AMENDED CLINICAL TRIAL PROTOCOL 4

COMPOUND: AVE0005 (VEGF Trap)

A Multicenter, Randomized, Double-Blind Study Comparing the Efficacy and Safety of Aflibercept Versus Placebo Administered Every 3 Weeks in Patients Treated with Docetaxel / Prednisone for Metastatic Androgen-Independent Prostate Cancer

STUDY NUMBER: EFC6546

STUDY NAME: VENICE

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CLINICAL STUDY DIRECTOR: [redacted]

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CLINICAL TRIAL SUMMARY

COMPOUND: AVE0005 STUDY No : EFC6546

TITLE	A multicenter, randomized, double-blind study comparing the efficacy and safety of aflibercept versus placebo administered every 3 weeks in patients treated with docetaxel / prednisone for metastatic androgen-independent prostate cancer
INVESTIGATOR/TRIAL LOCATION	Multicenter / Multinational
STUDY OBJECTIVES	**Primary objective**: To demonstrate the efficacy of aflibercept (Arm A) versus placebo (Arm B) in term of overall survival (OS) in patients treated with docetaxel / prednisone or prednisolone for metastatic androgen-independent prostate cancer (MAIPC). **Secondary objectives:** • To assess efficacy of aflibercept compared to placebo for: – PSA response – Pain response in patients with stable pain at baseline. – Time to occurrence of any skeletal related events (SRE). – Progression-free survival. – Tumor response in patients with measurable disease (RECIST). – PSA-Progression free survival (PSA-PFS). – Pain-Progression free survival (Pain-PFS). – Health-Related Quality of Life (HRQL). • To evaluate safety in both treatment arms. • To determine the pharmacokinetics of IV aflibercept, in this population. • To determine the immunogenicity of IV aflibercept.

STUDY DESIGN	This is a prospective, multicenter, multinational, randomized (1:1), double-blind, placebo-controlled, parallel-arm study comparing the efficacy of aflibercept (Arm A) versus placebo (Arm B) in terms of OS in patients treated with docetaxel / prednisone or prednisolone for MAIPC. Each patient will be treated until disease progression, unacceptable toxicity, or patient refusal. An Executive Committee will be responsible for supervising the progress of the trial. This committee will include the Study Chairman, the main investigators and Sponsor's representatives. An independent Data Monitoring Committee (DMC) will periodically assess the progress of the clinical trial, review the safety data and will advise the Executive Committee regarding patient safety, as well as the course of action regarding the conduct of the trial.The DMC will also be in charge of reviewing the formal statistical interim analyses planned on OS during the course of the study (see statistical considerations). Treatment allocation will be performed by an Interactive Voice Response System (IVRS). All eligible patients will be randomly assigned to either the control arm or the experimental arm in a 1:1 proportion. Allocation to the two treatment arms will be done using a permuted-block randomization according to baseline ECOG Performance status (0-1 vs 2).

STUDY POPULATION **Main selection criteria:**	**Main inclusion criteria:** • Histologically- or cytologically-confirmed prostate adenocarcinoma. • Metastatic disease. • Progressive disease while receiving hormonal therapy or after surgical castration documented by at least one of the following: 1. Increase in measurable disease**,** and/or 2. Appearance of new lesions, including those on bone scan (≥2 new lesions) consistent with progressive prostate cancer, and/or 3. Rising PSA defined as 2 sequential increases above a previous lowest reference value (see details in section 7.2, Figure 5). Each value must be obtained at least 1 week apart. A PSA value of at least 2 ng/ml is required at study entry. • Effective castration (serum testosterone levels ≤ 50 ng/dL) by orchiectomy and/or LHRH agonists with or without anti-androgens. If the patient has been treated with LHRH agonists (i.e., without orchiectomy), then this therapy should be continued. If patients were either started on complete androgen blockade, or had a PSA response (defined by any reduction in PSA sustained for at least 3 months) after adding an antiandrogen, prior anti-androgen therapy should be stopped before randomization: at least 6 weeks for bicalutamide and nilutamide, and at least 4 weeks for flutamide, megestrol acetate and any other hormonal therapy. **Main exclusion criteria:** • **Related to methodology:** – Prior cytotoxic chemotherapy for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed > 3 years ago. – Less than 28 days elapsed from prior treatment with estramustine, radiotherapy or surgery to the time of randomization. Patients may be on biphosphonates prior to study entry. – Prior isotope therapy, whole pelvic radiotherapy, or radiotherapy to > 30% of bone marrow. – Adverse events (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of grade >1(National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.3.0) at the time of randomization. – Prior treatment with VEGF inhibitors or VEGF receptor inhibitors. – Less than 18 years. – Eastern Cooperative Oncology Group (ECOG) performance status > 2.

Main selection criteria (continued):	– History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease. – Prior malignancy. Adequately treated basal cell or squamous cell skin cancer are allowed, as well as any other cancer for which chemotherapy has been completed >5 years ago and from which the patient has been disease-free for > 5 years. – Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization. – Any of the following within 6 months prior to study enrollment: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack. – Any of the following within 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event. – Occurrence of deep vein thrombosis within 4 weeks, prior to randomization – Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment. – Any severe acute or chronic medical condition which could impair the ability of the patient to participate to the study or interfere with interpretation of study results. – Absence of signed and dated Institutional Review Board (IRB)-approved patient informed consent form prior to enrollment into the study. – Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and for at least 6 months after the completion of the study treatment. The definition of "effective method of contraception" will be based on the investigator's judgment. – For patients enrolled in the United Kingdom, their partner (unless surgically sterile, post menopausal or for another reason have no chance of becoming pregnant) should use an effective mean of contraception described hereafter: oral contraceptives or intra uterine device. • **Related to aflibercept** – Urine protein-creatinine ratio (UPCR) > 1 on morning spot urinalysis or proteinuria > 500 mg/24h

Main selection criteria (continued):	– Serum Creatinine > 1.5 x ULN. If creatinine 1.0 - 1.5 x ULN, creatinine clearance will be calculated either according to Cockcroft-Gault formula for patients younger than 65 years or, according to aMDRD formula for patients ≥ 65 years) Creatinine clearance < 60 mL/min will exclude the patient (See Appendix A for calculation formulas). – Uncontrolled hypertension, defined as blood pressure >150/100 mm Hg (grade ≥ 2 according to NCI CTCAE v.3.0), or systolic blood pressure >180 mm Hg if diastolic blood pressure <90 mm Hg, on at least 2 repeated determinations on separate days, within 3 months prior to randomization. – Patients on anticoagulants with unstable dose of warfarin and/or having an out-of-therapeutic range INR (> 3), within the 4 weeks prior to randomization. – Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g. INR>1.5 without vitamin K antagonist therapy), non-healing wound. • **Related to docetaxel regimen** – History of hypersensitivity to docetaxel, or polysorbate 80. – Inadequate organ and bone marrow function as evidenced by: 1. Hemoglobin <10.0 g/dL 2. Absolute neutrophil count <1.5 x 10^9/L 3. Platelet count < 100 x 10^9/L 4. AST/SGOT **and/or** ALT/SGPT > 1.5 x ULN; 5. Total bilirubin > 1.0 x ULN – Contraindications to the use of corticosteroid treatment. – Symptomatic peripheral neuropathy grade > 2 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.3.0).
Total expected number of patients:	Approximately 1200 patients.
Expected number of sites:	Approximately 200 sites are planned

INVESTIGATIONAL PRODUCTS	
Formulations:	• Aflibercept (also referred as VEGF Trap or AVE0005 in preclinical sections of the protocol): in 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 20%(w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, supplied in sealed, sterile, single-use 5-mL vials filled with 4.4 mL with a withdrawable content of 4.0 mL at a concentration of 25 mg/mL. The content of the vial must be diluted prior to infusion. • Placebo for aflibercept: Sterile aqueous buffered vehicle pH 6.0, containing 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 20% (w/v) sucrose and 0.1% (w/v) polysorbate 20, supplied in sealed, sterile, single-use 5-mL vials filled with 4.4 mL with a withdrawable content of 4.0mL at a concentration of 25 mg/mL. The content of the vial must be diluted prior to infusion. • Marketed formulations will be used for associated products (docetaxel and prednisone or prednisolone).
Route of administration:	Aflibercept and placebo will be administered by the IV route.
Dose regimen:	Patients will be randomly assigned to receive either Arm A or Arm B: Arm A: Aflibercept 6 mg/kg over 1 hour IV,on Day 1, every 3 weeks. Or Arm B: Placebo 6 mg/kg over 1 hour IV, on Day 1, every 3 weeks. For Arm A and Arm B, immediately followed by: • Docetaxel 75 mg/m² IV over 1 hour, on Day 1. For docetaxel premedication see details in the package insert. In case of body surface area (BSA) > 2.2 m² the actual dose of docetaxel should be adjusted to a maximum BSA of 2.2 m², for safety reasons. • Prednisone or prednisolone, 5 mg PO twice daily, from day 1 continuously. Dose reduction and/or treatment delay and/or treatment discontinuation are planned in case of severe toxicity. A cycle is defined as a 3 week-period.

PRIMARY ENDPOINT AND MAIN SECONDARY ENDPOINTS	Primary endpoint: • OS defined as the time interval from the date of randomization to the date of death due to any cause. Secondary endpoints will include: • Efficacy: – PSA response defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. The duration of PSA response is defined as the time between the first evaluation at which the response criteria are met and the first documentation of PSA progression (defined in section 9.1.2.3). Early increase in PSA within 12 weeks, when followed by subsequent decline, are ignored in determining this endpoint. – Pain response defined as a 2-point reduction in present pain intensity (PPI) score from baseline without an increase in the analgesic score (AS) or as a reduction of at least 50% in the analgesic score without an increase in the PPI score, either of which is maintained for at least 3 weeks. Early increase in PPI or AS within 12 weeks, when followed by subsequent decline, are ignored in determining this endpoint. – Time to occurrence of SRE defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SRE (defined in section 9.1.2.4) or death due to any cause. – Progression-free survival defined as the time interval between the date of randomization and the date of the first documentation of any of the following events: 1. Radiological tumor progression by RECIST, 2. Occurrence of at least 2 new bone lesions, confirmed 6 weeks later by a bone scan showing at least 2 additionnal lesions, 3. PSA progression (defined in section 9.1.2.3), 4. Pain progression (defined in section 9.1.2.2), 5. Radiotherapy for cancer related symptoms, 6. Occurrence of SRE (defined in section 9.1.2.4), Or death due to any cause. – Tumor response in patients with measurable disease (RECIST) – PSA progression-free survival defined as the time interval between the date of randomization and the date of either first documented PSA progression (defined in section 9.1.2.3), or death due to any cause, whichever comes first. Early increase in PSA within 12 weeks, when followed by subsequent decline, are ignored in determining this endpoint.

	– Pain progression-free survival defined as the time interval between the date of randomization and the date of either first documented pain progression (defined in section 9.1.2.2) or death due to any cause, whichever comes first. Early increase in PPI or AS within 12 weeks, when followed by subsequent decline, are ignored in determining this endpoint. – Health-Related Quality of Life (HRQL) assessed using changes from baseline in scores derived from FACT P and its Trial Outcome Index (TOI). The TOI combines the physical (7 items) functional (7items) and prostate specific concern (12 items). • Safety: – Type according to MedDRA (Medical Dictionary forRegulatory Activities), frequency, severity according to NCI CTCAE V3.0, seriousness, and relatedness of study treatment-emergent adverse events will be assessed . – Laboratory abnormalities will be assessed according to the NCI CTCAE v.3.0. • Intended for all patients treated in approximately 50 selected centers, pharmacokinetic parameters and immunogenicity tests will be performed: - Blood sampling will be performed at specified time points during the study, in both arms. Pharmacokinetics parameters will include free aflibercept, VEGF: aflibercept complex. - Blood sampling will be performed at specified time points during the study, in both arms, in order to detect anti-aflibercept antibodies.

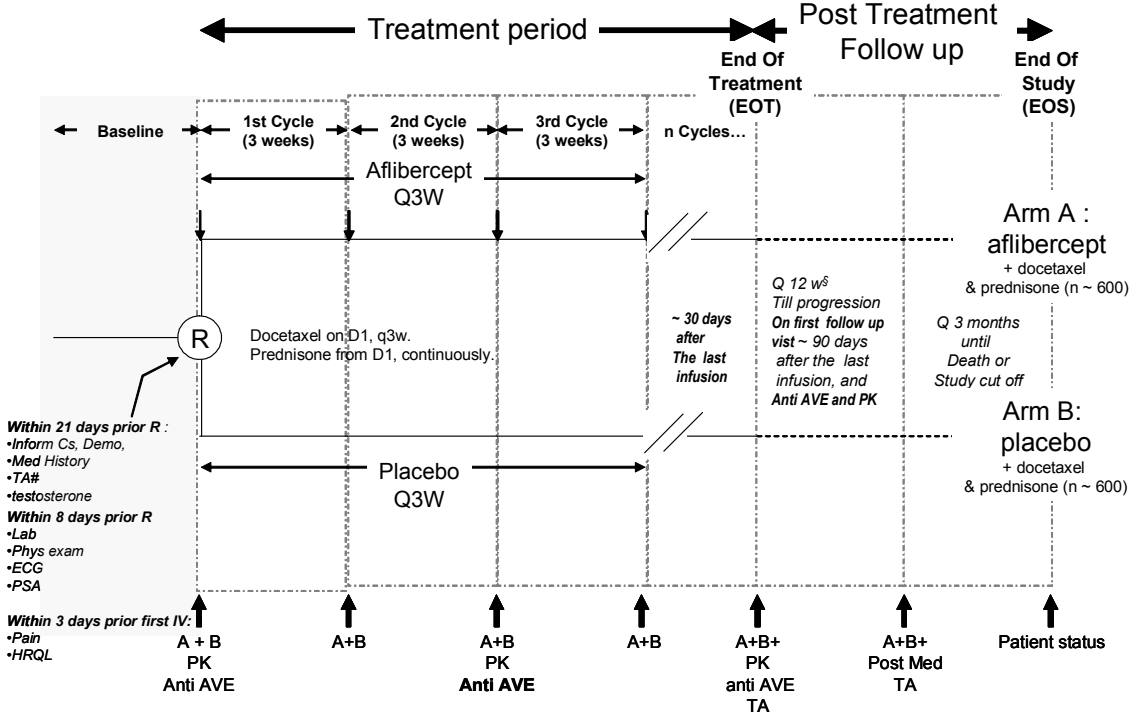
ASSESSMENT SCHEDULE	• Clinical examinations (including BP, weight, ECOG PS, SRE), laboratory tests (including complete blood counts, serum chemistry, and urinalysis) and adverse events will be obtained prior to drug administration, every cycle before treatment administration and up to 30 days after the last study treatment administration. • Serum testosterone will be measured at baseline. • PSA will be determined at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment, every 3 weeks until PSA progression is documented, or study cutoff, whichever comes first. • Pain assessment and completion of analgesic diary will be obtained at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment, every 3 weeks until pain progression is documented, or study cutoff, whichever comes first. • HRQL assessment (FACT-P) will be obtained at baseline, every 3 weeks at each visit before study treatment administration, at the end of treatment, every 3 weeks until disease progression is documented, or study cutoff, whichever comes first. • Tumor radiological evaluation including bone scan will be performed for all patients at baseline, every 12 weeks during study treatment period, at the end of treatment then every 12 weeks until tumor progression is documented, or study cut off whichever comes first. Confirmatory radiological evaluation will be performed 4 to 6 weeks after initial documentation of response. Confirmatory bone scan evaluation will be performed 6 weeks after initial documentation of response or progression. • Intended for all patients treated in selected centers: PK samples will be collected at predose and at the end of aflibercept/placebo infusion on day 1 of C1, then at predose every other cycle and then approximately 30 days and finally approximately 90 days after the last administered dose of aflibercept / placebo. Samples for anti-aflibercept antibody detection will be collected at baseline (predose cycle 1), predose every other cycle, then approximately 30 days and finally approximately 90 days after the last administered dose of aflibercept / placebo. **Samples for antibody detection and pharmacokinetic measurements should also be collected in patients who develop certain adverse event (e.g. hypersensitivity and proteinuria as defined in section 8.5.1)**. Sample for endogeneous VEGF level will be collected at baseline **in study sites equipped with a 4°C centrifuge (needed for preparation of the sample).** After disease progression is documented, patients will be followed every 3 months until death or withdrawal of patients' consent. Details of any further anticancer-therapy will be collected.

