form to Sponsor confirming patient withdrawal, PD or death.

7.4.3 Replacement of Patients

Patients who withdraw from the study will not be replaced.

7.4.4 Follow-up of Patients Discontinued from the Study Treatment Regimen

A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by the investigator.

Following discontinuation of study treatment, patients may receive any subsequent therapy for NS-NSCLC at the discretion of the investigator. After discontinuation of study treatment, all systemic anti-cancer treatment, radiotherapy or cancer surgery will be collected until death, loss to follow-up, withdrawal of consent or until the data cut-off (whichever occurs first).

Patients who discontinue study treatment prior to data cut-off will be followed up for progression in line with the Schedule of Assessment (Table 13), unless objective PD is documented or the patient has withdrawn consent to both study treatment and study assessments, or had died. At data cut-off all patients previously discontinued from study treatment and continuing in follow-up will complete the study. After data cut-off, there will be no follow-up required for patients discontinued from study treatment. The investigator will provide locally defined standard of patient care.

All ongoing and any new AEs/SAEs identified during the 30 calendar days after the last dose of study medication must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. New AEs including SAEs will be recorded into the eCRF.

SAEs occurring more than 30 days after the discontinuation of the study treatment should be reported if they are considered to be related to the study treatment by the investigator. These SAEs will be not entered into the study database but should be reported to the Sponsor within the requested timeframe.

Treatment discontinuation should be reported via Randomisation and Trial Supply Management (ClinPhone®RTSM) by the investigator.

7.4.5 Withdrawal from the Study

Patients are free to withdraw from the study at any time (study treatment and assessments), without prejudice to further treatment. A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs.

The term withdrawal from the study refers to both discontinuation from study treatment and study assessments.

Patients may be withdrawn from the study for the following reasons:

- Screening failure
- Death
- Withdrawal of consent

If a patient wishes to withdraw their consent to both study treatment and study assessments, they should be asked if they are willing to continue in a Follow-up Period (which can be conducted by telephone – see Section 7.7.4). If a patient wishes to withdraw their consent to further participation in the study entirely, including follow-up, this should be clearly documented in the patient notes and in the clinical study database.

7.4.6 Screening Failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not receive study treatment. These patients should have the reason for study withdrawal recorded as "Ineligible"(i.e., patient does not meet the required inclusion/ exclusion criteria). This reason for study withdrawal is only valid for screening failures (not patients who have received study treatment).

Patients who initially fail screening due to out of range laboratory values will be allowed to repeat the laboratory assessment within the Screening Period, and if the repeat laboratory values are within normal range, the patient may be randomized into the study and receive study treatment. For patients who experience a temporary acute medical event that would prohibit randomisation of the patient within the normal duration of the Screening Period, discussion of an extension of the Screening Period with the medical monitor may occur. Otherwise, patients will not be rescreened and the patient identification number for screen failures will not be used. Patients who discontinue from study treatment will not be replaced.

7.5 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be involved in the conduct of this study. The DMC has the responsibility for monitoring the progress of the clinical study and the safety of the study participants. The DMC will perform review of safety data and study conduct during the course of the clinical trial, as defined in the DMC Charter for this clinical trial. The DMC will not stop the trial for efficacy. The memberships of the DMC and reporting structure are defined in the DMC Charter.

7.6 Treatment of Patients

7.6.1 Treatments Administered

During the Study Treatment Period, paclitaxel + carboplatin (combination drugs) will be administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. Carboplatin AUC should be calculated by the Calvert formula and creatinine clearance calculated by the Cockcroft-Gault formula (APPENDIXE). The number of cycles is determined by patients' need and the investigator's assessment. FKB238 or EU-Avastin (IP) will also be administrated on Day 1 of each 21-day cycle until objective PD or other criteria for treatment discontinuation met. Paclitaxel, 200 mg/m^2, IV infusion over 3 hours should be immediately followed by carboplatin, area under the time curve 6.0, IV infusion over 15 to 60 minutes. FKB238 or EU-Avastin, 15 mg/kg, IV infusion should be administered immediately following carboplatin. The initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Patient weight will be assessed at Day 1 of every cycle during the Study Treatment Period.

If a patient's body weight changes by ≥10% from baseline, combination drug and IP doses should be recalculated. Baseline weight is initially defined as the weight collected during the Cycle 1 Day 1 visit. On any occasion if a patient's body weight changes ≥ ±10% from baseline (Cycle 1 Day 1), the combination drug and IP doses will be recalculated. Upon recalculation, that weight and combination drug and IP dose adjustment will become the new baseline. Each time a new baseline is established, it will be used to calculate a subsequent dose adjustment if a patient's body weight changes ≥ ±10% again.

FKB238 group:

- Paclitaxel 200 mg/m^2 on Day 1 for at least 4, and no more than 6 cycles
- Carboplatin area under the curve (AUC) 6.0 on Day 1 for at least 4, and no more than 6 cycles
- FKB238 15 mg/kg on Day 1 until objective PD or other criteria for treatment discontinuation are met

Avastin group:

- Paclitaxel 200 mg/m^2 on Day 1 for at least 4, and no more than 6 cycles
- Carboplatin AUC 6.0 on Day 1 for at least 4, and no more than 6 cycles
- EU-Avastin 15 mg/kg on Day 1 until objective PD or other criteria for treatment discontinuation are met

7.6.2 Identity of Investigational Product

The Sponsor will supply the following IPs:

FKB238

FKB238 is supplied as a concentrate for solution for infusion in 100 mg/4mL preservative-free, single-use vials to deliver FKB238 (25 mg/mL). FKB238 is a clear to slightly opalescent, colourless to pale brown, sterile, pH 5.5 solution for IV infusion.

FKB238 should be diluted in a total volume of 100 mL of 0.9% sodium chloride in the majority of the occasions. **DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.**

EU-Avastin

EU-Avastin is supplied as a concentrate for solution for infusion in 100mg/4mL preservative-free, single-use vials to deliver EU-Avastin (25 mg/ml). EU-Avastin is a clear to slightly opalescent, colourless to pale brown, sterile, pH 6.2 solution for IV infusion.

EU-Avastin should be diluted in a total volume of 100 mL of 0.9% sodium chloride in the majority of the occasions. **DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.**

The investigative site might be responsible for supplying additional medications identified in the protocol including, but not limited to, the chemotherapeutic agents paclitaxel and carboplatin, and supportive care products such as chemotherapy pre-medications and permitted haematopoietic growth factors, antibiotics, transfusions, etc., as well as the IV admixture solutions needed for the reconstitution of investigational and concomitant products.

7.6.2.1 Packaging and Labelling

IP vial will be re-packaged in a blinding carton containing 1 IP vial in a blinded manner with uniquely numbered kits of FKB238/EU-Avastin (IP kit). IP kit will be packaged, and labelled in accordance with Good Manufacturing Practice and distributed under Good distribution Practice. The labels will include all the information required by each country's regulatory requirements.

The quantity of IP kits in the initial shipment will depend on the recruitment expectations of the site, resupply of IP kits will be made automatically according to ClinPhone®RTSM.

TO MAINTAIN STUDY BLIND, THE BLINDING CARTON SHOULD NEVER BE OPENED.

7.6.2.2 Storage and Stability

FKB238/EU-Avastin

IP kits should be stored refrigerated at 2°C to 8°C (do not freeze), protect from light. Do

not shake. IP kits should be kept in their original package carton that should never be opened.

After dilution with 100 mL of 0.9% sodium chloride, the solutions may be stored in IV bags for up to 8 hours at temperature of 2-8°C, protected from light. The product must not be frozen or shaken.

HOWEVER, FROM A MICROBIOLOGICAL POINT OF VIEW, THE PRODUCT SHOULD BE USED IMMEDIATELY AFTER DILUTION.

The investigator should ensure that the IP, as well as other drug products used in the trial, is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor and defined in the Pharmacy Manual.

7.6.3 Investigational Product Accountability, Reconciliation, and Return

All IP will be administered at the study site by study personnel. Receipt, accountability and return of IP kits will be recorded in ClinPhone®RTSM.

A CRO study monitor will review the IP receipt, accountability and check all IP kit returns (both unused and used IP kits) in the ClinPhone®RTSM system prior to making arrangements for their return to the CRO depots or local contracted depots, in exceptional cases (eg, if required by local regulations) local destruction upon Sponsor authorization.

7.6.4 Study Drug Handling and Disposal

The study site has to ensure that the IP kits are accessible to authorized personnel only. Used, partially used and unused IP kits should be retained in a separate location from the unused IP kits until the study monitor has been able to complete drug accountability and reconciliation.

All IP kits used and/or unused are to be returned to the CRO depots or local contracted depots, these returns must be accompanied with the ClinPhone®RTSM accountability log and be clearly identified on the outermost shipping box. All returned IP kits should not have been removed from the original IP carton. It is the investigator's responsibility to arrange for disposal of all other non-IP, provided that procedures for proper disposal have been established according to applicable local, national and institutional guidelines and procedures, and provided that appropriate records of disposal are kept and a certificate of destruction is provided to the Sponsor or designated CRO.

TO MAINTAIN STUDY BLIND, THE BLINDING CARTON SHOULD NEVER BE OPENED.

7.6.5 Method of Assigning Patients to Treatment Groups and Measures to Minimise/Avoid Bias

7.6.5.1 Patient Identification

After signing the ICF, patients will be assigned a unique patient identification number using ClinPhone®RTSM. The patient identification number will be used to identify the patient on the eCRF and on all source documents.

7.6.5.2 Randomisation

Patients who qualify for participation will be randomly assigned to 1 of 2 blinded treatment groups in a 1:1 ratio using ClinPhone®RTSM. Randomisation will be stratified (using a dynamic allocation model) according to EGFR mutation and ALK gene arrangement status (both are tested and known negative versus status unknown for either), geographical region (North America, Western Europe, East Asia, All Other Regions), prior weight loss over the previous 6 months (< 5% yes versus no), and disease stage (advanced or recurrent). The following treatment groups will be included in this study:

FKB238 group: paclitaxel + carboplatin + FKB238

Avastin group: paclitaxel + carboplatin + EU-Avastin

The randomisation schedule will be developed by ClinPhone®RTSM. Details of the randomisation schedule are provided in the ClinPhone®RTSM specifications document.

7.6.5.3 Blinding

Investigators, site staff including pharmacy staff, patients, CRO personnel, and Sponsor personnel (except for a specified IP distribution manager) will be blinded to individual patient treatment assignment during the course of the study until data cut-off. ClinPhone®RTSM will develop the randomisation schedule.