STATISTICAL CONSIDERATIONS	**Statistical hypotheses and sample size calculation** The study is designed to detect a 20% reduction in the risk of death (or a hazard ratio of 0.8) in the aflibercept arm (estimated median survival of 23.75 months) as compared with placebo arm (median survival of 19.0 months) using a log rank test at the overall one-sided 0.025 level with a 90% power. The calculation takes into account 2 interim analyses of OS using a group sequential approach with efficacy boundaries based on an O'Brien-Fleming alpha spending function and gamma(-5) beta spending function for estimation of futility boundaries (see details below). The final analysis of OS is planned after approximately 873 deaths are observed. Assuming patients will be randomized at a uniform monthly rate over 36 months followed by a 24-month follow-up period after the end of accrual, the predicted sample size is 1200 patients (i.e., 600 patients / arm). **Analysis population** **Intent-to-treat (ITT) population**: this population includes all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number through the study treatment allocation system. This population is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by randomization. **All treated population:** the subset of the ITT population that received at least one dose of study medication. This population is the primary population for all safety parameters. All analyses using this population will be based on the treatment actually received. **Analysis of the primary endpoint** OS will be compared between the two treatments by the log-rank test procedure stratified by ECOG performance status. The estimates of the hazard ratio and corresponding 95% confidence interval will be provided using a stratified Cox proportional hazard model. Survival curves will be estimated using Kaplan-Meier method. **Interim and final analyses** Two interim analyses (IA) of OS are planned for the purpose of futility when approximately 437 OS events (50% information fraction) and for the purpose of efficacy when 655 OS events (75% information fraction) have occurred. Calculations are based on a O'Brien-Fleming spending function (for efficacy) and assuming that the interim looks will actually be carried out after the 437th and the 655th event. Although there is no intention to stop the trial for positive outcome at 50% information time, a conservative alpha is allocated at the first interim look using O-F spending function to protect the integrity of the trial as a single pivotal study for registration. A gamma(-5) beta spending function will be used for the futility analysis at the time 50% of the events have been observed. Futility will be considered if the hazard ratio is ≥1.01 in favor of the placebo arm. The one-sided nominal significance levels to terminate the study for efficacy at 75% information fraction is 0.0092. The IA will be carried out under the supervision of the DMC. The final OS analysis will be conducted when 873 deaths have been observed. The one-sided nominal significance level to declare superiority of aflibercept at the final analysis is 0.022.

DURATION OF STUDY PERIOD (per Patient)	Patients will be treated until progressive disease, unacceptable toxicity, patient's refusal of further study treatment. All patients will be followed when on study treatment and after completion of study treatment during follow up period until death or the study cutoff date, whichever comes first. The maximum study duration and the final study cutoff date for survival will be the date when approximately 873 deaths have occured.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



R: randomization; **A** = Phys exam, Conc Med, SRE, PSA, pain (PPI; AS), HRQL, AE (Adverse Events);
B = hematology, biochemistry, coagulation, urinalysis; **TA**: tumor assessment, performed q12 weeks **until progression**
AntiAVE =anti aflibercept antibody; **PK**: Pharmacokinetics
§: except for PSA and pain measured q3w **until progression**
#: Except for bone scan to be performed within 6 weeks prior R

1.2 STUDY FLOWCHART

Evaluation	**Baseline**		Treatment period First cycle within 3 days after randomization			Post- treatment follow-up period	
	Prior to randomization	**R A N D O M I Z A T I O N**	Every cycle	every 4 cycles	End of treatment (30 days after last treatment)	Every 12 weeks until progression (including specific assessment 90 days after last treatment)	Every 12 weeks (o)
Baseline documentation							
Informed Consent	Before any study procedure						
Inclusion/Exclusion Criteria	Within 8 days						
Patient demography	Within 21 days						
Prior Medical/Surgical & Oncologic History(a)	Within 21 days						
Clinical Examination (b)	Within 8 days		X		X	X	X (ECOG only) (o)
Laboratory Studies (c)	Within 8 days		X		X		
12 lead Electrocardiogram (d)	Within 8 days						
Randomisation (e)							
Study drug Administration (f)			X				
Other clinical assessments							
Adverse Events (g)			X		X	X	X
Prior/ Concomitant/ Post Medications (h)	Within 21 days		X		X	X (if indicated)(h)	X(if indicated)(h)
Other investigations	As clinically indicated						
Efficacy							
Tumor Assessment (i)	Within 21 days			X	X	X	X
Serum Testosterone Measurement (j)	Within 21 days						
PSA Measurement (k)	Within 8 days		X		X	X	X
Analgesic & Pain [over 7 days] (l)	Within 3 days		X			X	X
Health-Related Quality of Life**(m)**	Within 3 days		X		X	X	
Pharmacokinetics samples (n)			X		X (n)	X (n)	X
Anti aflibercept antibody (o)			X		X(o)	X(o)	
Survival status (p)						X	X

Study Flowchart Footnotes

a) **Prior Medical/Surgical & Oncologic History** Includes cancer diagnosis (primary tumor characteristics and metastatic sites), prior surgery for cancer, radiotherapy, systemic anticancer therapy, and concurrent illness.

b) **Clinical Examination:** Includes examination of major body systems (blood pressure, height (at baseline only), body weight, ECOG PS and SRE. BP will be measured and recorded once in between treatment visit, preferably during week 2.

c) **Laboratory Studies** Includes, prior each cycle, hematology (WBC, ANC, hemoglobin, platelet count). This blood count will be performed within the cycle in case of fever or infection (cf section 8.5.2)

blood biochemistry (sodium, potassium, calcium, phosphorus, blood urea nitrogen, magnesium, creatinine and if creatinine >ULN, creatinine clearance (calculated with Cockroft-Gault formula for patient <65 years or aMDRD formula for patients ≥65 years, see Appendix A), total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose,

coagulation (prothrombin time [expressed as international normalized ratio]), in patients under vitamin K antagonist therapy,

urinalysis (dipstick: WBC, RBC); Urinary protein and urinary creatinine and UPCR will be calculated on morning urine spot prior to dosing of each cycle. If proteinuria from renal origin (according to urine protein electrophoresis) is occuring please refer to Table 10 and section 8.5.1 for management. A urine microscopy examination should be also considered.

d) **12-lead ECG** to be repeated as clinically indicated

e) **Randomisation** All eligible patients will be randomly assigned to one of the two treatment groups (either aflibercept or placebo) using an Interactive Voice Response System (IVRS). Study treatment should be started within 3 days from randomization.

f) **Study drug Administration** Aflibercept / placebo will be administered on Days 1, immediately followed by docetaxel administered on Days 1 of each 21-day cycle. Cycle administration will start within 3 days of randomization, and then repeated every 3 weeks (see Section 8.4). In or out patient information will be collected.

g) **Adverse Events** The period of safety observation starts from the time the patient gives informed consent. All signs and symptoms observed from the time of signature of informed consent will be recorded as adverse event only if they are still present at the time of first study drug administration (and reported in cycle 1 of the CRF) or if they are serious. All adverse events will be recorded until 30 days after the last administration of study drugs. During the follow-up period, only ongoing related or new related adverse events will be recorded. Serious adverse events ongoing at the end of the study treatment will be followed during the follow-up period until resolution or stabilisation regardless of relationship with study drugs (see Sections 10.5 and 10.6).

h) **Prior/ Concomitant/ Post Medications** Concomitant medications and treatments will be recorded from 21 days prior to the start of study drug, before every cycle during the study treatment period, and up to 30 days after the final dose of study drug. Once the patient has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment related adverse events.

i) **Tumor Assessment** Chest, abdomen, and pelvic CT-scan or MRI and bone scan to be performed to assess disease status at baseline (bone scan performed within 6 weeks prior to randomization is allowed), then every 12 weeks until tumor progression, whenever disease progression is suspected, at the end of study treatment/withdrawal visit, using the same method for each assessment to follow all target and/ or non target lesions present at baseline. In addition, these radiological evaluations will be repeated to confirm a partial or complete response (4-6 weeks after initial documentation of response; 6 weeks for bone scan); In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to determine the nature of those lesions (metastatic or not).

j) **Serum testosterone measurement,** to be performed at baseline only

k) **PSA measurements** to be performed on pre dose of Cycle 1 Day 1 and then repeated on pre dose of Day 1 of each cycle, approximately 30 days after the last treatment administration, then every 3 weeks until PSA progression, or the study cutoff date, whichever comes first.

l) **Analgesic and pain** diary information should be collected daily for 7 consecutive days prior to each scheduled cycle start (at baseline, the last day should be within 3 days prior to first infusion); in case of delay: to be continued daily until the start of the next cycle. The collection will be done before each cycle, at the end of treatment and then every 3 weeks until pain progression or study cut off, whichever comes first.

m) **Health-Related Quality of Life:** FACT-P questionnaire (Appendix J) to be self-administered by the patient at the center, at each visit and prior to informing the patient about disease evolution and before the next study treatment (at baseline, questionnaire should be filled in within 3 days prior to first infusion). It is mandatory that a key person (e.g., research nurse) at each center be responsible for questionnaire data collection, in order to optimize compliance of the patient and to ensure completeness of the data. The collection will be done before each cycle, at the end of treatment and then every 3 weeks until disease progression, initiation of further anticancer therapy or study cut off, whichever comes first.

n) **Pharmacokinetics:** Intended for all patients treated in selected centers: Blood sample for measurement of free aflibercept, VEGF: aflibercept complex to be collected pre-dose and at the end of infusion on Day 1of Cycle 1, then at pre-dose of each every other cycle and then 30 days and 90 days after last administration aflibercept/placebo and for all patients in specific circumtances described in section 8.5.1. And Blood sample for measurement of VEGF endogeneous level will be collected at baseline, only. Refer to Appendix C for collection, handling, and shipping instructions.

o) In all patients treated in selected centers, serum for detection of anti-aflibercept antibodies will be collected pre-dose of cycle 1, pre-dose of each every other cycle then 30 and finally 90 days after last administration of aflibercept/placebo. Refer to Appendix C for collection, handling, and shipping instructions. For all patients in specific circumtances described in section 8.5.1.

p) **Survival status** Patients who discontinue study treatment without documented progression will continue to undergo clinical examination, including ECOG PS, BP, SRE and assessment for PSA, pain, and radiological assessment, until progression is documented, or until the study cutoff date, whichever comes first., HRQL will be assessed every 12 weeks until progression or further anti tumor therapy or cut off date, whichever comes first. In case of initiation of other anticancer treatment before disease progression, disease status will continue to be assessed until disease progression is documented (except HRQL). Then, patients will continue to be followed every 3 months for survival satus (dead, alive or lost to follow up), ECOG PS, BP, and collect further anticancer therapy data until death or study cut off date.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

Ab	Antibody
ACD	Acid citrate dextrose
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ANC	Absolute neutrophil count
ALT	Alanine Amino Transferase
ASCO	American Society of clinical oncology
AST	Asparatate Amino Transferase
BID	Twice daily
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
BP	Blood pressure
CALGB	Cancer And Leukemia Group B
CBC	Complete Blood Count
CHO	Chinese Hamster Ovary
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete response
CRF	Case Report Form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DEHP	Di (2-ethylhexyl) phthalate
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DRF	Discrepancy Resolution Form
DVT	Deep vein thrombosis
EC	Ethic Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme linked Immunosorbent Assay
EU	European Union
FDA	Food and Drug Administration
FU	Fluorouracil
GCP	Good Clinical Practice
HA	Health authority
HBP	High Blood Pressure
HDT	Highest Dose tested
HRQL	Health-Related Quality of Life
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IA	Interim Analysis

IB	Investigator brochure
ICH	International Conference on Harmonization
IFL	Irinotecan fluorouracil leucoverin
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-To-Treat
IV	Intra Venous
IVRS	Interactive Voice Response System
LD	Longest Diameter
LDH	Lactico-Dehydrogenase
LMW	Low Molecular Weight
MAIPC	Metastatic Androgen Independent Prostate Cancer
MBC	Metastatic Breast Cancer
MCRC	Metastatic Colorectal Cancer
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
Min	Minutes
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
NSCLC	Non Small Cell Lung Cancer
OS	Overall Survival
PE	Pulmonary Embolism
PI	Package Insert
PFS	Progression Free Survival
PlGF	Placental Growth Factor
PO	Per oral route
PPI	Present Pain Intensity
PR	Partial Response
PS	Performance status
PSA	Prostate-Specific Antigen
PT	Prothrombin time
PVC	Polyvinyl Chloride
Q	Every
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leuco-encephalopathy Syndrome
SC	Subcutaneous
SCID	Severe Combined Immunodeficient
SD	Standard deviation/ Stable disease
SGOT	Serum Glutamate-Oxalate Transferase
SGPT	Serum Glutamate-Pyruvate Transferase
SmPC	Summary of Product Characteristics

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRE	Skeletal-Related Event
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TID	Three times In Day
TMA	Thrombotic microangiopathy
TOI	Trial outcome index
TOTM	Tri-2-Ethylhexyl Trimellitate
TXT	Taxotere ®
ULN	Upper Limit of Normal
UPCR	Urine Protein:Creatinine Ratio
US	United States/Ultrasound
V	Version
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VPF	Vascular Permeability Factor
W	Week
WBC	White blood cells

4 INTRODUCTION AND RATIONALE

4.1 PROSTATE CANCER

Prostate cancer is a major worldwide health problem and is the most frequently diagnosed malignancy in male [1]. Worldwide, there were 542,990 new cases and 204,313 deaths due to prostate cancer alone during the year 2000. Prostate cancer is associated with extensive morbidity, as most patients experience significant pain as the result of osseous metastases. Patients with advanced disease usually receive treatment with hormonal agents (orchiectomy, luteinizing hormone-releasing hormone [LHRH] agonists and/or anti-androgens). However, the effect of hormonal manipulation is temporary, and most patients experience disease progression after 18 months of treatment.

4.1.1 Chemotherapy in prostate cancer

Although chemotherapy has historically been regarded as modestly effective for the treatment of metastatic androgen-independent prostate cancer (MAIPC), recent studies have suggested that this may be changing.

First mitoxantrone significantly increased the palliative effect of corticosteroid therapy ($p = 0.01$) [2,4] and became the first chemotherapy agent to be approved in 1996 by the Food and Drug Administration (FDA) for the treatment of prostate cancer. However, there was no difference in survival between treatment arms.

More recently, docetaxel (Taxotere®,TXT) has been evaluated in MAIPC patients [5,6]. A randomized study compared 2 doses and schedules of docetaxel (TXT q3w, docetaxel 75 mg/m^2 IV every 3 weeks; TXT qw, docetaxel 30 mg/m^2 IV every week for 5 out of 6 weeks) versus mitoxantrone (MTZ q3w, 12 mg/m^2 IV every 3 weeks) in 1006 men with MAIPC (TAX 327) [5]. Both the docetaxel every 3 weeks (TXT q3w) and the combined docetaxel (TXT q3w and TXT qw) groups were statistically superior in terms of overall survival to mitoxantrone (HR=0.761 [0.619-0.936], p=0.0094 for the TXT q3w group corresponding to a risk of death reduced by 23.9%; HR=0.834 [0.701-0.992], p=0.0398 for the combined docetaxel groups). The median overall survival was 18.92 months in the TXT q3w group, 17.38 months in the TXT qw group, 18.27 months in the combined docetaxel groups, and 16.49 months in the mitoxantrone q3w group. The safety and tolerability was acceptable and anticipated based on the known safety profile for docetaxel.

Based on these results docetaxel 75 mg/m^2 IV every 3 weeks in combination with prednisone was granted approval in US and Europe in 2004 for treatment of MAIPC patients (for detailed information please refer to Taxotere® package insert (PI).

4.1.2 Tumor angiogenesis

Several malignant tumors are dependent on angiogenesis to maintain a source of nutrition and oxygen from the body to support their growth and metastasis [7]. Vascular endothelial growth factor (VEGF), also known as Vascular Permeability Factor (VPF), is a cytokine that was discovered in the late 1970s [8]. It is a homodimeric protein, which binds to and activates two high-affinity receptors, Flt-1 (VEGFR1) and Flk-1 (VEGFR2), predominantly located on the vascular endothelium. VEGF is a powerful mitogen for endothelial cells, thus promoting formation of new vessels that are required for normal and neoplastic tissue growth. In addition, VEGF very potently increases vessel permeability [9]. Therefore, VEGF become a major target for anti-angiogenic therapy because its overexpression in several tumor types has been associated with increased tumor vascularity, proliferation, progression, invasion, metastasis, and poor prognosis [10,11,12].

Several studies in animal models and, more recently, human clinical trials, have demonstrated the efficacy of anti-VEGF approaches to cancer treatment. By additionally "normalizing" tumor vasculature and reducing tumor interstitial fluid pressure, VEGF antagonists may enhance intratumoral delivery of traditional cytotoxic agents thereby improving their antitumor efficacy without overlapping toxicity [13]. Convincing clinical evidence in support of this therapeutic approach was first demonstrated by the humanized anti-VEGF monoclonal antibody, bevacizumab (Avastin®), which was granted Food and Drug Administration (FDA) and European Union approvals in 2004 in combination with IV 5-Fluorouracil (5FU)-based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer (MCRC). Bevacizumab in combination with irinotecan/bolus 5-FU/Leucoverin (IFL) chemotherapy significantly improved the progression-free and overall survival of previously untreated MCRC patients as compared to patients treated with IFL alone [14], the approved standard first-line MCRC treatment control.

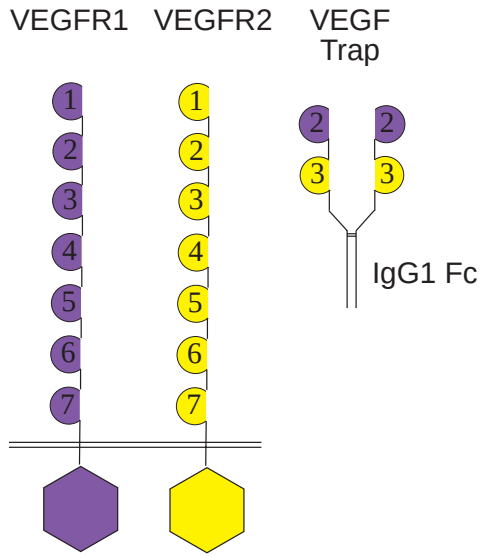
4.1.3 Angiogenesis and prostate cancer

VEGF is present in both localized and metastatic prostate tumors as well as in the plasma of patients with metastatic disease, and increasing expression may correlate with disease progression [18,19]. In addition both plasma and urine VEGF levels in MAIPC patients were recently found to be independent predictors of survival [20,21] and antibodies to VEGF have caused tumor regression in preclinical animal prostate tumor models, suggesting that VEGF blockade may be an interesting therapeutic approach [25-27]. Based on these data, the Cancer And Leukemia Group B (CALGB) evaluated the role of humanized anti-VEGF monoclonal antibody in patients with MAIPC, study CALGB90006 [28]. Seventy nine patients were treated every 3 weeks, with estramustine (280 mg po TID, on days 1-5) and docetaxel (70mg/m², on day 2) combined with bevacizumab (15mg/kg, on day 2). The preliminary data reported 9 partial responses on 17 patients (53%) with measurable disease. In 20 patients with available data, 65% had at least 50% decline of PSA.The survival was more than 20 months. Based on these encouraging results, the CALGB is conducting an ongoing phase 3 study assessing the impact on survival of bevacizumab when combined with docetaxel in MAIPC.

4.2 INVESTIGATIONAL PRODUCT

Aflibercept (also known as AVE0005 or VEGF Trap) is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains fused to the F_c portion of human Immunoglobulin G1 (IgG_1). It contains sequences encoding Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG_1 F_c domain. AVE0005 (VEGF Trap) is a dimeric glycoprotein with a molecular weight of 115 kDa. AVE0005 (VEGF Trap) is made recombinantly in Chinese hamster ovary (CHO) cells.

Figure 1 – Aflibercept structure



Aflibercept is a specific antagonist that binds and inactivates circulating VEGF in the bloodstream and in the extravascular space. Aflibercept was designed to prevent the growth of primary and metastatic tumors by reducing tumor vascularity and vascular permeability with several potential advantages over other VEGF blockers:

- Aflibercept has a much higher VEGF-A binding affinity (0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody (~800 pM)
- Aflibercept also binds VEGF-B plus the related factors PlGF1 and PlGF2 which may be advantageous in certain disease settings (e.g., malignant ascites where PlGF may mediate vascular permeability)
- Aflibercept has a longer circulating half-life compared to other soluble receptor constructs that have been studied in animals

4.3 OVERVIEW OF PRECLINICAL INFORMATION

Detailed information regarding the *in vitro* and *in vivo* pharmacology of aflibercept, including the results of preclinical efficacy, safety and pharmacokinetic studies, can be found in the Investigator's Brochure [15]. In particular, compound-related microscopic findings in primates were observed in the bone, kidney, and ovary. Most kidney findings were very slight or slight, and AVE0005 (VEGF Trap) was not highly immunogenic in monkeys. In all animal species evaluated, free AVE0005 (VEGF Trap) was characterized by a low clearance, a low volume of distribution, and a long apparent elimination half-life. AVE0005 (VEGF Trap) inhibition of tumor growth in mouse xenograft models was observed at ≥ 2.5 mg/kg twice weekly dose, which corresponded to a pharmacological exposure where free AVE0005 (VEGF Trap) increases approximately linearly in excess of plateauing VEGF:AVE0005 (VEGF Trap) complex (i.e., bound AVE0005 [VEGF Trap]) levels.

4.3.1 Preclinical study of aflibercept in a human prostate carcinoma model

Dose-response activity was observed against a human advanced prostate carcinoma model DU145 in SCID mice, with a high pharmacological index of AVE0005 (ratio of the highest active dose divided by the lowest active dose, >16) in this model. As a reference, typical cytotoxic agents have pharmacological indexes between 1 and 3.

4.3.2 Preclinical studies of aflibercept in combination with paclitaxel

The ability of systemically administered AVE0005 (VEGF Trap) to prevent the vascular leak induced by VEGF was evaluated in a model of ascites formation. Human ovarian cancer cells (OVCAR-3) were implanted into the peritoneum of nude mice. These animals developed significant tumor burden and ascites over a period of approximately 8 weeks. Treatment with AVE0005 (VEGF Trap) initiated 2 weeks after tumor cell inoculation prevented the formation of ascites and decreased tumor burden in these mice by >50% [16]. The combination of AVE0005 (VEGF Trap) and paclitaxel also caused a striking reduction in tumor burden and a complete inhibition of ascites formation in the OVCAR-3 model of ovarian cancer, and was clearly more active than each of the single agents [17].

4.3.3 Preclinical studies of aflibercept in combination with docetaxel

The combination of subcutaneous (SC) AVE0005 (VEGF Trap) plus IV docetaxel was found to be highly active, inducing a higher cell kill than each agent alone, although with some overlap in host toxicity [15]. This combination was evaluated in BALB/c nu/nu female mice bearing B16 melanoma. A 3-arm dose-response trial was conducted for each single agent and the simultaneous combination on Days 3, 6, and 9. In this model, each single agent was active: 4.2 log cell kill at the highest dose tested of AVE0005 (VEGF Trap) (40 mg/kg per day) and 1.5 log cell kill at the highest non-toxic dose of docetaxel (15 mg/kg per day). The highest non-toxic dose of the combination (AVE0005 [VEGF Trap] at 40 mg/kg per day and docetaxel at 9.3 mg/kg per day) resulted in a 5 log cell kill indicating that the combination was highly active and more potent than each single agent alone. When the highest non-toxic dose of docetaxel (15 mg/kg per day) was maintained, the dose of AVE0005 (VEGF Trap) had to be reduced to 10 mg/kg per day indicating some overlap in host toxicity. The highest non-toxic dose of docetaxel (15 mg/kg per day) induced 1.5 log cell kill, AVE0005 (VEGF Trap) (10 mg/kg per day) induced 2.5 log cell kill, and the combination of both agents at these doses was also more active, having induced 3.4 log cell kill.

4.4 SUMMARY OF PREVIOUS HUMAN EXPERIENCE

Detailed information regarding the clinical safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of aflibercept can be found in the AVE0005 Investigator's Brochure [15]. So far, around 500 patients have been treated with aflibercept, either in monotherapy or combined with various chemotherapies (oxaliplatin, 5-FU, CPT-11, gemcitabine, docetaxel, docetaxel/cisplatin and docetaxel/cisplatin/5-fluorouracil). In general, aflibercept has an acceptable safety profile at the dose levels evaluated to date, as the majority of adverse events encountered have been mild to moderate in severity. Adverse reactions linked to VEGF blockade have been consistent in incidence, severity, across all the studies.

4.4.1 Summary of experience of aflibercept in monotherapy

4.4.1.1 Clinical results

Study TED6115/6116 is an ongoing open-label dose-escalation study of aflibercept given in monotherapy in patients with various advanced cancers. Doses, ranging from 0.3 mg/kg to 7 mg/kg iv, administered once every 2 weeks, were investigated for a median of 3 to 7 cycles. Overall 46 patients have been enrolled and received 1 to 50 cycles.

Six out of 46 (13%) patients experienced dose limiting toxicity (ies) (DLT) within the first 4 weeks of study treatment, influencing dose escalation or cohort extension decision. One patient at the 1.0 mg/kg dose experienced grade 3 arthralgia associated with grade 3 dysphonia, at the 2.0 mg/kg dose, 1 patient experienced grade 3 dyspnea (patient with preexisting COPD). At 4.0 mg/kg dose,1 patient experienced grade 3 hypertension and another patient had grade 2 proteinuria (>2.0 g/24hours) associated with grade 3 manageable hypertension. Two patients at the 7.0mg/kg dose level reported DLTs, 1 grade 3 rectal ulcer and the other patient developped grade 3 proteinuria that recovered and continued treatment at the 4mg/kg dose.

Treatment emergent adverse events, consisting mostly of low grade events, were reported in most of the patients (Table 1). No evident particular pattern, in frequency or in severity of the adverse events, could be identified across the investigated doses. The five most frequent TEAEs reported were fatigue (84.8%), nausea (65.2%), constipation (54.3%), dysphonia (50.0%) and dyspnea (50.0%).
Adverse events that may be related to VEGF blockade, were observed across all dose levels. Overall incidences for these events were: dysphonia (50.0%), hypertention (41.3%), proteinuria (19.6%), epistaxis (13.0%). No arterial ischemic event was reported.

Table 1 - most common TEAEs all grades in studies TED6115 and TED6116 (in at least 10% of treated patients), regardless of relationship to study medication

	Dose Level							
MedDRA Preferred Term	0.3 mg/kg (N=3) N	1.0 mg/kg (N=7) N	2.0 mg/kg (N=6) N	3.0 mg/kg (N=7) N	4.0 mg/kg (N=7) N	5.0 mg/kg (N=4) N	7.0 mg/kg (N=12) N	Total Doses (N=46) N
Subjects With at Least 1 TEAE	3	7	6	7	7	4	10	44
Subjects Without Any TEAEs	0	0	0	0	0	0	2	2
Fatigue	3	6	6	7	7	2	8	39
Nausea	3	5	2	7	6	2	5	30
Constipation	1	4	6	5	4	1	4	25
Dysphonia	1	2	3	6	3	2	6	23
Dyspnoea	1	4	5	6	3	0	4	23
Vomiting	2	3	3	6	3	2	2	21
Hypertension	0	2	2	1	4	3	7	19
Abdominal pain	2	3	1	4	3	1	3	17
Anorexia	1	3	3	4	4	1	1	17
Arthralgia	1	3	2	3	2	2	4	17
Back pain	1	1	1	4	3	3	4	17
Headache	0	3	3	1	3	3	3	16
Diarrhoea	2	3	1	4	3	0	2	15
Pyrexia	1	3	3	3	2	1	2	15
Shoulder pain	0	3	1	1	3	3	3	14
Cough	0	3	3	2	2	0	1	11
Myalgia	0	2	2	2	1	1	3	11
Pain in extremity	0	1	2	2	0	2	4	11
Pharyngolaryngeal pain	0	2	2	2	1	1	2	10

The most frequently reported grade 3-4 AE was HBP, in 15/46 (32.6%) of the patients (see Table 2). At doses of 4 mg/kg or above, half of the patients (11 out of 23 treated patients) experienced a blood pressure increase (grade ≥3). Grade 3 HBP seems to occur earlier in the treatment as the dose is escalated from 4 mg/kg. Hypertension is reported within 2 weeks of the first drug administration. Severe proteinuria (grade 3) were observed in 2 (4.3%) patients. Fatigue was the only other Grade 3 AE to be reported in more than 5 patients.