The IP will be packaged and labelled in such a way that visual inspection of the IP or packaging will not reveal the treatment assignment; however, each individual kit of IP will be numbered so that, if necessary, the number can be used to break the treatment blind if this becomes necessary to protect the safety of the patient.

TO MAINTAIN STUDY BLIND, THE BLINDING CARTON SHOULD NEVER BE OPENED.

7.6.5.4 Breaking the Blind

This study will be conducted in a manner consistent with the protection of the blinded treatment assignment for all study participants. Treatment assignments should not be prematurely unblinded by the investigator ***unless there is an immediate and material medical need to know the patient's treatment assignment in order to protect patient***

safety. In most situations, lacking treatment-specific antidotes, the investigator should have time to discuss the reason for unblinding with the medical monitor/Sponsor before proceeding to unblinding. However, should it become necessary to break the treatment blind to protect the safety of the patient, the investigator may contact ClinPhone®RTSM to obtain the treatment assignment, as detailed in the Pharmacy Manual. If possible, the investigator should contact the medical monitor before breaking the treatment blind to obtain approval. If it is not possible to contact the medical monitor before breaking the blind, the medical monitor should be notified as soon as possible of this action after the blind is broken. At all times, the number of study participants who become unblinded to the patient's treatment assignment should be minimised. The Sponsor and medical monitor will determine whether the patient will remain under study treatment after breaking the blind or whether the patient will be withdrawn from study treatment and enter follow-up.

7.6.5.5 Scheduled Unblinding

After data cut-off and database lock, all patients will be unblinded.

7.6.6 Selection of Doses in the Study

Patients will receive 15 mg/kg of either FKB238 or EU-Avastin in combination with paclitaxel and carboplatin in line with the approved regiment for EU-Avastin outlined in the Package Insert and the SmPC.

7.6.7 Criteria for Schedule Adjustment, Dose Modifications, and Discontinuation of Study Treatment

If during treatment, a severe or intolerable AE occurs or the patient develops toxicity, study treatment should be temporarily withheld. If combination drugs are delayed, IP administration must also be delayed. The National Cancer Institute (NCI) CTCAE version 4.0 will be used to evaluate toxicity.

If the start of the cycle is delayed, the interval of 3 weeks must be kept for subsequent cycles. In most cases, patients who require combination therapy and/or IP to be held for more than 3 weeks will discontinue study treatment. In some cases, should re-start of study treatment after a delay of more than 3 weeks be required, a discussion should occur with the medical monitor. All such decisions need to be appropriately documented.

If IP treatment is discontinued due to toxicity, combination drugs will continue. If combination drugs are discontinued due to toxicity, IP treatment will continue. Missed doses of combination drugs and IP should not be administered later.

Guidelines for treatment of combination drug or IP-related toxicities are provided below.

7.6.7.1 FKB238/EU-Avastin

The dose of IP will not be reduced; dose modifications for IP toxicity will be limited to

dose delay or discontinuation only. Any IP-related AEs of hypertension, proteinuria, thromboembolism, or haemorrhage should be managed as described below:

Hypertension

CTCAE grade 1	Prehypertension (systolic BP 120 – 139 mmHg or diastolic BP 80 – 89 mmHg)	Give IP
CTCAE grade 2	Stage 1 hypertension (systolic BP 140 - 159 mmHg or diastolic BP 90 – 99 mmHg); medical intervention indicated; recurrent or persistent (≥ 24 hours); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits; monotherapy indicated	Give IP; Start anti-hypertensive therapy
CTCAE grade 3	Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg); medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated	Hold IP; Start or intensify anti-hypertensive therapy; Resume IP when BP returns to pre-treatment level or to < 160/100 mmHg, and continue to monitor BP
CTCAE grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); hypertension encephalopathy, urgent intervention indicated	Permanently discontinue IP

Proteinuria

Proteinuria by urinalysis or dipstick should be assessed before each IP administration.

Manage proteinuria as follows:

- ≤ 1+ proteinuria (dipstick or urinalysis): administer IP as planned
- 2 to 3+ proteinuria (dipstick or urinalysis): administer IP as planned and collect 24-hour urine for determination of total protein within 3 days before the next scheduled IP administration
    - 24-hour proteinuria ≤ 2 g: administer next IP dose as scheduled. Continue to follow 24-hour urinary protein before each cycle. If urinary protein falls to < 1 g, resume monitoring by dipstick method.
    - 24-hour proteinuria > 2 g: omit next scheduled IP dose and do 24-hour urine collection for determination of total protein within 3 days before the subsequently scheduled cycle. Delay IP treatment until proteinuria has decreased to ≤ 2 g. Do 24-hour urine before each scheduled dose until

proteinuria has improved to ≤1 g/24 hours, but omit IP only if >2g protein/24 hours.

- 4+ proteinuria (dipstick or urinalysis): hold IP and collect 24-hour urine for determination of total protein within 3 days before the next scheduled IP administration
    - Restart IP when 24-hour urinary protein falls to ≤ 2 g
- Nephrotic syndrome: permanently discontinue IP treatment

Thrombosis/Embolism

Arterial thromboembolism:

- Any CTCAE grade: permanently discontinue IP treatment

Venous thromboembolism (including pulmonary embolism):

- CTCAE grade 2 or 3: hold IP treatment for at least 2 weeks until the patient is medically stabilized. Anticoagulation therapy should be initiated. The IP may be resumed after initiation of therapeutic-dose anticoagulant therapy if the patient is on a stable dose of anticoagulant and, if on warfarin, has an INR within the target range (usually between 2 and 3) prior to restarting IP treatment.
- CTCAE grade 4: permanently discontinue IP treatment. Anticoagulation therapy should be initiated.

Haemorrhage

- Haemoptysis of ≥ 1/2 teaspoon: permanently discontinue IP treatment
- CTCAE grade 2 bronchopulmonary haemorrhage (moderate symptoms; medical intervention indicated): permanently discontinue IP treatment
- CTCAE grade 3 or 4 bleeding of any kind: permanently discontinue IP treatment
- Mild epistaxis/gingival bleeding is common with bevacizumab. Treatment does not need to be held if bleeding responds to usual first aid measures for epistaxis

Gastrointestinal Perforation/Fistulae

- Any CTCAE grade: permanently discontinue IP treatment

Wound-healing complications

- Wound dehiscence, fistulae, infection: permanently discontinue IP treatment

Posterior Reversible Encephalopathy Syndrome

- Permanently discontinue IP treatment

Left ventricular systolic dysfunction

- CTCAE grade 3 or 4: permanently discontinue IP treatment

Infusion reactions

- Severe infusion reaction (CTCAE grade 3 or 4): permanently discontinue IP treatment, and administer appropriate medical therapy

Haematological toxicity

- Asymptomatic decreases in levels of haematologic parameters, including neutrophils, leucocytes, platelets and haemoglobin:
    - CTCAE grade 3 or above: treat according to institutional guidelines
    - The ANC must be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L prior to the next scheduled dose. If ANC $< 1.5 \times 10^9$/L and/or platelets $< 100 \times 10^9$/L the dose should be delayed to allow recovery.
    - Erythropoietic growth factors and granulocyte-colony stimulating factor (G-CSF) may be used in accordance with institutional guidelines and the individual product information
- Febrile neutropenia:
    - Treat according to institutional guidelines
    - Hold further dosing until the patient is fully recovered (apyrexial for 2 days and ANC $\geq 1.5 \times 10^9$/L)
- See also Section 7.6.7.2 for guidance on carboplatin and paclitaxel dosing
- If G-CSF is used in the treatment of neutropaenia consider prophylactic use for subsequent cycles

Any Other CTCAE grade 3 or 4 FKB238/EU-Avastin -related Event

- First occurrence: hold IP until toxicity has improved to CTCAE grade ≤ 1

- Second occurrence: permanently discontinue IP treatment

7.6.7.2 Paclitaxel and Carboplatin

The chemotherapy dose level modifications to be followed for defined toxicities are displayed in the Table 4.

Table 4 Chemotherapy Dose Level Modifications for Defined Toxicities

Dose Level	Paclitaxel Dose	Carboplatin Dose*
0 (starting dose)	200 mg/m^2	AUC 6
-1	175 mg/m^2	AUC 5
-2	150 mg/m^2	AUC 4

* Carboplatin AUC should be calculated by Calvert formula and creatinine clearance calculated by Cockcroft-Gault formula (APPENDIX E).

A maximum of 2 dose reductions (to dose level -2) for chemotherapy are permitted. Patients who require more than 2 chemotherapy dose reductions to doses lower than dose level -2 as described in Table 4 will be discontinued from chemotherapy treatment in this study.

Except as discussed below for hepatic dysfunction/toxicity, for nausea and vomiting, and for haematologic toxicities, all dose reductions are permanent with no dose re-escalation permitted.

If multiple toxicities occur, the most stringent dose reduction modification will be followed. Dose reductions are not additive (ie, investigators should choose the most stringent dose reduction dictated by any toxicity and that will cover all the toxicities).

Haematologic Toxicity Dose Modification

The ANC must be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L on the first day of each cycle. If chemotherapy must be withheld due to haematologic toxicity (ANC $< 1.5 \times 10^9$/L and/or platelets $< 100 \times 10^9$/L), a complete blood count and platelet count should be obtained weekly until the counts reach the lower limits for treatment as stated. Do not re-treat until the ANC is $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. The doses of paclitaxel and/or carboplatin will be modified based on the worst toxicity observed during the preceding cycle.

Patients and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed. When a dose reduction in paclitaxel/carboplatin is made for decreased ANC, and/or decreased platelet count, or febrile neutropenia and the reduced dosage results in no toxicity in a subsequent chemotherapy cycle, re-escalation of the chemotherapy doses may occur in subsequent cycles based on the investigator's discretion.

Toxicities will be graded according to CTCAE. There will be no dose reductions for anaemia, which may be managed according to institutional guidelines. Erythropoietic growth factors may be used in accordance with local health authority stated indication criteria. No IP dose reductions should be implemented for haematologic toxicity.

Table 5 Chemotherapy Dose Modification at the Start of the Subsequent Cycle

Haematologic	**Paclitaxel**	**Carboplatin**
Worst Toxicity in Preceding Cycle		
Febrile neutropenia* for any duration OR ANC < 1000/mm^3 for 5 days OR ANC < 500/mm^3 for any duration * ANC < 1000/mm^3 with a single temperature of > 38.3°C	decrease 1 dose level	decrease 1 dose level
CTCAE grade 4 thrombocytopenia, or CTCAE grade 3 thrombocytopenia with bleeding or requiring transfusion	decrease 1 dose level	decrease 1 dose level

Note: First episode of febrile neutropenia will be managed with dose reduction. For a second episode of febrile neutropenia, prophylaxis with granulocyte colony-stimulating factor treatment may be instituted in lieu of a second dose reduction. Further febrile neutropenia despite granulocyte colony-stimulating factor treatment must be managed with a second dose reduction.

Hepatic Dysfunction/Toxicity Dose Modification

The dose of combination drugs will be adjusted for increased alanine transaminase (ALT) or aspartate transaminase (AST) or total bilirubin as indicated in Table 6:

Table 6 Dose Adjustments for Hepatic Toxicities

Hepatic Transaminases		**Total Bilirubin**	**Paclitaxel**	**Carboplatin**
Laboratory values at time of treatment should be used in determining paclitaxel dose.				
ALT and AST ≤ 5 x ULN	AND	≤ 1.25 x ULN	No change	No change
ALT or AST > 5, but ≤ 10 x ULN	OR	> 1.25, but ≤ 2 x ULN	Reduce to 175 mg/m^2	No change
ALT and AST ≤ 10 x ULN	AND	> 2, but ≤ 3 x ULN	Reduce to 150 mg/m^2	No change
ALT or AST > 10 x ULN	OR	> 3 x ULN	Withhold*	Withhold*

*If paclitaxel is withheld due to hepatic dysfunction/toxicity, carboplatin should also be withheld and administered when paclitaxel is resumed. If paclitaxel is withheld and hepatic values have not recovered

within 3 weeks, patients must be discontinued from study chemotherapy.

After any dose reduction of paclitaxel for hepatic clinical laboratory abnormalities, the dose of paclitaxel will not be re-escalated unless the hepatic abnormalities have:

- Resolved to ALT and AST ≤ 5 x ULN and to total bilirubin ≤ 1.25 x ULN;
- The cause of the hepatic clinical laboratory abnormalities is identified as other than paclitaxel induced; and
- Re-escalation is approved by the medical monitor.

All 3 conditions must be met to permit re-escalation of the paclitaxel dose.

Cardiac Toxicity (Paclitaxel) Dose Modification

Cardiac rhythm disturbances occur infrequently in patients given paclitaxel. Most are asymptomatic and cardiac monitoring is not required. Transient asymptomatic bradycardia has been reported but clinically significant atrioventricular block is rare. Cardiac toxicity should be managed according to Table 7 and follow local institutional guidelines if required.

Table 7 Dose Modifications for Cardiac Toxicity

Event	Management
Asymptomatic bradycardia	No intervention
Symptomatic arrhythmia during infusion	Discontinue study treatment; manage arrhythmia according to standard local practice
Chest pain and/or symptomatic hypotension (< 90/60 mmHg or requires fluid replacement)	Discontinue study treatment; obtain ECG; decide between cardiac pain vs non-cardiac infusion reaction and manage latter with H1 blocker (eg, chlorphenamine 10 mg IV or diphenhydramine 25 to 50 mg IV) and corticosteroid (eg, dexamethasone 10 mg IV). Also, consider epinephrine or bronchodilators if chest pain is not thought to be cardiac.

Neurologic Toxicity (Paclitaxel) Dose Modification

Peripheral neuropathy may occur in patients receiving paclitaxel, and should be graded according to CTCAE. Dose modification for paclitaxel is described in Table 8. No dose adjustment is necessary for carboplatin.

Table 8 Dose Modification for Neurologic Toxicity

Toxicity CTCAE grade	Paclitaxel Dose Modification
0	None
1	None
2	Hold chemotherapy until toxicity recovers to ≤ CTCAE grade 1, then resume chemotherapy with paclitaxel reduced to 175 mg/m^2
3	Hold chemotherapy until toxicity recovers to ≤ CTCAE grade 1, then resume chemotherapy with paclitaxel reduced to 150 mg/m^2
4	Permanently discontinue chemotherapy

Gastrointestinal Toxicity Dose Modification

Chemotherapy dose modifications will be made based on the worst toxicity in the preceding cycle as per Table 9. Nausea and/or vomiting in association with paclitaxel and carboplatin should be controlled with adequate antiemetics before administration, and for up to 48 hours following administration. If CTCAE grade 3 or 4 nausea/vomiting occurs in temporal association with paclitaxel/carboplatin administration in spite of aggressive anticipatory and/or follow-up antiemetics therapy, the dose of paclitaxel/carboplatin should be reduced as specified in Table9 below for the next cycle. A second dose reduction is at the investigator's discretion. If tolerated, increase paclitaxel/carboplatin back to 100% dose as soon as possible. If CTCAE grade 3 or 4 nausea/vomiting persist, study treatment should be permanently discontinued.

Table 9 Dose Modifications for Gastrointestinal Toxicity at the Start of the Subsequent Cycle

GASTROINTESTINAL	**Paclitaxel**	**Carboplatin**
Worst Toxicity in Preceding Cycle		
CTCAE grade 3 or 4 nausea or vomiting despite maximal antiemetic prophylaxis and therapy*	decrease 1 dose level	decrease 1 dose level
CTCAE grade 3 stomatitis	decrease 1 dose level	decrease 1 dose level
CTCAE grade 4 stomatitis	Reduce to lowest dose level, 150 mg/m^2; or discontinue chemotherapy if lowest dose level caused the CTCAE grade 4 stomatitis	Reduce to lowest dose level, AUC 4; or discontinue chemotherapy if lowest dose level caused the CTCAE grade 4 stomatitis

*Doses may be re-escalated 1 dose level per future chemotherapy cycle if nausea and vomiting are recovered to < CTCAE grade 3 by any current dose reduction.

Renal Toxicity (Carboplatin)

Recommendations are based on the NCI CTCAE scale for creatinine clearance values (chronic kidney disease). For creatinine clearance values corresponding to CTCAE grade 3 or 4 toxicity, carboplatin should be withheld until the patient recovers completely or to CTCAE grade 1 toxicity. The treatment should then be resumed at AUC 4. If recovery to CTCAE grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For CTCAE grade 1 and 2 toxicities, no special dose reductions will be made because application of the Calvert formula will accommodate the necessary dose adjustments.

Paclitaxel and Carboplatin Infusion Related Reactions (Hypersensitivity)

Anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment; angioedema; and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. Hypersensitivity to carboplatin has been reported in 2% of patients. These allergic reactions may include rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Management of infusion related reactions/hypersensitivity to paclitaxel and carboplatin is outlined in Table 10.

Table 10 Dose Adjustments Related to Infusion Reactions and Hypersensitivity

	Paclitaxel	**Carboplatin**
CTCAE grade 1	Monitor patient; no treatment or change to infusion required.	Monitor patient; no treatment or change to infusion required.
CTCAE grade 2	Stop paclitaxel infusion; administer H1 blocker (eg, chlorphenamine 10 mg IV or diphenhydramine 25 to 50 mg IV) and corticosteroid (eg, dexamethasone 10 mg IV); after recovery, resume paclitaxel infusion at reduced rate ($1/4^{th}$ original infusion rate) for 15 minutes, then ½ the original infusion rate for 15 minutes, and, if no symptoms, then at full-dose rate until infusion is complete. If symptoms recur at CTCAE grade 1 intensity, stop paclitaxel infusion and patient may be re-challenged at next scheduled chemotherapy. If symptoms recur at grade 2 intensity, stop infusion and discontinue patient from chemotherapy.	Stop carboplatin infusion; administer H1 blocker (eg, chlorphenamine 10 mg IV or diphenhydramine 25 to 50 mg IV) and corticosteroid (eg, dexamethasone 10 mg IV); after recovery, resume carboplatin infusion at reduced rate ($1/4^{th}$ original infusion rate) for 15 minutes, then ½ the original infusion rate for 15 minutes, and, if no symptoms, then at full-dose rate until infusion is complete. If symptoms recur at CTCAE grade 1 intensity, stop carboplatin infusion and patient may be re-challenged at next scheduled chemotherapy. If symptoms recur at CTCAE grade 2 intensity, stop infusion and discontinue patient from chemotherapy.
CTCAE grade 3 or 4	Stop paclitaxel infusion; administer H1 blocker (eg, chlorphenamine 10 mg IV or diphenhydramine 25 to 50 mg IV) and corticosteroid (eg, dexamethasone 10 mg IV) and manage additionally with epinephrine, bronchodilators, and/or O_2, as necessary. Discontinue patient from chemotherapy.	Stop carboplatin infusion; administer H1 blocker (eg, chlorphenamine 10 mg IV or diphenhydramine 25 to 50 mg IV) and corticosteroid (eg, dexamethasone 10 mg IV) and manage additionally with epinephrine, bronchodilators, and/or O_2, as necessary. Discontinue patient from chemotherapy.

Abbreviations: IV=intravenous.

Hypersensitivity prophylaxis and rate of administration of paclitaxel/carboplatin for subsequent cycles in patients who have previously experienced CTCAE grade 1 or 2 hypersensitivity reactions should be determined according to standard local clinical practice.

Other Chemotherapy Nonhaematologic Toxicity Dose Modification

Other chemotherapy nonhaematologic toxicities not addressed above will be managed according to Table 11.