Table 2 - Most common Grade 3-4 TEAEs in studies TED6115 and TED6116 (in at least 2 treated patients), regardless of relationship to study medication

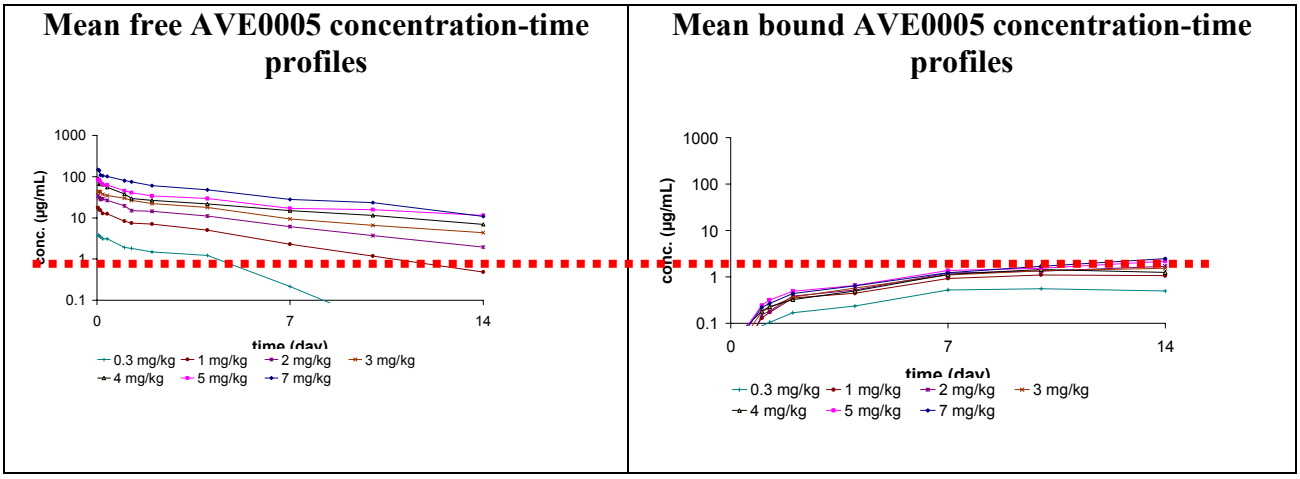
	Dose Level							
MedDRA Preferred Term	0.3 mg/kg (N=3) N	1.0 mg/kg (N=7) N	2.0 mg/kg (N=6) N	3.0 mg/kg (N=7) N	4.0 mg/kg (N=7) N	5.0 mg/kg (N=4) N	7.0 mg/kg (N=12) N	Total Doses (N=46) N
Subjects With at Least One Grade 3-4-5 TEAE	1	6	4	5	5	4	8	33
Subjects Without Any Grade 3-4-5 TEAEs	2	1	2	2	2	0	4	13
Hypertension	0	1	2	1	3	3	5	15
Fatigue	0	2	1	2	2	0	0	7
Dyspnoea	0	2	2	0	0	0	0	4
Abdominal pain	0	1	0	1	0	0	1	3
Nausea	0	0	0	1	0	2	0	3
Vomiting	0	0	0	1	0	2	0	3
Anorexia	0	0	0	1	0	1	0	2
Arthralgia	0	1	0	0	0	0	1	2
Blood alkaline phosphatase	0	1	0	1	0	0	0	2
Blood alkaline phosphatase increased	0	0	0	1	1	0	0	2
Blood sodium decreased	0	0	0	0	1	0	1	2
Colon cancer metastatic	0	0	0	0	1)	0	1	2
Hyperbilirubinaemia	0	0	0	1	0	0	1	2
Pleural effusion	0	1	0	0	0	1	0	2
Proteinuria	0	0	1	0	0	1	0	2

Three patients had a partial response. Responses were observed in a patient with a malignant thymoma, and 2 other patients with ovarian cancer had a partial response. All these tumor responses were observed in heavily pretreated patients.

4.4.1.2 Pharmacokinetics results

The pharmacokinetics of free aflibercept appeared to be linear between the 2 and 7 mg/Kg dose levels while bound aflibercept increased with dose between 0.3 and 2 mg/Kg, then plateaued between 2 and 7 mg/kg, suggesting that free aflibercept was present in sufficient amount to bind all endogenous VEGF at these higher dose levels. Free aflibercept levels have remained in excess of bound levels (ratio >1) throughout the dosing intervals at ≥ 2.0 mg/kg dose levels.

Figure 2 - Intravenous free versus bound aflibercept concentration time profile (Cycle 1)



4.4.1.3 Conclusion

Based on the above adverse events, thought to be related to VEGF blockade or not, formal DLTs as well as adverse events resulting in discontinuation, safety profile, pharmacokinetic results, and clinical benefit across dose levels, it was recommended to select 4 mg/kg every 2 weeks for aflibercept administered as a single agent. This is independently supported by the safety experience from currently ongoing phase II studies of aflibercept administered as single agent, in the indications of non small cell lung adenocarcinoma and advanced ovarian carcinoma (either at doses of 2 or 4 mg/kg every 2 weeks). The safety profile in these trials is similar to the phase I study described above with most adverse events being grade 1 or 2. The adverse events most frequently reported are: hypertension, proteinuria, epistaxis, dysphonia, pain (including abdominal pain and back pain), asthenia/ fatigue, nausea, vomiting, headache, constipation, increase in liver enzymes, myalgia, arthralgia, dyspnea, decreased appetite and diarrhea.

4.4.2 Summary of experience of aflibercept in combination with docetaxel

4.4.2.1 Clinical results

TCD6120 (AVE0005A/1004), an ongoing dose-escalation study of aflibercept administered every 3 weeks in combination with docetaxel, then with docetaxel/cisplatin was aimed to determine the recommended dose of aflibercept when combined with docetaxel in advanced solid tumor patients based on safety, tolerability, and pharmacokinetics.

Sequential cohorts of patients have been treated with successively higher doses of aflibercept first given with standard doses of docetaxel (75 mg/m²) every 3 weeks, then with standard doses of docetaxel (75 mg/m²) in combination with cisplatin (75 mg/m²) every 3 weeks. The 2.0 mg/kg dose level was the starting dose level of aflibercept with docetaxel, and 4.0 mg/kg was the starting dose of aflibercept with docetaxel/cisplatin.

Until October 30, 2006, a total of 38 patients were enrolled and treated in the escalation step of the study:

- 27 in the aflibercept and docetaxel combination cohort across 6 dose levels: 2mg/kg (7 pts/0 still ongoing), 4 mg/kg (3 pts/1 still ongoing), 5 mg/kg (6 pts/1 still ongoing), 6 mg/kg (4 pts/2 still ongoing), 7 mg/kg (5 pts/1 still ongoing) and 9 mg/kg (2 pts/2 still ongoing).

  Three out of 27 aflibercept and docetaxel treated patients experienced a dose limiting toxicity (DLT), one at the 2 mg/kg dose level (neutropenic infection, most probably due to docetaxel-related toxicity), one at the 7 mg/kg dose level (grade 3 dysphonia, knowing that this patient had a grade 1 dysphonia at baseline) and one at the 9 mg/kg dose level (hypertension). Of note, one patient treated at 7 mg/kg experienced a hypertension (HBP) event, which required medical management with several antihypertensive drugs but which was finally controlled with combination therapy, therefore not meeting protocol DLT criteria.

  As of database extract of December 15, 2006, twenty-seven (27/27, 100%) aflibercept and docetaxel treated patients had at least one treatment emergent adverse event (TEAE) (all grades, regardless of relationship to study medication, excluding laboratory adverse events). The most frequent TEAE (all grades, regardless of relationship to study medication) are described in Table 3.

Table 3 - Most common TEAEs in study TCD6120 (all grades, occurring in at least 10% of treated patients), regardless of relationship to study medication

	All doses	
Total number of treated patients [N]	27	
Total patients with any TEAE [N (%)]	27 (100%)	
Total patients with any Grade 3-4 TEAE [N (%)]	17 (67.0%)	
MedDRA SOC term	**All Gr**	**Gr 3**
By MedDRA body system		
Eye disorders	12 (44.4)	-
Conjunctivitis	6 (22.2)	-
Lacrimation increased	3 (11.1)	-
Gastrointestinal	24 (88.9)	2 (7.4)
Stomatitis	12 (44.4)	-
Constipation	11 (40.7)	-
Diarrhoea	11 (40.7)	-
Nausea	8 (29.6)	-
Abdominal pain	7 (25.9)	1 (3.7)
Dyspepsia	4 (14.8)	-
Haemorroids	6 (22.2)	-
Odynophagia	3 (11.1)	-
General disorders and administration site conditions	22 (81.5)	8 (29.6)
Fatigue [a]	11 (40.7)	4 (14.8)
Asthenia [a]	10 (37.0)	2 (7.4)
Mucosal inflammation	7 (25.9)	-
Pyexia	7 (25.9)	-
General physical health deterioration	3(11.1)	1 (3.7)
Infections and infestations	14 (51.9)	4 (14.8)
Lung Infection	3 (11.1)	1 (3.7)
Investigations	7 (25.9)	
Weight decrease	7 (25.9)	

	All doses	
Total number of treated patients [N]	27	
Total patients with any TEAE [N (%)]	27 (100%)	
Total patients with any Grade 3-4 TEAE [N (%)]	17 (67.0%)	
MedDRA SOC term	**All Gr**	**Gr 3**
By MedDRA body system		
Metabolism and nutrition disorders	7 (25.9)	-
Anorexia	6 (22.2)	-
usculoskeletal and connective tissue disorders	9 (33.3)	-
Bone pain	3 (11.1)	-
Nervous system disorders	14 (51.9)	-
Dysgeusia	8 (29.6)	-
Headache	5 (18.5)	-
Paresthesia	4 (14.8)	-
Neuropathy	2 (7.4)	-
Neuropathy peripheral	1 (3.7)	-
Peripheral sensory neuropathy	1 (3.7)	-
All neuropathy (including the 4 AEs listed above)	8 (29.6)	-
Psychiatric disorder	8 (29.6)	-
Anxiety	5 (18.5)	-
Respiratory, thoracic and mediastinal disorders	27 (100.0)	2 (7.4)
Dysphonia	20 (74.1)	1 (3.7)
Epistaxis	20 (74.1)	-
Dyspnoea	7 (25.9)	1 (3.7)
Rhinorrhea	6 (22.2)	-
Skin and subcutaneaous tissue disorders	21 (77.8)	2 (7.4)
Nail disorder [b]	13 (48.1)	2 (7.4)
Onycholysis [b]	6 (22.2)	-
	All doses	
Alopecia	12 (44.4)	-
Palmar-plantar erythrodysaesthesia syndrome	5 (18.5)	2 (7.4)
Vascular disorders	17 (63.0)	2 (7.4)
Hypertension	15 (55.6)	2 (7.4)
Thrombosis	1	-

a Patient #1503 had both asthenia and fatigue
b Patient 1601 had both nail disorder and onycholysis
Infections and events of fever in absence of infection include the corresponding neutropenic complications.

Table 4 - Hematological toxicity, worst grade by patient, in study TCD6120

	Initial planned aflibercept dose level (mg/kg) administered every 3 weeks						
	2	**4**	**5**	**6**	**7**	**9**	**All doses**
Total number of treated patients [N]	7	3	6	4	5	2	27
Total number of evaluable patients [a] [N]	7	3	6	4	5	2	27
Leucopenia N (Gr 3-4 N)	7 (7)	3 (3)	6 (5)	4 (4)	4 (2)	2 (2)	26 (23)
Total number of evaluable patients [a] [N]	7	3	6	4	5	2	27
Neutropenia N (Gr 3-4 N)	7 (7)	3 (3)	6 (4)	4 (3)	5 (3)	2 (2)	27 (22)
Total number of evaluable patients [a] [N]	7	3	6	4	5	2	27
Anemia N (Gr 3-4 N)	6 (3)	2 (1)	5 (3)	3 (2)	4 (2)	0 (0)	20 (11)
Total number of evaluable patients [a] [N]	7	3	6	4	5	2	27
Thrombocytopenia N (Gr 3-4 N)	2 (0)	0 (0)	1 (0)	0 (0)	0 (0)	-	3 (0)

[a] A patient is evaluable if having at least a blood count for the given test between two infusions.
Patient #2206 is reported as having a false Grade 4 thrombocytopenia due to unit error. These data was not taken into account on this table.

Three confirmed partial response (in breast cancer at dose levels of 2.0; 4.0 and 6.0 mg/kg) and 15 stabilizations (including 1 in prostate cancer) were reported.

- 11 patients in the aflibercept and docetaxel/cisplatin combination cohort across 2 dose levels: 4 mg/kg (6 pts/0 still ongoing) and 5 mg/kg (5 pts/3 still ongoing).

  One out of 11 aflibercept +docetaxel/cisplatin treated patients experienced a DLT at 4 mg/kg (febrile neutropenia, most probably due to docetaxel-related toxicity). Dose escalation is still ongoing.

4.4.2.2 Pharmacokinetics results

Pharmacokinetics of free and bound AVE0005 were determined in patients for which blood samples have been analyzed as of 27 October 2006. The results are summarized in Table 5.