Table 11 Dose Modifications for Nonhaematologic Toxicity

Toxicity Grade (CTCAE)	**Paclitaxel and/or Carboplatin Dose Modification**
Baseline or CTCAE grade 1	No dose reduction
CTCAE grade 2	Identify whether the toxicity is attributable to paclitaxel, carboplatin, or both: • If Day 1 of a cycle: delay chemotherapy until toxicity resolves to ≤ CTCAE grade 1 • If toxicity occurred during preceding cycle but has already resolved to ≤ CTCAE grade 1, then decrease suspected chemotherapy drug(s) 1 dose level • If toxicity occurred during preceding cycle but has not resolved to ≤ CTCAE grade 1, then suspend suspected chemotherapy drug(s) until the toxicity resolves to ≤ CTCAE grade 1 for maximum of 3 weeks. Decrease suspected chemotherapy drug(s) 1 dose level. If the toxicity doesn't resolve to ≤ CTCAE grade 1 within 3 weeks, then discontinue patient from suspected chemotherapy drug(s)
CTCAE grade 3 or 4	Identify whether the toxicity is attributable to paclitaxel, carboplatin, or both: • If Day 1 of a cycle: delay chemotherapy until toxicity resolves to ≤ CTCAE grade 1 or baseline • If toxicity occurred during preceding cycle but has already resolved to ≤ CTCAE grade 1 or baseline, decrease suspected chemotherapy drug(s) to lowest dose level per Table 4; if already at lowest dose level per Table 4, then discontinue patient from chemotherapy • If toxicity occurred during preceding cycle but has not resolved to ≤ CTCAE grade 1 or baseline, then suspend suspected chemotherapy drug(s) until the toxicity resolves to ≤ CTCAE grade 1 or baseline for maximum of 3 weeks. Decrease suspected chemotherapy drug(s) to lowest dose level per Table 4; if already at lowest dose level per Table 4, then discontinue patient from chemotherapy. If the toxicity doesn't resolve to ≤ CTCAE grade 1 or baseline within 3 weeks, then discontinue patient from chemotherapy

7.6.8 Pre-study and Concomitant Medications

Prior to data cut-off, all concomitant medication(s) must be recorded on the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should also be recorded. Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics, where applicable. The reason(s) for treatment and treatment dates should also be recorded.

After data cut-off (during the Extended Treatment Period), concomitant medications will only be reported in the event of an SAE, using the paper SAE form. See Section 7.7.5 for information regarding patient management and reporting after data cut-off (during Extended Treatment Period).

7.6.8.1 Restrictions

Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 12) from the time of screening and must agree to continue using such precautions for 6 months after the last dose of study treatment. Male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the study and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 6 months after the last dose of study treatment. Not engaging in sexual activity for the total duration of the study and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period. Female partners of a male patient must use a highly effective method of contraception throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menses without an alternative medical cause).

Highly effective methods of contraception are described in Table 12. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 12 Highly Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) (This is also considered a hormonal method)	• Etonogestrel implants: eg, Implanon or Norplan • Intravaginal device: eg, ethinylestradiol and etonogestrel • Medroxyprogesterone injection: eg, Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

Note: a highly effective method has a failure rate of <1% per year

Breastfeeding women are to be excluded from the study unless the patient is willing to discontinue breastfeeding throughout their participation in the study and for 6 months after the last dose of study treatment.

7.6.8.2 Premedication

Premedication for carboplatin/paclitaxel chemotherapy with corticosteroids (such as dexamethasone), diphenhydramine, H_2 antagonist (such as cimetidine or ranitidine) and antiemetic medication should be given according to institutional standards.

7.6.8.3 Prohibited Medications

No additional systemic anti-cancer treatment including other chemotherapies, radiotherapy, anti-cancer agents, and investigational agents is allowed to be used prior to discontinuation of study treatment. Palliative radiotherapy for painful bone metastases (except for thoracic region) are allowed during the study treatment. Herbal medications intended for anti-cancer use are prohibited.

7.6.8.4 Other Concomitant Medications

Special warnings and precautions for the use of paclitaxel and carboplatin should be observed according to each drug's label.

The metabolism of paclitaxel is catalysed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the CYP isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers

(eg, rifampin) of CYP2C8.

Other warnings mentioned in the carboplatin label include: Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be excised when a patient received both drugs.

For the details, please see each drug's label.

Supportive care therapies including but not limited to analgesics, antipyretics, anti-infectives, other medical therapies, blood product transfusions, and other supportive and palliative therapies are permitted per investigator judgment and local standards of practice provided they are not otherwise explicitly prohibited by this protocol.

Low dose of anticoagulation for maintenance of patency of permanent indwelling IV catheters is permitted. Prophylactic use of anticoagulants after enrolment and while participating in the study (eg, during periods of hospital confinement) is permitted. However, the patients should be treated with caution.

Patients who develop CTCAEgrades 2 to 3 venous thromboembolism (VTE) (or CTCAE grade 1 venous thrombosis where treatment is to include full-dose therapeutic anticoagulation) after enrolling and while participating in the study should have IP temporarily held while they are medically stabilized and started on full-dose therapeutic anticoagulation, either low molecular weight heparin or oral. Please see Section 7.6.7.1 for more detail.

Plasma levels of anticonvulsant agents may become sub-therapeutic during platinum therapy. Concomitant use of drugs with a potential ototoxic or nephrotoxic effect (eg, aminoglycosides, cefalotine, furosemide, amphotericin B) should be avoided or adequately monitored.

Before, during, and after combination drug administration, adequate hydration and diuresis should be ascertained and should be performed according to each centre's practice. Appropriate antiemetic medication should be given.

Concomitant haematopoietic growth factor and prophylactic or therapeutic use of granulocyte colony-stimulating factor is permitted according to the American Society of Clinical Oncology or local regulatory authority guidelines and should be recorded on the eCRF.

Therapy with bisphosphonates or denosumab is permitted in accordance with local health authority product labels.

If surgery is required during study treatment, the IP should be interrupted for a washout period of at least 28 days between the last dose of IP and the performance of surgery when possible. If a shorter washout period is required on the basis of the investigator's medical judgement, the investigator should discuss the reduction of the washout duration with the study medical monitor, and the discussion should be documented appropriately.

Re-initiation of IP following surgery should be discussed with the study medical monitor and requires documented approval from the investigator.

7.6.9 Treatment Compliance

All doses of IP will be administered to patients at the study site by study site personnel. Investigational product accountability will be captured as described in Section 7.6.3, and IP compliance will be reported in by-patient listings.

7.7 Study Procedures

7.7.1 Schedule of Assessments

The schedule of study assessments is provided in Table13. See Section 7.7.5 for information regarding patient management and reporting after data cut-off (during Extended Treatment Period).

Table 13 Schedule of Assessments Prior to Data Cut-Off

Day	Screening/ baseline[a]	Study Treatment Period (all visits within ± 3 days of schedule)									Study treatment discontinuation (± 7 days)	30 days follow-up after last dose of study treatment (± 7 days)	Follow-up
		Cycle 1			Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycles 5 Day 1	Cycle 6 Day 1	Cycle 7 and sub-sequent cycles Day 1			
		1	8	15									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Visit 10 onwards**			
Informed consent	X												
Inclusion/exclusion criteria[b]	X												
EGFR/ALK status[c]	X												
Demographics	X												
Medical history	X												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (blood pressure, pulse rate, and body temperature)	X[d]	X	X	X	X	X	X	X	X	X	X	X	
Height[e], weight	X	X			X	X	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X	X	X	X	X		

[a] Within 28 days before randomisation.
[b] Hepatitis B or C and HIV status should be included as part of the medical history.
[c] Testing for EGFR activating mutation and ALK gene rearrangement is not required for this study; however, the status EGFR and ALK testing results collected before or during Screening OR the status of EGFR and ALK mutation as 'unknown' should be recorded.
[d] Blood pressure needs to be assessed 3 times with at least 5 minute intervals for each assessment.
[e] Height completed at baseline only.

Day	Screening/ baseline[a]	Study Treatment Period (all visits within ± 3 days of schedule)									Study treatment discontinuation (± 7 days)	30 days follow-up after last dose of study treatment (± 7 days)	Follow-up
		Cycle 1			Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycles 5 Day 1	Cycle 6 Day 1	Cycle 7 and sub-sequent cycles Day 1			
		1	8	15									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Visit 10 onwards**			
Radiological evaluation (CT/MRI scan) of tumour lesions	X[f]					X[g]		X[g]		X[g]			X[f,g,h]
12-lead ECG	X	X[i]									X	X	
LVEF by cardiac ultrasound or MUGA scan[j]	X										X		
Haematology, biochemistry	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis or urine dipstick[k]	X	X	X	X	X	X	X	X	X	X	X		

[f] The chest and the upper abdomen (including liver and the adrenal glands). Brain CT/MRI is required within 4 weeks prior to randomization. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients.

[g] Tumour assessments of all regions where tumour lesions have been identified will be performed every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the remainder of the treatment period. The methods of assessment of tumour burden used at baseline CT or MRI scans of chest and upper abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be appropriately imaged. To be performed within ± 7 days until PD.

[h] Patients who discontinue study treatment for reasons other than PD will continue to undergo tumour assessments every 12 weeks (± 1 week) until PD, until death or until the data cut-off.

[i] ECG will be performed Day 1 predose and postdose.

[j] The modality of the cardiac function assessments needs to be consistent throughout the study, i. e., if a MUGA scan is used for LVEF at screening, then a MUGA scan should also be used for subsequent visits such as the visit of study treatment discontinuation. The patients should also be examined using the same machine and operator whenever possible.

[k] To be performed predose on Day 1 of each cycle. In the event that the urine dipstick or urinalysis shows ≥ 2 + proteinuria, a 24-hour urine should be collected.

Day	Screening/ baseline[a]	Study Treatment Period (all visits within ± 3 days of schedule)									Study treatment discontinuation (± 7 days)	30 days follow-up after last dose of study treatment (± 7 days)	Follow-up
		Cycle 1			Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycles 5 Day 1	Cycle 6 Day 1	Cycle 7 and sub-sequent cycles Day 1			
		1	8	15									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Visit 10 onwards**			
Coagulation	X	X			X	X	X	X	X	X	X		
ADA sampling[l, m]		X			X		X		X		X		X[m]
Sampling for serum drug concentration[m, n, o]		X[o]			X		X[o]		X		X		X[m]
Serum/urine pregnancy test – for women of childbearing potential[p]	X												
Randomisation		X											
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Combination drugs administrations [q]		X			X	X	X	X	X				

[l] To be performed at predose at Cycles 1, 2, and 4, Cycle 6 predose, study treatment discontinuation visit, and Follow-up period.
[m] Follow-up samples will be taken every 12 weeks (up to 1 year [± 14 days] after randomisation) until death, or the patient is lost to follow up, whichever occurs first.
[n] To be performed at predose at Cycles 1, 2, and 4, Cycle 6 predose, study treatment discontinuation visit, and Follow-up period. Additional samples at immediately after completion of IP infusion on Cycles 1 and 4 are required.
[o] Additional samples at immediately after completion of IP infusion on Cycles 1 and 4 are required.
[p] A negative serum/urine pregnancy test within 7 days of starting study treatment in premenopausal women and women < 2 years after the end of menopause is required for inclusion in this study.
[q] At least 4, and no more than 6 cycles. The number of cycles is determined by patients' need and the investigator's assessment.

Day	Screening/ baseline[a]	Study Treatment Period (all visits within ± 3 days of schedule)									Study treatment discontinuation (± 7 days)	30 days follow-up after last dose of study treatment (± 7 days)	Follow-up
		Cycle 1			Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycles 5 Day 1	Cycle 6 Day 1	Cycle 7 and sub-sequent cycles Day 1			
		1	8	15									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Visit 10 onwards**			
Study drug (IP) administration		X			X	X	X	X	X	X			
Subject disposition notification											X		
Survival status													X[r]
Post Study Treatment therapy [s]											X	X	X

[r] Assessments for survival should be made every 8 weeks (± 1 week) following objective PD up to the data cut-off. In addition, patients should be contacted in the week following the data cut-off for the final survival analyses to provide complete survival data.
[s] Any systemic anti-cancer treatment, radiotherapy or cancer surgery conducted after discontinuation of study treatment will be collected until death, loss to follow-up, withdrawal of consent or until the data cut-off (whichever occurs first).

7.7.2 Screening Procedures

All screening activities must be performed within 28 days before randomisation. The following lists the preferred sequence of screening activities:

- Informed consent
- Inclusion and exclusion criteria
- Demographics
- EGFR mutation and ALK gene rearrangement status. No tests are required. Results available from standard of care testing and obtained prior to collection of informed consent will be acceptable. If the EGFR or ALK status is unknown, that should be recorded
- Medical history: medical history, surgery history, and prior chemo/radiation treatment history
- Physical examination. For additional information, refer to Section 7.8.2.5.3
- Vital signs: blood pressure (mm Hg), pulse rate (bpm), and body temperature (°C). Blood pressure needs to be assessed 3 times with at least 5 minute intervals for each assessment. For additional information, refer to Section 7.8.2.5.1
- Height (cm) and weight (kg)
- ECOG PS. For additional information, refer to Section 7.8.2.5.5 and APPENDIX B
- Baseline RECIST v1.1 assessment will be performed using CT (or MRI scans where CT is clinically contra-indicated) at screening no more than 28 days prior to start of Study Treatment (Cycle 1 Day 1) and ideally should be performed as close as possible to the start of the study treatment. Baseline radiological assessments should cover the chest and the upper abdomen (including liver and the adrenal glands). Brain CT/MRI is required within 4 weeks prior to randomisation
- Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. For additional information, refer to Section 7.8.1.3
- 12-lead ECG. For additional information, refer to Section 7.8.2.5.4
- Left ventricular ejection fraction (LVEF) by cardiac ultrasound or multiple-gated acquisition (MUGA) scan

- Laboratory assessments: haematology, biochemistry, urinalysis or urine dipstick (if proteinuria ≥ 2+, 24-hour urine should be collected), and coagulation. For additional information, refer to Section 7.8.2.4

- Pregnancy test - if applicable: serum or urine human chorionic gonadotropin (hCG) test will be performed for women of childbearing potential. For additional information, refer to Section 7.8.2.3.

- AEs

- Concomitant medications

7.7.3 Study Treatment Period Procedures Prior to Data Cut-Off

7.7.3.1 Cycle 1

Days 1, 8, and 15

- On Day 1 only, eligible patients will be randomised in a ratio of 1:1 to either the FKB238 group (paclitaxel and carboplatin plus FKB238) or the Avastin group (paclitaxel and carboplatin plus EU-Avastin)

- Physical examination

- Vital signs: blood pressure, pulse rate, and body temperature

- ECOG PS

- On Day 1 only, weight

- On Day 1 only, 12-lead ECG, 2 hours within predose and postdose

- Laboratory assessments: haematology and biochemistry

- Coagulation (Day 1 only)

- Urinalysis or urine dipstick performed predose. If urinalysis or urine dipstick shows ≥ 2 + proteinuria, 24-hour urine should be collected

- Antidrug antibody sampling at Day 1 predose

- Sampling for serum drug concentration at Day 1 predose and immediately after completion of IP infusion

- AEs

- Concomitant medications

- On Day 1 only, combination drug administration (paclitaxel + carboplatin)
- On Day 1 only, IP administration (FKB238 or EU-Avastin, depending on treatment assignment)

7.7.3.2 Cycle 2 to Cycle 6

Day 1

- Physical examination
- Vital signs: blood pressure, pulse rate, and body temperature
- Weight
- ECOG PS
- Laboratory assessments: haematology and biochemistry
- Coagulation
- Urinalysis or urine dipstick. If urinalysis or urine dipstick shows ≥ 2 + proteinuria, 24-hour urine should be collected
- Antidrug antibody sampling (predose at Day 1 of Cycles 2, 4, and 6)
- Sampling for serum drug concentration (predose at Cycles 2, 4, and 6). Additional samples at immediately after completion of IP infusion on Cycle 4 are required)
- RECIST v1.1 assessment using CT (or MRI scans where CT is clinically contra-indicated) will be performed every 6 weeks (± 1 week) until objective PD. The methods of assessment of tumour burden used at baseline CT or MRI scans of chest and upper abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. No further radiological tumour assessments will be done after objective PD is documented. Every effort should be made to adhere to the original schedule of RECIST v1.1 scans
- AEs
- Concomitant medications
- Combination drug administration (paclitaxel + carboplatin). The number of cycles is determined by patients' need and the investigator's assessment

- IP administration (FKB238 or EU-Avastin, depending on treatment assignment). Treatment will be continued until objective PD or other criteria for treatment discontinuation are met

7.7.3.3 Cycle 7 and Subsequent Cycles

Day 1

- Physical examination
- Vital signs: blood pressure, pulse rate, and body temperature
- Weight
- ECOG PS
- Laboratory assessments: haematology and biochemistry
- Coagulation
- Urinalysis or urine dipstick. If urinalysis or urine dipstick shows ≥ 2 + proteinuria, 24-hour urine should be collected
- RECIST v1.1 assessment using CT (or MRI scans where CT is clinically contra-indicated) will be performed every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the remainder of the treatment period, until objective PD. The methods of assessment of tumour burden used at baseline CT or MRI scans of chest and upper abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. No further radiological tumour assessments will be done after objective PD is documented. Every effort should be made to adhere to the original schedule of RECIST v1.1 scans
- AEs
- Concomitant medications
- IP administration (FKB238 or EU-Avastin, depending on treatment assignment). Treatment will be continued until objective PD or other criteria for treatment discontinuation met

7.7.3.4 Study Treatment Discontinuation Visit

- Physical examination

- Vital signs: blood pressure, pulse rate, and body temperature
- Weight
- ECOG PS
- 12-lead ECG
- Laboratory: haematology, biochemistry, and urinalysis or urine dipstick
- Antidrug antibody sampling
- Sampling for serum drug concentration
- LVEF by cardiac ultrasound or MUGA
- Coagulation
- AEs
- Concomitant medications
- Post Study Treatment therapy

7.7.3.5 Follow-up 30 Days After Last Dose of Study Treatment

A follow-up visit should be conducted 30 days after the last dose of study treatment.

- Physical examination
- Vital signs: blood pressure, pulse rate, and body temperature
- 12-lead ECG
- AEs
- Concomitant medications
- Post Study Treatment therapy

7.7.4 Follow-up Period

Assessments for survival should be made every 8 weeks (± 1 week) following objective PD. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected. Survival data will be collected up to the time of data cut-off. In addition, patients should be contacted in the week following the data cut-off for the final survival analyses to

provide complete survival data. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Patients who discontinue study treatment for reasons other than PD will continue to undergo RECIST v1.1 tumour assessments every 12 weeks (± 1 week) until PD, until death, or until the data cut-off (whichever occurs first).

Follow-up antidrug antibody and serum drug concentration samples will be taken every 12 weeks (up to 1 year [± 14 days] after randomisation) until death, or the patient is lost to follow-up, whichever occurs first.

At data cut-off all patients previously discontinued from study treatment and continuing in follow-up will complete the study and no further study assessments will be performed.

All ongoing and any new AEs/SAEs identified during the 30 calendar days after last dose of study treatment must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

7.7.5 Patient Management Post Data Cut-Off (Extended Treatment Period)

Patients receiving IP at the time of data cut-off will be offered the option of continuing IP in an Extended Treatment Period if the investigator believes the patient is gaining clinical benefit. See Table 14 for a schedule of assessments during the Extended Treatment Period.

The IP provided during the Extended Treatment Period will be consistent with the patient's treatment allocation at the time of randomisation. IP vials will continue to be packaged in a blinding carton containing 1 IP vial in a blinded manner with uniquely numbered kit of FKB238/EU-Avastin (IP kit). The IP kit will be packaged, and labelled in accordance with Good Manufacturing Practice and distributed under Good Distribution Practice. The labels will include all the information required by each country's regulatory requirements. The IP kits will continue to be allocated automatically according to ClinPhone®RTSM.

Sponsor will continue to supply FKB238 after the data cut-off until either it is licensed in and commercial and reimbursement routes become available in that country, or it is determined that the benefit to risk profile does not support continued development of FKB238, or the national health authority has deemed the drug not approvable.

Patients receiving Avastin, where the investigator believes patients are gaining clinical benefit, will be provided the drug continuously until it is licensed in and commercial and reimbursement routes become available in that country.

In the Extended Treatment Period, patients will have vital signs, physical examinations, laboratory analyses, and radiological assessments performed by the investigator according to local standard of care practices. Complete assessments for safety, efficacy, pharmacokinetics, and immunology will not be collected by Sponsor during this period.

The investigator will perform patient assessments according to locally defined standard of care practices. Investigators will be required to report to the Sponsor any SAEs, pregnancies, overdoses, and AEs that lead to discontinuation of treatment or death. Discontinuation from treatment will be considered discontinuation from the study.

SAEs, including any associated concomitant medications, will continue to be reported to the Sponsor for any patients who continue on FKB238/EU-Avastin until 30 days after study treatment is discontinued, in accordance with Section 7.8.2.1.13. Additionally, any SAE or non-SAE that is ongoing at the end of the study must be followed up to resolution unless the event is considered by the investigator to be unlikely to be resolved, or the patient is lost to follow-up.

Table 14 Schedule of Assessments After Data Cut-Off

Day	Prior to entry into Extended Treatment Period	Extended Treatment Period cycles Day 1	Treatment discontinuation
Informed Consent	X		
Study drug (IP) administration		X	
Collection and follow-up[a] for SAEs and AEs leading to withdrawal and death		X	X
Subject disposition notification			X

[a] SAE-related treatments and concomitant medications needed to assess the SAE will be collected and reported on the SAE form.