Table 5 - Mean (SD) pharmacokinetic parameters of free and bound AVE0005 in TCD6120

		Free AVE0005 (cycle 1)			Bound AVE0005	
Dose (mg/kg)	No of patients	Cmax (µg/mL)	Clast (µg/mL)	CL (mL/day/kg)	End of cycle 1	Median of following cycles
2	7	43.2 ± 12.0	0.45 ± 0.58	18.8 ± 5.6	1.61 ± 0.58	2.84 ± 1.06
4	9	106 ± 47	2.22 ± 1.88	13.3 ± 4.5	1.96 ± 0.42	3.44 ± 0.92
5	7	116 ± 47	4.39 ± 2.94	12.6 ± 4.4	2.33 ± 0.47	3.29 ± 1.05
6	4	105 ± 19	3.44 ± 2.14	14.7 ± 5.0	1.93 ± 0.40	2.54 ± 0.38
7	1	182	-*	-*	-*	-*

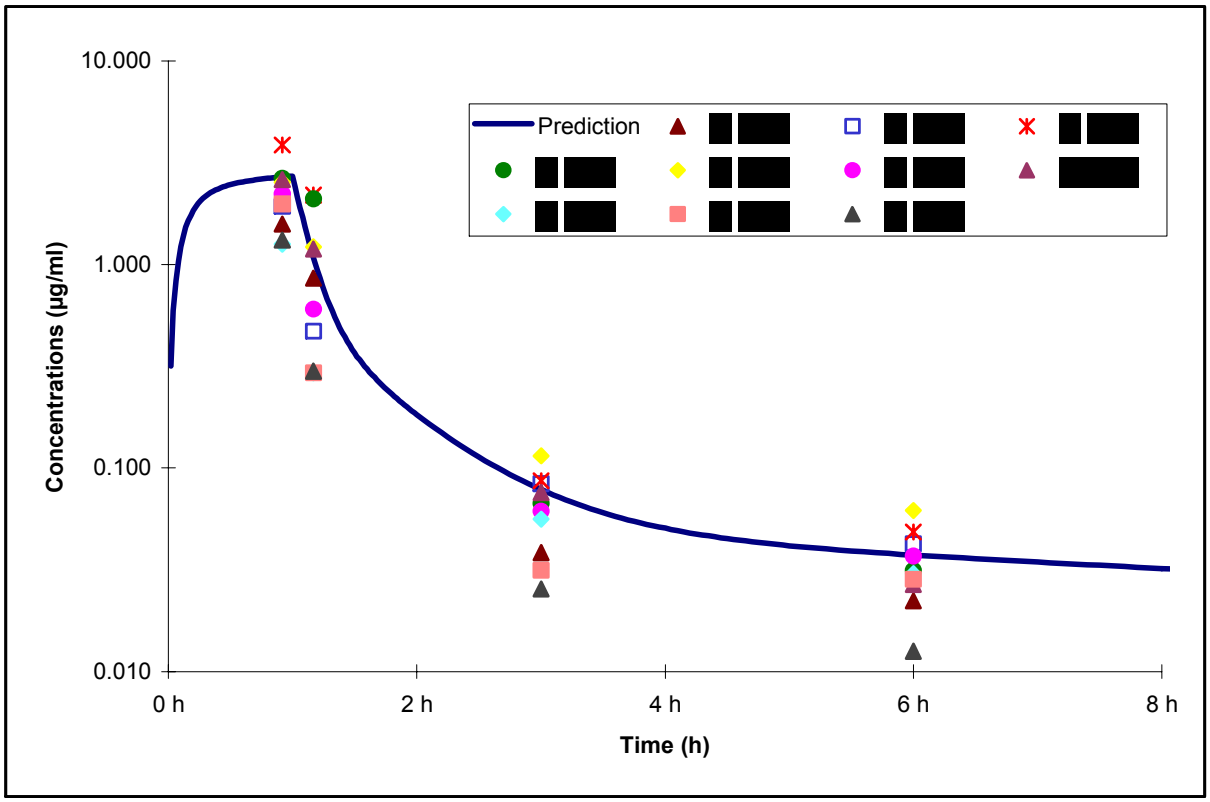
*: no data available (studies on going)

Free and bound AVE0005 concentrations are comparable to those observed in a monotherapy study, suggesting that docetaxel has no influence on the pharmacokinetics of AVE0005. The kinetics of free AVE0005 is dose-independent (clearance does not change with dose). Bound AVE0005 concentrations estimated at the end of cycle 1 are approximately two times lower than that measured all along the following cycles.

The ratio of free/ bound AVE0005 was maintained above 1 at the end of cycle 1 administration, for all the patients from dose level 6mg/kg.

Furthermore, the preliminary results of docetaxel are compared to a pharmacokinetic profile given by the population PK and illustrated hereunder.

Figure 3- Individual plasma concentrations of docetaxel in comparison with the prediction given by the population pharmacokinetics



Preliminary data indicate that AVE0005 has likely no impact on the pharmacokinetics of docetaxel.

These preliminary data indicate the absence of interaction between docetaxel and AVE0005.

4.4.2.3 Conclusion

Aflibercept and docetaxel in combination were well tolerated with acute and reversible adverse reactions linked to VEGF blockade (mainly HBP), no cumulative or late toxicity were observed. In addition, no evidence of exacerbation of background chemo-related toxicities was observed. The safety profile appears to be quite similar across the 4 dose levels explored even at the highest dose tested. Antitumor activity was observed at each dose level. Around one third of patients had a HBP requiring treatment from the dose of 5 mg/kg and above. A trend for more severe episodes of HBP is observed at the two highest dose level explored (7 and 9 mg/kg). The criteria for recommended-dose selection took into account the combination of DLTs/overall safety profile and pharmacokinetics together. The aflibercept dose of 6 mg/kg in combination with docetaxel 75 mg/m², given every 3 weeks has been selected, and the expansion cohort is ongoing.

4.5 STUDY RATIONALE

The combination regimen of docetaxel / prednisone is the standard of care for the treatment of MAIPC. However, this treatment is not curative, and thus new therapeutic options for patients with this disease are still desperately needed.

Induction of new blood vessels is required for expansive prostate tumor growth, and upregulation of VEGF has been shown to be inversely correlated with survival. Therefore, VEGF is a legitimate target, and it is hypothesized that the addition of a VEGF inhibitor to standard treatment will improve overall survival of MAIPC patients. Aflibercept has a high affinity for binding VEGF and other related pro-angiogenic factors. In vivo preclinical models showed an additive activity of aflibercept / taxane combination and dose response activity was observed in human prostate cancer model. Furthermore, convincing clinical evidence in support of VEGF blockade approach demonstrated in randomized studies, may be independent of tumor type [14, 22, 23, 24].

There is a clinical evidence in support of this study in the first-line treatment of MAIPC from, extrapolation of the favorable results of randomized clinical trials of bevacizumab in combination with standard chemotherapy [14, 22, 23, 24], and promising efficacy results of the CALGB 90006 study in MAIPC [28] and by higher VEGF-A binding affinity compared to than a humanized monoclonal antibody.

Therefore, the present randomized placebo-controlled study has been designed to evaluate the efficacy and safety of the addition of aflibercept at the dose of 6mg/kg (Section 4.4)) to the registered doses of docetaxel/prednisone (Section 4.1.1) in the first-line treatment of patients with MAIPC. Stratification will be done according to ECOG PS (0-1 vs 2)[35].Overall survival will be the primary efficacy endpoint, which will be analyzed after approximately 873 patients have died.

5 STUDY OBJECTIVES

5.1 PRIMARY

- To demonstrate the efficacy of aflibercept versus placebo in terms of overall survival (OS) in patients treated with docetaxel / prednisone or prednisolone for metastatic androgen-independent prostate cancer (MAIPC).

5.2 SECONDARY

- To assess the efficacy of aflibercept compared to placebo in term of:
  - PSA response
  - Pain response in patients with stable pain at baseline
  - Time to occurrence of skeletal related events (SRE)
  - Progression Free survival (PFS)
  - Tumor response in patients with measurable disease (RECIST)
  - PSA Progression-Free Survival (PSA-PFS)
  - Pain Progression-Free Survival (Pain-PFS)
  - Health related quality of life (HRQL)

All those criteria are defined in section 9.1.2.

- To evaluate safety in both treatment arms,

Intended for all patients treated in selected centers:

- To determine the pharmacokinetics of free and bound aflibercept, including Population pharmacokinetics, of IV aflibercept.
- To determine the immunogenicity of IV aflibercept.

6 STUDY DESIGN

This is a prospective, multicenter, multinational, randomized (1:1), double-blind, placebo-controlled, parallel-arm study comparing the efficacy of aflibercept (Arm A) versus placebo (Arm B) in terms of OS in patients treated with docetaxel / prednisone or prednisolone for MAIPC.

6.1 DESCRIPTION OF THE PROTOCOL

Each patient will be treated every 3 weeks, in the absence of definitive treatment discontinuation criteria outlined in Section 11.1.

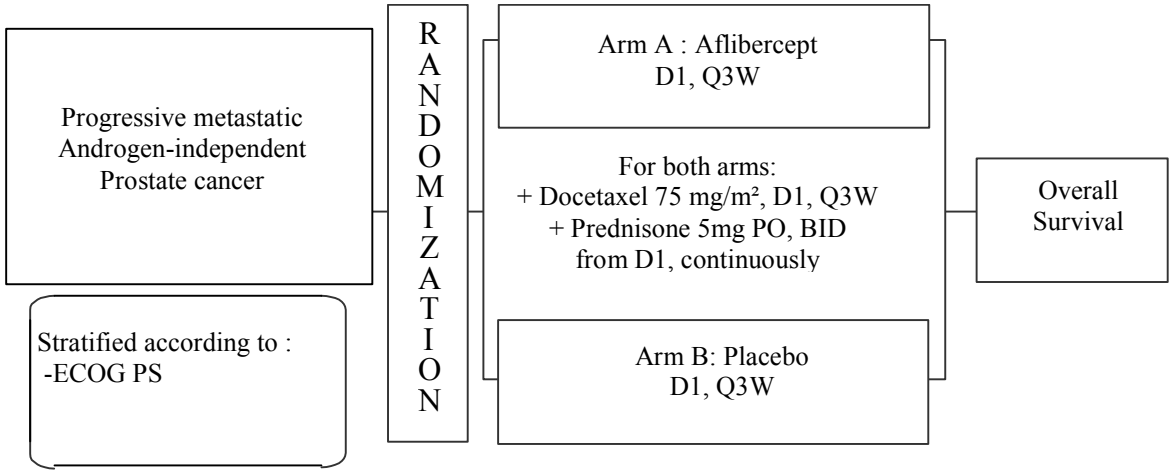
An Executive Committee will be responsible for supervising the progress of the trial. This Committee will include the Study Chairman, designated main investigators and Sponsor's representatives.

An independent Data Monitoring Committee (DMC) will periodically assess the progress of the clinical trial and the safety data. They will also be in charge of reviewing the planned interim analyses and to provide the Executive Committee with their recommendations regarding the continuing safety as well as the course of action regarding the conduct of the trial.

Patients will be centrally randomized to a treatment arm by an Interactive Voice Response System (IVRS). All eligible patients will be randomly assigned to either the control arm or the experimental arm in a 1:1 proportion. Randomization between the two treatment arms will be done according to baseline ECOG PS (0-1 vs 2).

- The study design is summarized in Figure 4:

Figure 4 – Study design



6.2 DURATION OF STUDY PARTICIPATION

Patients will be considered on study upon signing the informed consent and randomization performed. As shown in the graphical study design and study flowchart (Sections 1.1 and 1.2), the study consists of a 21-day baseline phase prior to randomization, start of study treatment administration randomly assigned within 3 days of randomization, 21-day study treatment cycles, safety evaluation at Day 30 and a follow-up phase (every 12 weeks until disease progression is documented and then every 3 months until death).

During the baseline period, all baseline procedures (see Sections 1.1 and 1.2 will have to be performed within defined timelines, including review of eligibility criteria see section 7.2 and section 7.3).

During the treatment period, the study treatment, either aflibercept or placebo (combined with docetaxel/prednisone or prednisolone), should be administered every 3 weeks unless a definitive treatment discontinuation criterion is met as described in Section 11.1, and the patients will be followed for safety for a minimum of 30 days following the last administration of the study drugs (either aflibercept /placebo or docetaxel). Cycle lengths may be extended in case of unresolved toxicity (see section 8.4.3). All study drug-related AEs and all SAEs should be followed until resolution/stabilization. Possible study drug-related AEs brought to the attention of the investigator at any time after cessation of study medication should be reported to the monitoring team.

During the post-treatment follow-up period, all patients will be followed with the same frequency for disease status (including PSA, pain, SRE and radiological assessments), until progression (as defined in Section 9.1.2) is documented, or until the study cutoff date, whichever comes first, and for HRQL every 3 weeks until further antitumor therapy or until progression (as defined in Section 9.1.2) is documented, or until the study cutoff date, whichever comes first.

All patients will be followed for survival status, ECOG performance status and collection of data regarding further anticancer therapy, every 3 months until death or study cut off date, whichever comes first.

The maximum duration of the study and the final data cutoff date for survival will be the first date when it is determined that approximately 873 deaths have occurred.

6.3 INTERIM ANALYSIS

Two formal interim analyses (IA) of the primary efficacy endpoint (OS) are planned when approximately half (50%) and three quarter (75%) of the deaths are observed to stop for futility at the first interim analysis or for outstanding efficacy at the second interim analysis. Statistical operating characteristics of these analyses e.g. stopping boundaries based on α- and β- spending function to maintain trial design error rates are described in the statistical considerations (see section 13.6). The IA will be reviewed by the DMC.

6.4 STUDY COMMITTEES

An Executive Committee will include the Study Chairman, the main investigators and Sponsor representatives and will be responsible for:

- Supervising the progress of the trial towards its overall objectives,
- Reviewing at regular intervals relevant information that may affect the study conduct,
- Discussing the implementation of the recommendations of the independent Data Monitoring Committee.

This committee will have no access to unblinded data.

A Data Monitoring Committee (DMC) consisting of at least 3 external independent members not associated with the conduct of the study or other study committees will meet regularly to:

- Review the progress of the trial,
- Review the unblinded safety data,
- Review unblinded results on OS planned twice during the course of the study (IA),
- Advise the Executive Committee on potential modifications or communications that may be necessary to ensure the patient safety or protect the scientific integrity of the trial

The first safety review of the trial by the DMC will be the earlier of either 6 months after the first patient has been enrolled, or the time 100 patients have been treated with at least 3 cycles. The DMC meeting will be set up semiannually. Ad-hoc DMC meetings may also be held if a significant safety issue or any other issue deemed important for discussion arise, on this or any other studies of aflibercept. After each meeting, the DMC will advise the Executive Committee regarding the patients' safety, as well as the course of action regarding the conduct of the trial.

Two interim analyses of OS are planned to compare efficacy of aflibercept to placebo during the course of the study based on a group sequential approach with efficacy and futility stopping boundaries. The DMC will review the data analyses and meet on these occasions to rule on the conclusions of the interim analyses and provide the Executive committee with their recommendations on continuation of the study.

The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS PLANNED

A total of approximately 1200 MAIPC patients (600 in each arm) will be enrolled and treated in this study. It is planned to recruit this sample from approximately 200 sites within 36 months. No site shall enroll beyond 60 patients without prior written approval from the sponsor. Sponsor approval will be based on both consideration of the potential for statistical analysis impact and the quality of work performed to date by the site as assessed through monitoring and/or auditing. Enrollment will be stopped when the anticipated or actual patient numbers have been achieved across all study sites. No patient may be randomized into the study more than once.