The investigator will be required to submit a paper Subject Disposition Form to the Sponsor or Sponsor's delegate confirming patient withdrawal or death.

All paper forms should be submitted to the Sponsor via Fax. See Table 15 for contact information for submitting paper forms after data cut-off.

Table 15 Contact Information for Submitting All Paper Forms After Data Cut-Off

	Fax	Email
North America	[redacted]	[redacted]
All other countries	[redacted]	[redacted]

7.8 Efficacy and Safety Variables

7.8.1 Efficacy Assessments

Radiological imaging will be assessed by investigators as well as an independent central radiological committee based on RECIST v1.1 criteria. Primary efficacy assessment will be presented based on the investigators' assessment results as well as the independent central radiological assessment results, but primary efficacy assessment based on the independent central radiological assessment results will be used as a pivotal result of the study. As per protocol requirement, efficacy assessments will only be performed prior to data cut-off. See Section 7.7.5 for information regarding patient management and reporting after data cut-off (during Extended Treatment Period).

7.8.1.1 Primary Efficacy Assessment

The primary variable in this study is the best overall response (BOR) that is either CR or PR (by RECIST v1.1). A BOR is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all post-baseline disease assessments that occur until progression, or last evaluable assessment in the absence of progression prior to the initiation of subsequent anti-cancer therapy, irrespective of whether or not subjects discontinued the study treatment. Overall response rate (ORR) is defined as the proportion of subjects with BOR of either CR or PR according to RECIST v1.1.

7.8.1.2 Secondary Efficacy Assessments

The secondary variables of this study are: ORR at week 19, PFS, OS, DOR, and DCR as assessed in both treatment arms.

7.8.1.3 Tumour Assessments by Imaging Techniques Using RECIST

RECIST v1.1 criteria will be used to assess patient response to treatment by determining ORR, DOR, PFS, and DCR. The RECIST v1.1 Guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (CR, PR, SD or PD) are presented in APPENDIX C. Chest X-ray must not be used for the assessment of target lesions. The methods of assessment of tumour burden used at baseline (CT or MRI scans where CT is clinically contra-indicated of chest and upper abdomen including adrenal glands) must be used at each subsequent follow-up assessment unless this is medically contra-indicated (eg, the development of an allergy to contrast medium).

Baseline RECIST v1.1 assessment will be performed using CT (or MRI scans where CT is clinically contra-indicated) at screening no more than 28 days prior to start of study treatment (Cycle 1 Day 1) and ideally should be performed as close as possible to the start of the study treatment. Baseline radiological assessments should cover the chest and the upper abdomen (including liver and the adrenal glands). Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Brain CT/MRI is required within 4 weeks prior to the randomisation.

After start of study treatment, RECIST v1.1 assessment using CT (or MRI scans where CT is clinically contra-indicated) will be performed every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the remainder of the treatment period, until objective PD. The methods of assessment of tumour burden used at baseline CT or MRI scans of chest and upper abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR, PR, SD, and PD. Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment, or sooner if clinically indicated, and re-assess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

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

No further radiological tumour assessments will be done after objective PD is documented. Patients who discontinue study treatment for reasons other than PD will continue to undergo RECIST v1.1 tumour assessments every 12 weeks (± 1 week) until PD, until death, or until the data cut-off (whichever occurs first).

Every effort should be made to adhere to the original schedule of RECIST v1.1 scans.

Please consider the following recommendations upon determining measurable/non-measurable lesions, and target/non-target lesions:

- Previously irradiated lesions should be accessed as NTLs
- Brain lesions should be selected as non-measurable lesions
- Osteoblastic should be selected as non-measurable lesions
- Osteolytic bone lesions or mixed bone metastasis with measurable soft tissue component should only be selected as TLs, if the soft tissue component meets the criteria of measurability

- Skin lesions documented by colour photography should be selected as NTLs due to significant variability and suboptimal reproducibility of lesion measurements

Central Reading of Scans

An independent central review of all scans used in the assessment of tumours using RECIST v1.1 will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to a Sponsor appointed CRO for central analysis. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST v1.1 assessment conducted by the investigator.

7.8.2 Safety Assessments

Safety will be monitored throughout the study for all patients. The analysis of the safety data will be performed using the Safety Population. Limited safety reporting will be performed during the Extended Treatment Period as detailed in Section 7.7.5.

7.8.2.1 Adverse Events

7.8.2.1.1 Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.8.2.1.2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

7.8.2.1.3 Recording of Adverse Events

Time period for collection of adverse events

AEs will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30-days after the last dose of study treatment. Prior to data cut-off, all ongoing and any new AEs/SAEs identified during the 30 calendar days after last dose of study treatment must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. See Section 7.7.5 for information regarding patient management and reporting after data cut-off (during Extended Treatment Period).

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any SAE or non-serious AE that is ongoing at the time of the 30 day follow-up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

The Sponsor retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post Follow-up adverse events

After study treatment completion (ie, after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow-up period (30 days). If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify the Sponsor.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut-off and / or post study completion then as a minimum all SAEs must continue to be collected and reported to the Sponsor within the usual timeframe.

7.8.2.1.4 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped

- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Reason that AE is serious ("due to")
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

7.8.2.1.5 Severity of AEs

For each episode on an AE, all changes to the CTCAE grade attained as well as the highest attained CTCAE grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.8.2.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without

assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

7.8.2.1.6 Causality Collection

The investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

7.8.2.1.7 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.8.2.1.8 Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported if they fulfil any of the SAE criteria. If these data are the reason for discontinuation of treatment with the IP, then this must be recorded as an AE and a description included whether this is temporary or permanent.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a patient shows an AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN may need to be reported as SAEs (for details, refer to APPENDIX A).

7.8.2.1.9 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the signs and symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

7.8.2.1.10 New Cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 7.8.2.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

7.8.2.1.11 Lack of Efficacy

When there is deterioration in the lung cancer, for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

7.8.2.1.12 Deaths

All deaths that occur prior to data cut-off, or within the protocol-defined 30-day post study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the DEATH eCRF.

Deaths with an unknown cause should always be reported as a SAE. A post-mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the Sponsor within the usual timeframes.

After data cut-off, patient deaths will be reported using a paper Patient Disposition Form. See Section 7.7.5 for information regarding patient management and reporting after data cut-off (during Extended Treatment Period). Death not due (or not clearly due) to progression of the disease under study or death with an unknown cause must continue to be reported as an SAE using the paper SAE Form.

7.8.2.1.13 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF prior to data cut-off. After data cut-off, SAEs will be reported on a paper SAE form. See Section 7.7.5 for information regarding patient management and reporting after data cut-off (during Extended Treatment Period).

If any SAE occurs in the course of the study, then investigators or other site personnel should complete the eCRF (prior to data cut-off) or paper SAE form (after data cut-off) immediately, or no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the eCRF, an automated e-mail alert is sent to the designated PAREXEL representative. If the eCRF is not available, the investigator or other study site personnel reports a SAE by sending a SAE form by fax / e-mail to the designated PAREXEL representative. The PAREXEL representative will advise the investigator/study site personnel how to proceed.

The designated PAREXEL representative works with the investigator to ensure that all the necessary information is provided .

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform PAREXEL representatives of any follow-up information on a previously reported SAE immediately, or no later than 24 hours of when he or she becomes aware of it.

7.8.2.2 Overdose

Investigators are advised that any patient, who receives a higher dose than intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Prior to data cut-off, such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

After data cut-off, overdoses should be reported using the paper Overdose form. See Section 7.7.5 for information regarding patient management and reporting after data cut-

off (during Extended Treatment Period).

If an overdose on FKB238/Avastin occurs in the course of the study, then the investigator or other site personnel must report the event (using the Overdose eCRF prior to data cut-off or paper Overdose form after data cut-off) **no later than 24 hours** of when he or she becomes aware of it.

The designated PAREXEL representative works with the investigator to ensure that all relevant information is provided to the safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 7.8.2.1.13. For other overdoses, reporting must occur within 30 days.

7.8.2.3 Pregnancy

7.8.2.3.1 Maternal exposure

All pregnancies and outcomes of pregnancy should be reported during the course of the study and within 30 days of the last dose of study treatment.

A serum/urine pregnancy hCG test will be performed for women of childbearing potential at screening. If a patient becomes pregnant during the course of the study, study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

Any pregnancy that occurs in the course of the study or within 30 days of the final dose of the investigational product must be reported by the investigator or other site personnel within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Before data cut-off, an eCRF must be completed. After data cut-off, pregnancies will be reported via a paper pregnancy form. See Section 7.7.5 for information regarding patient management and reporting after data cut-off, during Extended Treatment Period.

The designated PAREXEL representative works with the investigator to ensure that all relevant information is provided to the safety data entry site within 5 calendar days for SAEs.

7.8.2.3.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy,

normal birth or congenital abnormality) should if possible be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing should be followed up and documented.

7.8.2.4 Safety Laboratory Determinations

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken predose at the times indicated in the schedule in Table 13. If clinical chemistry, haematology and urinalysis screening assessments have been performed within 14 days prior to staring study treatment, they do not need to be repeated on Cycle 1 Day 1 if the patient's condition has not changed (no new treatment during this period of time, no new complication or aggravation).

Additional safety laboratory samples may be collected if clinically indicated at the discretion of the investigator. The date and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are summarised in Table 16.

Table 16 Laboratory Variables

Chemistry	**Haematology (whole blood)**
Serum (S) / plasma (P)-Albumin	Haematocrit
S/P-ALP	Haemoglobin
S/P-ALT	Platelet count
S/P-AST	Red blood cell count
S/P-BUN or Urea	Reticulocytes
S/P-Calcium total	White blood cell count
S/P-Chloride	White blood cell differential (% or absolute):
S/P-Creatinine and creatinine clearance	Basophils
S/P-GGT	Eosinophils
S/P-Glucose	Lymphocytes
S/P-LDH	Monocytes
S/P-Phosphorus	Neutrophils
S/P-Magnesium	
S/P-Potassium	
S/P-Sodium	**Coagulation**
S/P-Total Bilirubin	PTT
S/P-Total Protein	Prothrombin time or INR*
Urinalysis or urine dipstick	
U-blood	
U-Protein	
U-Glucose	

* Either prothrombin time or INR may be assessed; there is no need for performing both tests.

The volume of blood to be collected is summarised in Table 17.