7.2 INCLUSION CRITERIA

Patients meeting all of the following criteria will be considered for enrollment into the study:

1. Histologically- or cytologically-confirmed prostate adenocarcinoma.
2. Metastatic disease.
3. Progressive disease while receiving hormonal therapy or after surgical castration and documented by at least one of the following:
   - Increase in measurable disease (RECIST**),** and/or
   - Appearance of new lesions, including those on bone scan (≥2 new lesions) consistent with progressive prostate cancer, and/or
   - Rising PSA defined as *2 sequential increases* above a previous lowest reference value (see Figure 5); all of those PSA values must be obtained at least 1 week apart and within the past 12 months. A PSA value of at least 2 ng/ml is required at study entry.
4. Effective castration (serum testosterone levels ≤ 50 ng/dL) by orchiectomy and/or LHRH agonists with or without anti-androgens. If the patient has been treated with LHRH agonists (i.e., without orchiectomy), then this therapy should be continued. If patients were either started on complete androgen blockade, or had a PSA response (defined by any reduction in PSA sustained for at least 3 months) after adding an antiandrogen, prior anti-androgen therapy should be stopped before randomization: at least 6 weeks for bicalutamide and nilutamide, and at least 4 weeks for flutamide, megestrol acetate and any other hormonal therapy.

Figure 5 - Defining rising PSA

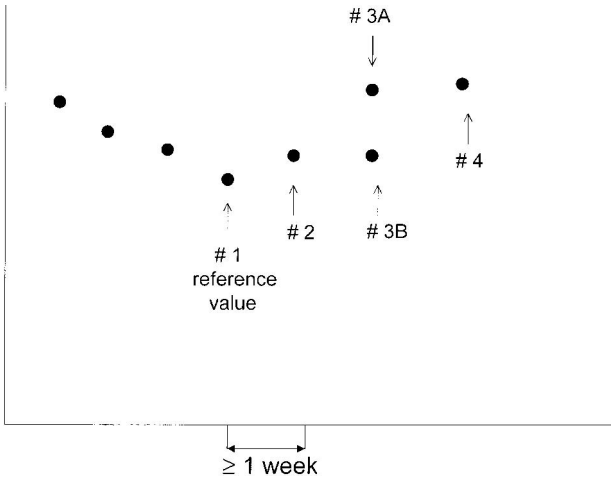


Figure 5 : For defining eligibility [28], the reference value (no. 1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point no. 3 (value no. 3A) is greater than at time point no. 2, then the requirement for a sequence of two increases has been met. If the third value (value #3B) is not greater than value no. 2, but value no. 4 is, then increasing PSA has been confirmed, and the patient can be eligible. In all cases, value no. 3A or no. 4 must be greater than or equal to 2 ng/mL.

7.3 EXCLUSION CRITERIA

Patients presenting with any of the following will not be included in the study:

Related to methodology:

1. Prior cytotoxic chemotherapy for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed > 3 years ago.
2. Less than 28 days elapsed from prior treatment with estramustine, radiotherapy, surgery to the time of randomization. Patients may be on biphosphonates prior to study entry.
5. Prior isotope therapy (e.g., strontium, samarium, etc.), or whole pelvic irradiation, or prior radiotherapy to > 30% of bone marrow (see Appendix G). Prior radiotherapy < 30% of bone marrow that is less than 4 weeks since the completion of radiation therapy. Or if the patient has not recovered from side effects of radiotherapy.
3. Adverse event (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of grade >1(National Cancer Institute Common Terminology Criteria [NCI CTCAE] v3.0) at the time of randomization.
4. Prior treatment with VEGF inhibitors or VEGF receptor inhibitors.
6. Less than 18 years.

7. Eastern Cooperative Oncology Group (ECOG) performance status > 2.
8. History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease.
9. Prior malignancy. Adequately treated basal cell or squamous cell skin cancer are allowed, as well as any other cancer for which chemotherapy has been completed >5 years ago and from which the patient has been disease-free for > 5 years.
10. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.
11. Any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, cerebrovascular accident or transient ischemic attack.
12. Any of the following within 3 months prior to randomization: treatment-resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.
13. Occurrence of deep vein thrombosis within 4 weeks prior to randomization.
14. Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral therapy.
15. Any severe acute or chronic medical condition which could impair the ability of the patient to participate to the study or interfere with interpretation of study results.
16. Absence of signed and dated Institutional Review Board (IRB)-approved patient informed consent form prior to enrollment into the study.
17. Patient with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and for at least 6 months after the completion of the study treatment. The definition of "effective method of contraception" will be based on the investigator's judgment.

    For patients enrolled in the United Kingdom, their partner (unless surgically sterile, post menopausal or for another reason have no chance of becoming pregnant) should use an effective mean of contraception described hereafter: oral contraceptives or intra uterine device.

Related to aflibercept:

18. Urine protein-creatinine ratio (UPCR) > 1 on morning spot urinalysis or proteinuria > 500 mg/24 hours
19. Serum Creatinine > 1.5 x ULN.

If creatinine 1.0 - 1.5 x ULN, creatinine clearance will be calculated either according to Cockcroft-Gault formula for patients younger than 65 years or, according to a MDRD formula for patients ≥ 65 years . Creatinine clearance < 60 mL/min will exclude the patient (see Appendix A for calculation formulas).

20. Uncontrolled hypertension, defined as blood pressure >150/100 mm Hg (NCI CTCAE v.3.0 grade ≥ 2), or systolic blood pressure >180 mm Hg if diastolic blood pressure <90 mm Hg, on at least 2 repeated determinations on separate days, within 3 months prior to randomization.
21. Patients on anticoagulants with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3), within 4 weeks prior to randomization.
22. Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g. INR>1.5 without vitamin K antagonist therapy), non-healing wound.

Related to docetaxel regimen:

23. History of hypersensitivity to docetaxel, or polysorbate 80.
24. Inadequate organ and bone marrow function as evidenced by:
    - Hemoglobin <10.0 g/dL
    - Absolute neutrophil count < 1.5 x 109/L
    - Platelet count < 100 x 109/L
    - AST/SGOT and/or ALT/SGPT > 1.5 x ULN
    - Total bilirubin > 1.0 x ULN
25. Contraindications to the use of corticosteroid treatment.
26. Symptomatic peripheral neuropathy grade > 2 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v3.0).

8 TREATMENTS

8.1 DETAILS OF TREATMENTS

8.1.1 Names and formulations

Study treatment details are summarized in Table 6 below.

Table 6 - Details of treatments

Drug code	**AVE0005**	**Placebo for aflibercept**	**RP56976**	**-**
INN	**aflibercept**	**Not applicable**	**docetaxel**	**prednisone or prednisolone**
Trade name	-	**Not applicable**	**Taxotere®**	**Various**
Formulation	Aflibercept in 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 20% (w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, supplied in sealed, sterile, single-use 5-mL vials containing 4.4-mL in order to withdraw 4 mL aflibercept at a concentration of 25 mg/mL.	Sterile aqueous buffered vehicle pH 6.0, containing 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (w/v) polysorbate 20 and 20% (w/v) sucrose. single-use 5-mL vials containing 4.4-mL in order to withdraw 4 mL placebo at a concentration of 25 mg/mL.	Marketed formulation (refer to the local labeling)	Marketed formulation (refer to the local labeling)
Storage conditions	Aflibercept must be refrigerated at 2–8°C (36-46°F) in a locked area with restricted access and handled in accordance with the manufacturer's instructions.	placebo must be refrigerated at 2–8°C (36-46°F) in a locked area with restricted access and handled in accordance with the manufacturer's instructions.	Store between 2-25°C (36-77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.	Refer to the local labeling.

8.2 INVESTIGATIONAL PRODUCT

8.2.1 Description of aflibercept

Aflibercept is formulated as a sterile liquid to a final concentration of 25 mg/mL. Aflibercept in 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 20% (w/v) sucrose, and 0.1% (w/v) polysorbate 20, pH 6.0, will be supplied in sealed, sterile, single-use 5-mL vials containing 4.4-mL aflibercept in order to withdraw 4.0mL.

8.2.2 Description of placebo

Placebo for aflibercept is formulated in bulk aqueous buffered solution, pH 6.0, containing 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (w/v) polysorbate 20, and 20% (w/v) sucrose, supplied in sealed, sterile, single-use 5-mL vials containing 4.4-mL in order to withdraw 4mL.

8.2.3 Preparation, reconstitution and administration for aflibercept / placebo

Sealed, sterile, single-use 5-mL vials containing 4.4-mL with a withdrawable content of 4.0-mL aflibercept/placebo at a concentration of 25 mg/mL will be supplied by the Sponsor.

Aflibercept/placebo must be diluted in 0.9% NaCl (normal saline) or 5% dextrose prior to IV administration.

The dilution must be carried out under aseptic conditions.

Diluted aflibercept/placebo solution at 0.6 to 8.0 mg/ml can be stored up to 24 hours under refrigerated conditions (2° to 8°C) or for up to 8 hours at ambient temperature (approximately 25°C) in polypropylene syringe or in infusion bags made of the following materials:

- PVC containing DEHP
- Polyolefin (PVC free DEHP free)

Diluted solutions of aflibercept/placebo can be administered using infusion tubing made of the following materials:

- PVC containing DEHP
- DEHP-free PVC containing TOTM
- Polypropylene
- Polyethylene lined PVC

The infusion sets must contain a 0.2 μm polyethersulfone filter.

The research pharmacist or designee at the study site will prepare all aflibercept/placebo infusion solutions according to one of the following 2 methods:

Multiple vials may be required depending on the patient's weight and the intended dose in the preparation of each dose. Patient's weight needs to be reevaluated before each administration.

- Calculate the number of vials needed according to body weight

Either method 1:

- Dilute the entire volume of each vial in the infusion bag of 0.9% NaCl or 5% dextrose in order to obtain the final concentration of the diluted solution ranging between 0.6 to 8.0 mg/ml.
- Retrieve the excess of the diluted solution in order to obtain the exact amount of aflibercept/placebo to be administered to the patient.

Or method 2:

- Withdraw the necessary volume of aflibercept /placebo from each vial.
- Dilute directly into the infusion bag of 0.9% NaCl or 5% dextrose. The final concentration of the diluted solution can range between 0.6 to 8.0 mg/ml.

Infusion can be conducted by gravity or, with an IV infusion pump, or with a syringe pump using administration sets made of above materials.

The infusion should not exceed 2 hours at ambient temperature (approximately 25°C).

8.2.4 Precautions

All drug packages are to be inspected upon receipt at the study site and the individual vials inspected prior to being drawn up. If a vial is chipped or any particulate matter or cloudiness is detected, the vial is not to be used. Cloudy or damaged vials are to be reported to the sponsor and returned to the refrigerator until instructions have been given. As aflibercept is a protein, the study vials are not to be shaken.

Given the investigational nature of the product and to provide the patients with the maximum level of safety in case of an unexpected event, the following requirements must be fulfilled before any administration of the investigational product can start and for a minimum of 1 hour following the completion of the infusion:

1. Immediate access to appropriate resuscitative equipment
2. Appropriately qualified and trained personnel must be on site (see also section 15.1 for delegation of investigator duties)

Aflibercept/placebo should not be administered less than 48 hours following minor surgical procedures (e.g., fine needle biopsy/aspiration, placement of a central venous access device, or removal/biopsy of a skin lesion), or until evidence of wound healing (e.g., scab formation) is observed, whichever is longer. A peripheral venous catheter may be inserted prior to and removed immediately after individual study drug doses, for the purpose of study drug administration.

Infusion and hypersensitivity reactions may occur during or shortly after intravenous administration of protein therapeutics. If infusion or hypersensitivity reactions occur in a given patient, institutional treatment guidelines for similar therapeutic agents or protocol guidelines should be followed (see Table 9). In case of severe reaction, grade ≥ 3, aflibercept/placebo should be permanently discontinued. For grade ≥ 2 events, samples for anti-aflibercept antibodies detection and concomitant pharmacokinetic evaluation should be collected within 2 weeks (see Appendix C for sample collection, handling methods and shipping procedures) and then sampling have to be collected every 2-3 months, for follow-up, up to 6 months from last dose.

8.3 ASSOCIATED PRODUCTS: DOCETAXEL AND PREDNISONE / PREDNISOLONE

Marketed formulation of docetaxel and prednisone or prednisolone will be used.

For docetaxel, refer to the docetaxel package insert or summary of product characteristics for details on description, preparation, administration, and precautions for use.

For dexamethasone (or equivalent), antiemetics premedication, prednisone, and prednisolone, refer to the respective package insert and summary of product characteristics for details on description, administration, and precautions for use.

8.4 DOSAGE SCHEDULE

Patients will be randomly assigned to receive either arm A: Aflibercept or arm B: Placebo. Within 3 days after randomization, patients will receive either aflibercept or placebo, depending on arm assigned. Immediately after, patients will receive docetaxel plus prednisone or prednisolone.

This treatment schedule will be repeated, every 3 weeks.

The treatment should continue for at least 12 weeks in the absence of clinical evidence of disease progression defined in section 9.1.2.1 or unacceptable toxicity or patient refusal of further treatment.

Subsequently, no decision of treatment discontinuation should be made in case of PSA increase ALONE or pain increase ALONE, within the first 12 weeks see section 9.1.2.

8.4.1 Aflibercept/placebo

Aflibercept: 6 mg/kg will be administered IV over 1 hour once on Day 1, every 3 weeks, prepared and administered as described in Section 8.2.3.

Or

Placebo: 6 mg/kg will be administered IV over 1 hour once on Day 1, every 3 weeks, prepared and administered as described in Section 8.2.3.

8.4.2 Docetaxel regimen

8.4.2.1 Treatment

Immediately after aflibercept/placebo administration, all the patients will receive:

Docetaxel: 75 mg/m^2 in 250 mL dextrose 5% or NaCl 0.9% IV over 1 hour, once on Day 1 every 3 weeks.

Plus

Prednisone or prednisolone 5 mg twice daily per oral route, from Day 1, continuously

In case of body surface area (BSA) > 2.2 m² the actual dose of docetaxel should be adjusted to a maximum BSA of 2.2 m², for safety reasons.

BSA will be calculated prior to each treatment cycle from body weight in kg, recorded prior to each treatment cycle, and height in cm, recorded at baseline. The preferred Dubois and Dubois equation is below:

BSA in units of m^2 = wgt. in kg $^{0.425}$ x hgt. in cm $^{0.725}$ x 0.007184

8.4.2.2 Premedication

For docetaxel premedication with oral dexamethasone 8 mg (or equivalent) please refer to details contained in the package insert of docetaxel.

Antiemetic: Appropriate prophylactic antiemetic therapy is left to current hospital practices.

Granulocyte-colony stimulating factor (G-CSF): The use G-CSF is left to the current hospital practices [34].

8.4.3 Schedule modification

For both arms, it is a 3 weekly schedule. Plus or minus 2-day time windows for each treatment day are permitted, as are treatment delays of up to 2 weeks in case of unresolved toxicity. Doses may be modified or infusion delayed for toxicity as described in Section 8.5. New cycles of therapy may not begin until any study drug-related toxicities have been adequately resolved. Study treatment will continue until a definitive treatment discontinuation criterion is met (see section 11.1).

Investigators are encouraged to give a minimum of 4 cycles and to continue for at least 10 cycles, in the absence of major toxicity or disease progression as defined in section 11.1.1.

Details of the exact dose, and time of administration of medication (day/month/year, h:min) and the labeling on the investigational product containers (including batch and/or lot numbers) will be documented in the case report form (CRF). In addition, complete Drug Accountability Records must be maintained at each site.

8.5 DOSAGE MODIFICATION:

Dose adjustment and/or cycle delay are planned in case of toxicity. Dose adjustments will be made according the worst grade of toxicity. Toxicities will be graded according the NCI-CTC AE V. 3.0 scale. Patient will receive the next cycle after recovery of the toxicity.

If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity) should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

No more than 1 dose reduction, as well as no more than 2 weeks delay in infusion of aflibercept/placebo per patient are permitted. Two consecutive omissions are not permitted. Aflibercept/ placebo will be discontinued in patients requiring > 1 dose reduction or 2 consecutive dose omissions of aflibercept/placebo or > 2 weeks delays due to aflibercept/ placebo toxicity. Omission is planned in certain circumstances described in Table 8 and Table 10.

No more than 2 dose reductions as well as no more than 2 weeks delay infusion of docetaxel per patient are permitted. Docetaxel will be discontinued in patients requiring > 2 dose reductions of docetaxel or > 2 weeks delays due to docetaxel toxicity.

- If docetaxel and prednisone/prednisolone are permanently discontinued, then aflibercept / placebo will be continued alone until disease progression or unacceptable toxicity or patient refusal of further treatment. The end of study treatment will be the date of the last aflibercept or placebo administration
- If aflibercept /placebo are permanently discontinued, then docetaxel and prednisone/prednisolone will be continued alone until disease progression or unacceptable toxicity or patient refusal of further treatment. The end of study treatment will be the date of the last docetaxel and prednisone /prednisolone administration.

In both cases the end of the study is death, date of cut off or withdrawal of consent, whichever comes first.

8.5.1 Aflibercept /Placebo

Aflibercept/placebo doses will be modified according to the dose level described in Table 7 below. Only 1 dose reduction is permitted.

Table 7 - Aflibercept /Placebo Dose reduction level

	Initial dose (mg/kg)		Dose reduction 1 (mg/kg)
Aflibercept /Placebo	6	→	3

Actions to be taken for aflibercept/placebo according the type of toxicity are described in Table 8, Table 9, Table 10.

Table 8 - Dose modifications for aflibercept/placebo

Toxicity	Grade	Action to be taken
hypertension	Grade ≤ 2	Initiate antihypertensive drug therapy (see recommendation below) and closely monitor BP for further adjustment of therapy as needed. No dose modification and no delay.
	Grade 3 (requiring more than one drug or more intensive therapy than previously)	Modify antihypertensive drug therapy (see monitoring and recommendation below). Delay the administration of both docetaxel/ prednisone or prednisolone and aflibercept/placebo, for a maximum of 2 weeks, until recovery to BP ≤ 150/100 or to systolic BP < 180 if diastolic BP < 90 for patients with known history of isolated systolic hypertension: • If BP is controlled within 2 weeks delay: -First episode: readminister docetaxel/ prednisone or prednisolone and aflibercept/placebo at the same dose. -Second episode: readminister docetaxel/ prednisone or prednisolone and aflibercept/placebo, with aflibercept/placebo reduced to dose level 1*. - Third episode, discontinue aflibercept/placebo. • If BP is still uncontrolled despite appropriate anti hypertensive treatment and after 2 weeks delay: -administer docetaxel/prednisone or prednisolone alone and omit aflibercept/placebo for 1 cycle. The reintroduction of aflibercept/placebo at a dose reduced to dose level 1* will be reconsidered at the time of the administration of the subsequent cycle (in combination with docetaxel/prednisone or prednisolone), only if BP is controlled at the time of re- administration. • In case of reoccurence of grade 3 BP despite dose reduction of aflibercept/placebo, or if BP is still uncontrolled despite 1 omission of administration of aflibercept/placebo, the patients will be discontinued from aflibercept /placebo. Docetaxel/ prednisone or prednisolone will be continued if the investigator thinks the patient is benefiting from it.
	Grade 4	Consult Cardiologist, and discontinue aflibercept/placebo.

Toxicity	Grade	Action to be taken
arterial thromboembolic events (e.g.: Myocardial infarction, or stroke) **(**Documented by appropriate tests)	Grade 3-4	Discontinue aflibercept/placebo
Hemorrhage [a]	Grade 3-4	Discontinue aflibercept/placebo
GI perforation (see below) **or Fistula**	Any Grade	Discontinue study treatments
Reversible Posterior Leukoencephalopathy syndrome (Documented by appropriate tests see below)	Any Grade	Discontinue study treatments
Venous Thromboembolic Event (Documented by appropriate tests)	Grade 3 (DVT)	First episode: Treat DVT with heparins and Continue study treatment** Second episode despite appropriate anticoagulation: Discontinue aflibercept/placebo
	Grade 4 (PE)	Treat PE and discontinue aflibercept/placebo***

*Dose reduction levels provided in Table 7
** Based on investigator's judgement in assessing potential risk of extension and/or embolization.
*** Discussion with the sponsor if investigator wishes to continue aflibercept/placebo in case of asymptomatic, incidentally discovered PE in a patient with a US evidence of DVT
[a] In case of grade 3 hemorrhage, continuation of aflibercept/placebo may be considered depending on individual Benefit/Risk assessment.

Hypertension therapy recommendations:

BP will be measured and recorded before each treatment cycle and once between 2 treatment visit (preferably during week 2), refer to Table 8 and associated recommendations.

- *For patients without prior antihypertensive therapy*, the initiation of calcium-channel blockers should be considered as a first-intent treatment.Ultimately, antihypertensive treatment must be individualized based on the presence of comorbidity such as diabetes, cardiovascular or renal disease. In addition, oral and/or intravenous sodium intake should be carefully monitored in these patients. BP will be closely monitored for further adjustement in therapy as needed (in between scheduled treatment visit).
- *For patients already under anti-hypertensive therapy*, efforts should be done to optimize (in between scheduled treatment visit the existing therapy before adding other agents as required to control the blood pressure. BP will be closely monitored for further adjustement in therapy as needed (in between scheduled treatment visit, as medically necessary).

When hypertension is accompanied by signs or symptoms of end organ damage such as hypertensive retinopathy, kidney function abnormalities (like progressive proteinuria), or any signs or symptoms of cardiovascular or central nervous system morbidity, treatment with aflibercept/placebo should be interrupted.

Hypersensitivity reaction

In case of hypersensitivity reaction, institutional treatment guidelines for this type of adverse event, or the following proposed guideline in Table 9 can be applied. Venous blood samples for anti- aflibercept antibody measurements and for pharmacokinetics measurements should be collected in any patient developping grade ≥ 2 systemic immunologic adverse event considered at least possibly related to study drug.

Adverse event driven evaluations:

In addition to the per protocol prospectively scheduled immunogenicity evaluations, patients will be sampled for both anti-aflibercept antibody detection and pharmacokinetics in a symptom driven manner when the occurrence of antibodies is suspected.

Patients experiencing infusion related reactions Grade ≥2 will be sampled for anti-aflibercept antibodies detection and pharmacokinetics within a maximum of 2 weeks following the occurrence of the event, then every 2-3 months for follow up, up to 6 months from last aflibercept/placebo dose.

Table 9 - Acute infusion reaction management

Symptom Severity	Intervention Recommendation
Mild-Moderate e.g., NCI CTCAE grade ≤ 2 cutaneous reaction, pruritus, flushing, rash, dyspnea, tachycardia, hypotension, anxiety, headache, myalgias, edema, nausea	Stop aflibercept/placebo infusion; Give diphenhydramine 50 mg IV and/or IV dexamethasone 10 mg; For Gr 2: Collect blood sample for detection of anti-aflibercept antibodies and for pharmacokinetics measurements within a maximum of 2 weeks, and then every 2-3 months for follow up, up to 6 months **from last aflibercept/placebo dose**. Resume aflibercept/placebo infusion after subject recovery.
Severe e.g., symptomatic bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema, anaphylaxis	Stop aflibercept/placebo infusion; Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg and/or epinephrine as needed; Collect blood sample for detection of anti-aflibercept antibodies and for pharmacokinetics measurements within a maximum of 2 weeks, and then every 2-3 months for follow up, **up to 6 months from last aflibercept/placebo dose**. Withdraw from aflibercept/placebo.

Proteinuria:

Determination and management of proteinuria:

Prior to administration of aflibercept /placebo, perform an UPCR and dipstick.

Urinary protein creatinine ratio (UPCR) corresponds to the ratio of urinary total protein and urinary creatinine concentrations (both expressed in mg/dL). There is a high correlation between morning UPCR and 24-hour proteinuria in patients with normal or reduced renal function, UPCR demonstrated very good to excellent performance for the diagnosis of both abnormal and nephrotic proteinuria at all renal function levels. This ratio provides an accurate quantification of 24-hours urinary protein excretion [37].

UPCR to detect proteinuria, will be done on morning urine spot. If UPCR > 1, 24-hour urine collection to grade proteinuria will be performed. Then, please follow the proteinuria management described in Table 10.

The clinical work up to rule-out thrombotic microangiopathy may include the following tests: LDH, haptoglobin, schistocytes and orosomucoïd (if available) will be measured in blood and a medical consultation with a nephrologist should be considered as detailed in Table 10 and should not be delayed by the availibility of part of the results.

Proteinuria should always be assessed taking into account the presence or absence of hematuria and the blood pressure status of the patient.

Actions to be taken are described in Table 10:

Adverse event driven evaluations:

In addition to the per protocol prospectively scheduled immunogenicity evaluations, patients will be sampled for both anti-aflibercept antibody detection and pharmacokinetics in a symptom driven manner when the occurrence of antibodies is suspected.

Patients experiencing patients reporting proteinuria >3.5 g/24h, or protenuria of renal origin associated with hematuria will be sampled for anti-aflibercept antibodies detection and pharmacokinetics within a maximum of 2 weeks following the occurrence of the event, then every 2-3 months for follow up, up to 6 months from last aflibercept/placebo dose.

Table 10 - Proteinuria management

	Cycle n	24h -Proteinuria performed on D1 of cycle n	24h -Proteinuria performed within cycle n	Cycle n+1	24h-Proteinuria prior Cycle n+2	Cycle n+2
If **UPCR [0-1]**	Aflibercept/placebo: same dose Docetaxel: same dose	-				
If **UPCR]1-2]** without **Hematuria**	**Administer** the cycle with no delay Aflibercept/placebo: same dose Docetaxel: same dose then **Perform** 24h urine collection to assess the proteinuria rate and urinary protein electrophoresis . 24h proteinuria will be repeated weekly	≤ 3.5g [Gr1 or 2]	If Proteinuria return to ≤ 2g within 2 weeks	Aflibercept: same dose Docetaxel: same dose		
			If Proteinuria return to ≤ 2g between 2-3 weeks	Aflibercept/placebo: dose level 1* Docetaxel: same dose		
			If Proteinuria >2g – ≤ 3.5g	Omit Aflibercept/placebo Docetaxel: same dose	> 2g	Stop Aflibercept/placebo Docetaxel: same dose
					≤ 2g	Aflibercept/placebo: dose level 1* Docetaxel: same dose
			If Proteinuria ≤ 2g	Aflibercept/placebo: dose level 1* Docetaxel: same dose		
		> 3.5 g [Gr3] **	If Proteinuria >2g – ≤ 3.5g	Omit Aflibercept/placebo Docetaxel: same dose	> 2g	Stop Aflibercept/placebo Docetaxel: same dose
					≤ 2g	Aflibercept/placebo: dose level 1* Docetaxel: same dose
			If Proteinuria >3.5 g	Discontinue Aflibercept/placebo Docetaxel: same dose		

* Dose reduction levels provided in Table 7
**detection of anti aflibercept antibodies and pharmacokinetics measurements

Proteinuria management (to be continued)

	24h -Proteinuria value	Cycle n	24h -Proteinuria at the time of administration of cycle n+1	Cycle n+1	24h-Proteinuria prior Cycle n+2	Cycle n+2
If **UPCR > 2** or If **UPCR]1-2]** With **Hematuria**	If TMA is ruled out and If Proteinuria return to ≤2g within 2 weeks	When proteinuria return to ≤ 2 g administer: Aflibercept/placebo: same dose Docetaxel: same dose				
then **Delay** cycle n for a maximum of 2 weeks and **Perform** Biological work-up** and **Perform** 24h urine collection to assess the rate of proteinuria and urinary protein electrophoresis . 24h proteinuria will be repeated weekly	If TMA is ruled out and If Proteinuria > 2g after 2 weeks delay	Omit Aflibercept/placebo Docetaxel: same dose	≤ 2g	Aflibercept/placebo: dose level 1* Docetaxel: same dose		
			> 2g	Stop Aflibercept/placebo: Docetaxel: same dose		
and **Nephrologist** consultation	If TMA is diagnosed Or nephrotic syndrome [gr4]	Discontinue Aflibercept/placebo Administer docetaxel as appropriate with a delay ≤ 3 weeks upon nephrologist advice				

* Dose reduction levels provided in Table 7
** Perfom: urinary protein electrophoresis & 24H urine collection to assess proteinuria rate & collect blood samples for haptoglobin + orosomucoid + schistocytes + LDH + detection of anti aflibercept antibodies and pharmacokinetics measurements

Gastro-intestinal Perforation: If a patient develops new or increase in severity of abdominal pain, with or without accompanying symptoms such as: vomiting, nausea and constipation the patient should be evaluated by a physician for possible gastro intestinal perforation. This has been reported with anti-VEGF agents.

Reversible posterior leuko-encephalopathy (RPLS) or clinical symptoms related to vasogenic edema of the white matter: Clinical presentations are variable and may include headache, altered mental status, seizure and cortical visual deficit. Hypertension is a risk factor. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypodensity in T1 images) predominently in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure, or other CNS findings. RPLS is potentially reversible with early recognition of symptoms and timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, which are important in order to prevent progression to irreversible tissue damage.