Table 17 Volume of Blood to be Collected

Assessment		Volume (mL/visit)
Safety	Haematology	3 (approximately)
	Biochemistry	5 (approximately)
	Coagulation	Assessment to be included in biochemistry sample
Serum drug concentration		3.5
Antidrug antibody		3.5

Note: If PK and ADA sample are taken at the same time, a total of 6 mL of blood will be collected for both PK and ADA. More detail is available in the Laboratory Manual.

Additionally, at the Screening Visit, a pregnancy test (serum or urine tests are acceptable based on the site's standard clinical practice) will be collected for women of childbearing potential only.

The investigator should make an assessment of the available results with regard to

clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 7.8.2.1.8.

NB. In case a patient shows an AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase of alkaline phosphatase (potential Hy's Law), please refer to APPENDIXA 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

A urine dipstick test or urinalysis will be performed at screening, predose on Day 1 of each cycle and on Days 8 and 15 of Cycle 1 and at the study treatment discontinuation visit. In the event that the urinalysis or urine dipstick shows ≥ 2 + proteinuria, a 24-hour urine should be collected. Dose adjustment for proteinuria should be handled as described in Sections 7.6.7.1 and 7.6.7.2.

7.8.2.5 Vital Signs, Physical Examination, and Other Safety Evaluations

7.8.2.5.1 Vital Signs

Vital signs will be assessed according to the schedule in Table13 and will include systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), and body temperature (°C). Assessments will be performed predose, at the visits as shown in the schedule in Table 13, and on occurrence of any cardiac AE. Additionally at the discretion of the investigator if clinically indicated. Home monitoring of blood pressure is encouraged when the patient is taking IP.

Any changes in vital signs should be recorded as an AE if applicable.

Patients should be seated and allowed to rest for at least 5 minutes before taking the blood pressure measurement (standardize body position and allow for patients to be calm) and pulse rate. At the Screening Visit, blood pressure needs to be assessed 3 times with at least 5 minute intervals for each assessment. Each visit's blood pressure measurement should be taken before any infusion of pre-medications, combination drugs, or FKB238/ EU-Avastin. A blood pressure cuff appropriate for the size of the patient's arm should be used to ensure accuracy of the measurement.

7.8.2.5.2 Weight and Height

Weight will be performed at screening and then Day 1 of each cycle as well as the Discontinuation Visit. Height will be assessed at screening only.

7.8.2.5.3 Physical Examination

Physical examinations will be conducted according to the schedule in Table13. A physical examination will be performed and include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including

spine and extremities) and neurological systems. Findings during the screening and baseline visits should be recorded as medical history on the eCRF.

7.8.2.5.4 12-lead Electrocardiogram

ECGs are required within 7 days prior to starting study treatment, on Day 1 of Cycle 1, 2 hours within predose and postdose, and when clinically indicated and at the Follow-up visit after the patient has discontinued the study treatment.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. The investigator or designated physician will review the data each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. A copy of the ECG indicating the study number and E-code will be included in the study file. Additional ECGs may be performed at the investigator's discretion.

7.8.2.5.5 ECOG PS

Patients should have an ECOG PS of 0 or 1 at Screening to be included in the study. The investigator will assess ECOG PS at Screening, and during the Study Treatment Period, and Follow-up Period as noted in Table 13. An ECOG PS that worsens during the study will not require withdrawal from treatment. Refer to APPENDIX B for definitions of ECOG PS grades.

7.8.3 Other Assessments

7.8.3.1 Immunogenicity Assessment

Serum for measurement of the presence of ADAs for FKB238 and EU-Avastin will be collected according to the schedule in Table18 and will be analysed using validated methods. A tiered analysis approach will be followed where samples positive for ADA at screening step will be confirmed for ADA presence. The confirmed positive samples will then be assessed for ADA titre and the presence of neutralising antibodies.

Table 18 Schedule of Pharmacokinetic and Antidrug Antibody Sampling

	Cycle 1 Day 1	**Cycle 2 Day 1**	**Cycle 4 Day 1**	**Cycle 6 Day 1**	**Study treatment discontinuation visit**	**Follow-up**
Predose	PK/ADA	PK/ADA	PK/ADA	PK/ADA	PK/ADA	PK/ADA[1]
Immediately after completion of IP infusion	PK		PK			

[1] Follow-up samples will be taken every 12 weeks (up to 1 year [± 14 days] after randomisation) until death, or the patient is lost to follow-up, whichever occurs first.

7.8.3.2 Pharmacokinetics Measurement

Serum for IP concentration measurement will be collected to obtain pharmacokinetics of IP according to the schedule in Table 18 and will be analysed using validated methods.

7.9 Statistical Methods

7.9.1 Determination of Sample Size

Assuming a dropout rate of 10%, it is anticipated that approximately 730 patients will be randomised into the study in a 1:1 ratio (365 patients in the FKB238 group and 365 patients in the Avastin group) in order to have a total of 656 patients who complete study treatment. Sample size was determined to meet both the EMA and FDA requirements, which differ in several aspects.

To fulfil the EMA requirements, a meta-analysis of available randomised clinical studies of Avastin demonstrated that the risk-difference for the ORR for the control arm compared to the Avastin treatment arms was calculated to be 0.1938 (80% confidence interval [CI]: [0.1564, 0.2312]). Based on the result of the meta-analysis, an equivalence margin for the risk-difference was determined to be 0.1221, which preserves 22% of the treatment effect characterised by the lower 80% CI for the risk-difference of ORR.

The NCSS PASS 2005 statistical software was used for the sample size calculation. With the adverse events margin for the risk-difference of 0.1221, an expected response rate of 35% in both treatment arms, the study design employing a two one-sided test (TOST) procedure, and an overall Type I error rate of 2.5%, a sample size of 656 patients (328 per group) was calculated to provide 80% power to demonstrate that the 95% CI about the risk-difference comparing FKB238 and EU-Avastin falls completely within ± 0.1221. Approximately 730 NS-NSCLC patients (allowing for a dropout rate of 10%) will be randomised either to the FKB238 group or Avastin group in a 1:1 ratio in a parallel group study.

Per the FDA requirements, a meta-analysis was performed on data from relevant clinical trials of Avastin, resulting in an estimate of the risk-ratio of 0.5212 along with a 70% CI, (0.4775, 0.5689). With lower and upper equivalence margins of 0.73 and 1.38, which preserve 50% treatment effects determined by the lower and upper limits respectively of the 70% CI, an expected response rate of 35% in both treatment arms, a TOST procedure for equivalence, and the overall Type I error rate at 5%, a sample size of 656 patients (328 per group) provides 80% power to demonstrate that the 90% CI for the risk-ratio comparing FKB238 and EU-Avastin is entirely enclosed within 0.73 to 1.38. Accounting for potential 10% dropouts, approximately 730 patients will be randomised.

7.9.2 Patient Populations Analysed

The following analysis populations will be included for this study:

ITT: all patients randomised to treatment. Patients will be included in the treatment group according to the randomisation assigned, regardless of the treatment actually given.

All efficacy analyses will be performed on the ITT population. These analyses will be treated as the primary analysis for the FDA requirement and as sensitivity analysis otherwise.

PPS: all patients randomised to treatment who received at least 1 dose of IP with no important protocol violations or deviations (see Section 7.9.4). Patients will be included in the treatment group according to the treatment actually given. All efficacy analyses will be performed on the PPS population. These analyses will be treated as the primary analysis for the EMA requirement and as sensitivity analysis otherwise.

Safety Population: all patients randomised to treatment who received at least 1 dose of IP. Patients will be included in the treatment group according to the treatment actually given. All safety analyses will be performed on the Safety Population.

PK Population: all PPS patients who have at least one serum drug concentration data, which is defined in the study protocol, after IP administration.

7.9.3 General Considerations

Safety and efficacy analyses will be based on data collected prior to data cut-off.

Descriptive summary statistics for continuous variables will include the number of patients (N), mean, standard deviation, minimum, median, and maximum.

Descriptive summary statistics for categorical variables will include frequency counts and percentages (n [%]). Unless otherwise stated, the denominator for percentage calculations will be the number of patients in the analysis population.

Unless otherwise stated, associations of treatment with clinical outcomes will be adjusted for the following covariates:

- EGFR mutation and ALK gene arrangement status (both are tested and known negative versus status unknown for either)
- ECOG PS (0 versus 1)
- Geographical region (North America, Western Europe, East Asia, All Other Regions)
- Prior weight loss over the previous 6 months (< 5% yes versus no)
- Disease stage (advanced or recurrent)
- Gender
- Smoking history
- Age

The primary endpoint analysis will be performed using a TOST procedure. All data processing, summarisation and analyses will be performed using SAS Enterprise Guide version 5.1 (or higher) on the SAS Hosted Environment.

7.9.4 Important Protocol Violations

Protocol violations and deviations will be tracked and recorded throughout the study and presented in a by-patient Listing. Patients with important protocol violations will be excluded from the PPS. Important protocol violations will be identified before database lock and will be described in the SAP.

7.9.5 Efficacy Analysis

7.9.5.1 Primary Efficacy Outcome Measures

The number (%) of patients with a best response of CR or PR will be presented by treatment arm.

The TOST procedure will be used for testing the null hypothesis of non-equivalence against the alternative hypothesis of equivalence. To fulfil the EMA's requirement, the TOST procedure will be carried out using PPS by comparing a 95% CI for the ORR difference between FKB238 and EU-Avastin to the margin [± 0.1221], which is deemed to represent a clinically acceptable difference with respect to ORR. If the true CI is within the interval [± 0.1221], an equivalence between FKB238 and EU-Avastin, with respect to the ORR, is confirmed. To meet the FDA's requirements, the TOST procedure will be performed based on ITT population by comparing a 90% CI for the ORR ratio between FKB238 and EU-Avastin to the margin [0.73, 1.38], which is deemed to represent a clinically acceptable difference with respect to ORR. If the true CI is within the interval [0.73, 1.38], an equivalence between FKB238 and EU-Avastin, with respect to the ORR, is confirmed.

7.9.5.2 Secondary Efficacy Outcome Measures

The logistic regression model will be fitted for the overall response and treatment adjusted for the covariates. The adjusted odds ratio and corresponding 95% CI will be presented.

Kaplan-Meier curves for PFS, OS, and DOR showing medians and corresponding 95% CI based on the Kaplan-Meier estimator per treatment arm will be presented.

The multiple Cox proportional hazards model will be fitted for all time to event endpoints including treatment group adjusted for the covariates. The hazard ratios and corresponding 95% CI for treatment effect and the covariates will be presented.

DCR and ORR at week 19 will be estimated and compared between treatment groups, using descriptive statistics.

7.9.6 Safety Analysis

Safety variables include incidence of AEs, laboratory test results, vital signs, ECG results, ECOG PS, and physical examination findings. All safety analyses will be based on the Safety Population. No formal statistical analysis of the safety data will be performed.

Summary tables will be provided for all AEs by treatment group. The incidence of AEs, SAEs, AEs leading to discontinuation of the study treatment, AEs leading to death, AEs of special interest (well-known AEs of Avastin), etc., will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term.

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than 1 episode of a particular AE, the patient will be counted only once for that event. If a patient has more than 1 AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than 1 AE within a SOC, the patient will be counted only once in that SOC.

Laboratory test variables will be summarised by treatment group and visit using descriptive statistics (number of patients, mean, standard deviation, minimum, maximum, and mean change from baseline). Shift tables from baseline to the worst NCI CTCAE grade at post-baseline will be produced for the laboratory parameters. Data obtained from laboratory tests not required by the protocol will not be summarised, but will be listed.

Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment group. Physical examination findings will be listed for each patient.

7.9.7 Other Outcome Measures

7.9.7.1 Immunogenicity Outcome Measures

The ADA incidence rate produced by FKB238 and EU-Avastin at each time point will be assessed using descriptive statistics. The impact of ADA formation on serum drug concentrations will be assessed using descriptive statistics, if relevant.

7.9.7.2 Pharmacokinetics Outcome Measures

C_{trough} will be compared between treatment groups and descriptive statistics will be provided. The impact of ADA on C_{trough} will be assessed descriptively. The PK data from this study may be combined with that previously obtained in healthy volunteers using a population PK analysis method. If done, this analysis will be reported separately from the CSR for this study.

7.9.8 Interim Analysis

Review of study safety data by the DMC will be conducted during the study. For additional information, refer to Section 7.5.

There is no formal interim analysis for efficacy planned.

8. STUDY MANAGEMENT BY PAREXEL

8.1 Pre-study Activities

Before the first patient is screened for the study, it is necessary for a representative of PAREXEL to visit the investigational study site. For details, please refer to the study manual.

8.2 Training of Study Site Personnel

Before the first patient is entered into the study, a PAREXEL representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study specific procedures.

The investigator will ensure that appropriate training relevant to the study is given to all of the staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The investigator will maintain a training record of all individuals involved in the study (medical, nursing and other staff). For details, please refer to the study manual.

8.3 Monitoring of the Study

During the study, a PAREXEL representative will have regular contacts with the study site. For details, please refer to the study manual.

8.4 Source Data

Refer to the Clinical Study Agreement for location of source data.

8.5 Study Agreements

The investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail. For details, please refer to the study manual.

8.6 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

9. DATA MANAGEMENT AND QUALITY CONTROL BY PAREXEL

9.1 Electronic Data Capture

The investigator should keep the original document of all patient data, including case history and visit record, in the original source documentation, to be stored at the study site. All individual, patient-specific study data will also be entered into an electronic data capture (EDC) system or eCRF in a timely fashion. For data that will only be documented in the eCRF (eg, CTCAE grade, investigator assessed tumour response, etc.), respective eCRF data will be regarded as source data.

An eCRF must be completed for each patient who signs an ICF and undergoes any pre-screening or screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

All data generated from external sources (eg, PK, ADA, central readers of radiological imaging) will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

SAEs, pregnancies, and patient disposition will be collected via paper forms during the Extended Treatment Period as detailed in Section 7.7.5.

9.2 Monitoring

A Sponsor or CRO study monitor will be given access, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. The study monitor will verify the study conduct, completed ICF documentation, accurate eCRF completion, source documentation completion and retention, accurate study drug accountability, and other records relevant to the conduct of this study.

The study monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the study monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the study monitor will adhere to all requirements for patient confidentiality as outlined in the ICF and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and local regulations. The investigator and investigator's staff will be expected to cooperate with the study monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.3 Data Quality Assurance

Data quality will be monitored by a study monitor through programmed edit checks in the EDC system, and through data review meetings. The study monitor will visit the study sites on a regular schedule and verify data entered into the eCRF against source documents stored at the study site. Queries and clarifications will be entered into the EDC system and the changes will be tracked according to the requirements of 21 US Code of Federal Regulations (CFR) Part 11. Edit checks programmed into the EDC system will flag data that does not conform to the required data entry specifications and programmed cross-checks will ensure that data entry is consistent if entered in more than 1eCRF page. Flagged data will trigger a query to the site in the EDC system and responses and changes will be tracked. Periodic reviews for data consistency across eCRF pages will also be performed by data management personnel and CRO clinical personnel and any queries to the site will be issued in the EDC system.

9.4 Records Retention

All source data, or copies thereof (eg, laboratory records, data sheets, hospital records, X-rays, autopsy reports, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study will be retained by the investigator. Source data should be retained until at least 2 years after the last approval of the study drug marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug.

The Sponsor (or its designee), the IRB/IEC, and regulatory agencies will be permitted access to the study records, upon request, for trial-related monitoring and audits.

9.5 Confidentiality

All data collected and stored for this study will conform to the principles of patient right to protection against invasion of privacy, HIPAA, and applicable local regulations. All patient data will be identified via a unique numerical code and all personal identifying information will be redacted from any records supplied to the Sponsor or CRO as part of the study conduct. All unpublished information that the Sponsor gives to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

However, in compliance with US FDA and ICH guidelines, to verify compliance with this protocol, the investigator will permit the study monitor, Sponsor representatives, regulatory agency representatives, and IRB/IEC representatives to review a patient's primary medical records (source data), which can include (but are not limited to): laboratory test results, ECG reports, hospital discharge summaries during a patient's study participation, and autopsy reports for deaths occurring during the study.

10. REFERENCES

1. FKB238 Investigator's Brochure. Fujifilm Kyowa Kirin Biologics Co., Ltd. 2009. version 1.

2. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550.

3. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J Clin Oncol*. 2009;27(8):1227-1234.

4. Reck M, von Pawel 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 randomized phase III trial (AVAiL). *Ann Oncol*. 2010;21(9):1804-1809.

5. Hurwitz HI, Bekaii-Saab TS, Bendell JC, et al; ARIES Study Investigators. Safety and effectiveness of bevacizumab treatment for metastatic colorectal cancer: final results from the Avastin® Registry – Investigation of Effectiveness and Safety (ARIES) observational cohort study. *Clin Oncol (R Coll Radiol)*. 2014;26(6):323-332.

6. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2009;26(12):2013-2019.

11. APPENDICES

APPENDIX A

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with PAREXEL and Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of

laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

The investigator will remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the investigator will:

- Notify the PAREXEL representative
- Request a repeat of the test (new blood draw) by the local laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from local laboratory results, the investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including local laboratory results)

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the PAREXEL representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the investigator will:

- Inform the PAREXEL representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 6)
- Notify the PAREXEL representative who will then inform the central Study Team

The PAREXEL medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact, the investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the PAREXEL medical monitor
- Complete the relevant Liver CRF Modules as information becomes available
- If at any time (in consultation with the PAREXEL medical monitor) the PHL case meets seriousness criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the PAREXEL medical monitor contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor (or its representative) will also be involved in this review.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law').
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
    - If there is no significant change no action is required
    - If there is a significant change notify the PAREXEL representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the PAREXEL representative if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: follow the process described in Section 4.2 of this Appendix

If Yes: Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the PAREXEL representative if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX B – Eastern Collective Oncology Group Performance Status

Description	**Scale**
Normal activity	0
Symptomatic but ambulatory self-care	1
Ambulatory more than 50% of the time	2
Ambulatory 50% or less of time, nursing care needed	3
Bedridden, may need hospitalisation	4

APPENDIX C – Response Evaluation Criteria (RECIST v1.1)

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the FKB238-002 study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

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

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis at baseline*)
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI
- Previously irradiated lesions**
- Brain metastasis***
- Skin lesions assessed by clinical examination***

* Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as non-target lesions (NTL) at baseline and followed up as part of the NTL assessment.

***Skin lesions assessed by clinical examination and brain lesions are considered as NTL in this study.

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as TLs.

Target lesions:

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

Non-Target lesions:

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

3. METHODS OF ASSESSMENT

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

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1: Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone Scan
		FDG-PET

3.1 CT and MRI

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

In the FKB238-002 study it is recommended that CT examinations of the chest and abdomen will be used to assess tumour burden at baseline and follow-up visits. CTexamination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the FKB238-002 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-Ray

3.3.1 Chest X-Ray

In the FKB238-002 study, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-Ray

In the FKB238-002 study, plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the FKB238-002 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the FKB238-002 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the FKB238-002 study, tumour markers will not be used for tumour response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the FKB238-002 study, histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

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

In the FKB238-002 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the FKB238-002 study, FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per-protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments will be performed every 6 weeks (± 1 week) for 24 weeks, then every 9 weeks (± 1 week) for the remainder of the treatment period. Any other sites at which new disease is suspected should also be appropriately imaged. To be performed within ±7days until PD (Progressive Disease) as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

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

Table 2: Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response

should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3: Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

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

4.4 New lesions

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

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

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

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

4.5 Symptomatic deterioration

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

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

4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4: Overall Visit Response

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable.

5. CONFIRMATION OF RESPONSE

Not applicable.

6. CENTRAL REVIEW

The CRO appointed by the Sponsor to perform the independent central review for this study will provide specifications for radiological imaging protocols in standard acquisition guidelines documentation.

7. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

7.1 CT scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. **IV contrast administration**: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contra-indicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then

CT without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

7.2 MRI scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

7.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and

serial scans in the clinical trial.

7.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

8. REFERENCES

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247.

APPENDIX D – Excipients of the IPs

FKB238

Monosodium Glutamate

Sorbitol

Polysorbate 80

Diluted Hydrochloric Acid

Water for injections

EU-Avastin

Trehalose dehydrate

Sodium phosphate

Polysorbate 20

Water for injections

APPENDIX E – Cockcroft-Gault Formula [i]

The Cockcroft- Gault formula for estimated glomerular filtration rate (GFR, mL/min) is:

$$\frac{(140 - age) \cdot weight \cdot (0.85\ if\ female\ or\ 1.0\ if\ male)}{72 \cdot serum\ creatinine}$$

where age is in years, weight is in kg and serum creatinine is in mg/dL.

i Cockcroft DW and Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976;16(1):31-41.