Osteonecrosis of the jaw (ONJ) is the death of bone as a result of decreased vascular supply. In particular, ONJ has been reported in cancer patients with the use of biphosphonates, biphosphonates + anti- angiogenic agents , and antiangiogenics agents alone. Dental procedures such as tooth extraction or dental implant insertion may precipitate ONJ. Symptoms include, but are not limited to: pain, swelling, or infection of the gums or jaw, gums that are not healing, loose teeth, numbness or a feeling of heaviness in the jaw, drainage, exposed bone. So good oral hygiene and regular monitoring is recommended. Patients, should not undergo invasive dental procedures while receiving Aflibercept/Placebo without first consulting with the investigator. If osteonecrosis develops, Afibercept/Placebo should be permanently discontinued and the patient referred to an oral surgery specialist for further management.

8.5.2 Docetaxel

Patients will be monitored closely for toxicity. In addition to optimizing supportive care as described in Section 8.13, docetaxel dosages may be adjusted after the first cycle of therapy according to Table 11. Further dosing is acceptable only if the patient has recovered to grade ≤ 1, provided that definitive treatment discontinuation criteria described in Section 11.1.1 have not been met.

Table 11 - Docetaxel dose reduction levels

	Initial dose (mg/m²)		Dose reduction 1		Dose Reduction 2
Docetaxel	75	→	60	→	45

Modifications for docetaxel are based on the last prior date of docetaxel administration. For example, a dose delay of up to 2 weeks refers to a dose delay of up to 2 weeks since the last prior date of docetaxel administration.

Both Table 12 and Table 13 describe recommended chemotherapy dose modifications on Day 1 of a new cycle based on the worst toxicity encountered during the previous cycle:

In case of fever during any cycle, perform blood count, prescribe antibiotherapy and apply dose modification.

Table 12 - Chemotherapy dose modifications for hematologic toxicity*

Hematologic Toxicity	Grade 3	Grade 4
Neutropenia. If duration ≥ 7 days, or if complicated by T ≥ 38.5°C, or T ≥ 38.1°C x 3 during a 24-hour period, or infection	Delay** infusion until ANC ≥ 1.5 x 10^9/L: 1st episode: administer prophylactic treatment with GCSF in subsequent cycles 2rd episode: Reduce docetaxel by 1 dose level 3rd episode: Reduce docetaxel by a second dose level 4th episode: Discontinue docetaxel	
Thrombocytopenia	Delay** infusion until platelets ≥ 75 x 10^9/L. No dose reduction is required	Delay** infusion until platelets ≥ 75 x 10^9/L and reduce docetaxel by 1 dose level. Discontinue docetaxel in case of recurrence.

*Dose reduction levels provided in Table 11
**Delay infusion by maximum of 2 weeks until recovery to grade ≤ 1 (repeat blood count every 2 days) and apply dose reduction according to worst grade observed. Other wise docetaxel will be permanentely discontinued.

Table 13 - Chemotherapy dose modifications for non-hematologic toxicity*

Non-hematologic toxicity§	Grade 2	Grade 3	Grade 4
Diarrhea	No dose reduction required	1st episode: Reduce docetaxel by 1 dose level 2nd episode: Reduce docetaxel by a second dose level 3rd episode: Discontinue docetaxel	
Stomatitis	No dose reduction required	1st episode: Reduce docetaxel by 1 dose level 2nd episode: Reduce docetaxel by a second dose level 3rd episode: Discontinue docetaxel	
Cutaneous Reactions	No dose reduction required	1st episode: Reduce docetaxel by 1 dose level 2nd episode: Discontinue docetaxel	Discontinue docetaxel
Peripheral Neuropathy	Reduce docetaxel by 1 dose level	Discontinue docetaxel	
Ototoxicity	No dose reduction required	Discontinue docetaxel	
Transaminase and Alkaline Phosphatase Elevation	Reduce docetaxel by 1 dose level	Discontinue docetaxel	

§ Delay infusion by a maximum of 2 weeks until recovery to grade ≤ 1 and apply dose reduction according to worst grade observed. Other wise docetaxel will be permanentely discontinued
* Dose reduction levels provided in Table 11.

No dose reduction is allowed for abnormal bilirubin levels (> 1.0 x ULN) during the study, but the next cycle will be delayed by a maximum of 2 weeks until bilirubin levels ≤ 1.0 x ULN.

Hypersensitivity reaction to docetaxel

Refer to Table 14 or the institutional guidelines to manage this kind of toxicity.

Table 14 - Treatment recommendation for hypersensitivity reactions to docetaxel

Severity and symptoms	Treatment recommendations
Mild symptoms: localized cutaneous reactions, e.g., pruritus, flushing, rash	- Decrease the rate of infusion until recovery of symptoms, stay at bedside. - Then, complete docetaxel infusion at the initial planned rate. At subsequent cycles use the same corticosteroid premedication outlined in package insert.
Moderate symptoms: any symptom not listed above (mild symptoms) or below (severe symptoms), such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg	- Stop docetaxel infusion. - Give IV antihistamine and IV corticosteroids[a]. - Resume docetaxel infusion after recovery of symptoms. At subsequent cycles, antihistamines[a] and steroids[a] are to be given IV, 1 h before infusion, in addition to the corticosteroid premedication planned in package insert
Severe symptoms: such as bronchospasm, generalized urticaria, hypotension with systolic BP ≤80 mmHg, angioedema	- Stop docetaxel infusion. - Give IV antihistamine and steroids[a]. - Add epinephrine[b] or bronchodilators and/or IV fluids macro-molecules if indicated. - Once all signs and/or symptoms of HSR disappear, docetaxel may be re-infused within 24 h from the interruption, if medically appropriate, and whenever possible. Premedication regimen as described in package insert is only recommended when docetaxel is re-infused more than 3 h after the interruption. At the subsequent cycles, dexamethasone is to be given at 20 mg orally 24, 18, 13, 7, and 1 h before docetaxel infusion. Additionally diphenhydramine (or equivalent) is to be given at 50 mg i.v. 1 h before Docetaxel infusion. If a severe reaction recurs, discontinue docetaxel.

[a] Antihistamines: dexchlorpheniramine intravenous. 5-10 mg, or clemastine intravenous 2 mg, or diphenhydramine intravenous 25-50 mg, or promethazine intramuscular 50-100 mg; Corticosteroids: dexamethasone or equivalent, intravenous 5-10 mg of dexamethasone.

[b] Epinephrine: administered at a 1:1000 dilution (0.01 mL per kg with a maximum dose of 0.5 mL subcutaneously repeated every 20 min as necessary).

mmHg = millimeters of mercury; BP = Blood pressure; IV = Intravenous; h = Hour; i.m. = Intramuscular; HSR = Hypersentivity reaction

8.5.3 Prednisone or prednisolone

Prednisone or prednisolone doses should not be delayed or modified or stopped (unless there is a contraindication to continue, the decision will be let to the investigator's discretion).

If prednisone or prednisolone is stopped, the patient will be still treated in the study.

8.5.4 Other toxic effects

Any other dose reductions in study treatment that are not described above may be performed at the discretion of the investigator, provided that criteria for patient withdrawal from study treatment described in Section 11.1 have not been met. Study treatment should be held for a maximum of two weeks from the planned date of reinfusion until resolution to ≤ grade 1, then reinstituted, if medically appropriate. A modification of subsequent doses will be considered. These patients will be withdrawn from study treatment if >2 dose reductions for docetaxel, or >1 dose reduction or 2 consecutive omissions for aflibercept/placebo are needed.

8.6 DESCRIPTION OF BLINDING METHODS

Aflibercept and placebo are indistinguishable as described in section 8.1.1.

Please refer also to Section 8.10, and 9.4.

8.7 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Treatment allocation will be performed centrally via an Interactive Voice Response System (IVRS), using a permuted-block randomization according to baseline ECOG Performance status (0-1 vs 2). All eligible patients will be randomly assigned to either the control arm or the experimental arm in a 1:1 proportion.

Once the informed consent signed and after each patient has completed the necessary baseline procedures and the patient is deemed eligible for study entry by the investigator or designee, the study site will contact the IVRS. The site will need to enter the following information regarding the clinical site and study patient:

- Personal identifier number,
- Patients's date of birth,
- Current ECOG performance status,
- Intended total dose of aflibercept/placebo, in mg.

The information above will be used to identify the study treatment arm assigned for the patient according to the predifined randomization schedule in blinded fashion by assigning the patient a randomized treatment number corresponding to specific kit number(s) available at the study site containing either aflibercept or placebo.

Details of the IVRS procedure will be provided in the IVRS Site Manual.

Study treatment should begin within 3 days after randomization.

The investigational product will be administered only to patients included in this study following the procedures set out in this clinical trial protocol. Patients withdrawn from the study retain their patient number, and new patients must always be allotted a new patient number.

Before each dose of investigational product during the treatment period, the IVRS will need to be accessed again, giving the personnal identifier number, 9-digit number patient (3-digit country, 3-digit centre, 3-digit patient), patient's date of birth, intented total dose of aflibercept/placebo in mg, in order to receive another kit number(s) containing the same investigational product as the one assigned at randomization.

8.8 PACKAGING AND LABELING

Please also refer to Section 9.4.

This is a double-blind study.

Aflibercept or placebo vials will be supplied in identical boxes corresponding to patient kits. Each kit will be labeled with a unique kit number.

Before each cycle, the IVRS will be accessed and patients will be assigned, depending on his intended total dose (mg) 1 or 2 kits numbers corresponding to 1 or 2 boxes available on site.

8.8.1 Aflibercept or Placebo

Aflibercept or placebo (as described in Section 8.1.1) will be packaged by the Sponsor or an approved contractor, in sealed, sterile, single-use vials. The vials containing aflibercept or placebo will be labeled in accordance with the local regulatory specifications. Batch number and quantity of the products dispensed to the patient will be recorded by the investigator or pharmacist to allow drug accountability.

8.8.2 Prednisone or prednisolone

Commercially available prednisone or prednisolone will be used. Batch number and quantity of the products dispensed to the patient will be recorded by the investigator or pharmacist to allow drug accountability.

8.8.3 Docetaxel (Taxotere®)

Commercially available docetaxel will be used. Batch number and quantity of the products dispensed to the patient will be recorded by the investigator or pharmacist to allow drug accountability.

8.9 STORAGE CONDITIONS

Aflibercept / placebo must be refrigerated at 2 - 8°C (36 - 46°F) in a locked area with restricted access and handled in accordance with the manufacturer's instructions.

For docetaxel, prednisone or prednisolone, refer to the respective package insert or summary of product characteristics.

8.10 ACCESS TO THE RANDOMIZATION CODE DURING THE STUDY

Please refer to Section 9.4 - Measures to protect the blinding of the trial.

The investigational products will be administered only to patients included in this study following the procedures set out in this clinical trial protocol. Patients withdrawn from the study retain their subject number, and new patients must always be allotted a new subject number.

Only in exceptional circumstances, when knowledge of the Investigational Product is essential for treating the patient, the code can be broken by the investigator. If possible, a contact should be initiated with the Monitoring Team before breaking the code.

The IVRS center should be called if code-breaking is necessary. Only if this fails, code-breaking material can be opened.

For each patient, code-breaking material is supplied, containing the name of the treatment. Each treatment box will be labeled with a 3-panel label. The third panel, which is masked by a scratch off laminate, contains emergency and treatment (aflibercept or placebo) information. It will be kept in a safe place on site throughout the Clinical Trial. The Sponsor will retrieve all code-breaking material (opened or sealed) on completion of the Clinical Trial.

If the blind is broken, the Investigator will document the date, time of day, and reason for code breaking in the CRF, and the patient will discontinue permanently the investigationnal product (see section 11.1.1).

8.11 RESPONSIBILITIES

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense aflibercept/placebo will be responsible for ensuring that aflibercept/placebo used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All aflibercept/placebo shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of aflibercept/placebo issued and returned is maintained.

Any quality issue noticed with the receipt or use of aflibercept/placebo (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply aflibercept/placebo to a third party, allow the aflibercept/placebo to be used other than as directed by this Clinical Trial Protocol, or dispose of aflibercept/placebo in any other manner.

8.12 RETRIEVAL AND/OR DESTRUCTION OF TREATMENTS

All unused, partially used or used treatment vials (aflibercept/placebo and/or docetaxel) will be destroyed by the study site after an accurate accountability has been performed and signed by the investigator.

A detailed treatment log of the Investigational Product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the vials of aflibercept/placebo unless the Sponsor provides written authorization.

A potential defect in the quality of aflibercept/placebo may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall aflibercept/placebo and eliminate potential hazards.

8.13 CONCOMITANT TREATMENT

All treatments being taken by the patient on entry to the study or at any time during the study in addition to the study treatments are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF (as defined in the flowchart section 1.2).

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the investigator and recorded in the CRF.

The following concomitant treatments are permitted during this study treatment:

- LHRH agonists or antagonists
- All supportive measures (including blood transfusions and erythropoietin) consistent with optimal patient care will be given throughout the study and should be documented in the CRF.
- Therapeutic or secondary prophylactic use of hematopoietic growth factors may be given at the investigator’s discretion and should follow American Society of Clinical Oncology guidelines for their use [34].
- Antihypertensive medications are permitted as described in Section 8.5.1.

- Bisphosphonates: Ongoing treatment at study entry are permitted. No initiation of new treatment, and no modification/ or adaptation of the dose (except if this change is related to a toxicity) is allowed during the study period.
- Antiemetic and corticosteroid medication before docetaxel treatment must be administered. The addition of a benzodiazepine, e.g., lorazepam IV or orally, may also be considered if clinically indicated.
- Medications for chronic pain management, including narcotic analgesics, are permitted as clinically indicated.
- Heparins medications are permitted as clinically indicated.

The following concomitant treatments must be used with caution during this study treatment:

- Vitamin K antagonists.

The following concomitant treatments are not permitted during this study treatment:

- Concomitant anticancer therapies, investigational therapies and investigational devices.
- Concomitant radiotherapy.

Patients taking any of the above prohibited concomitant medications or treatments at the time of baseline visit will be ineligible to enter the study until administration of the prohibited agent can be safely discontinued and an appropriate period of time has elapsed as per inclusion/ exclusion criteria to permit dissipation of any clinical effects of the drug.

If a patient's clinical status requires administration of a prohibited concomitant medication or treatment, then administration of study drug should be stopped, and the patient will be withdrawn from the study treatment. The change in clinical status mandating the use of the medication in question must be reported as the reason for study drug discontinuation.

8.14 POST-STUDY TREATMENT

Patients will continue to be treated as long as they are benefiting from study treatment and have not met definitive treatment discontinuation criteria as defined in Section 11.1.

After withdrawal from study treatment, further treatment, if any, is at the discretion of the investigator. Please note that in the absence of documented progressive disease, patients should be followed every 12 weeks until progression or study cutoff date, whichever comes first. Then, all patients will be followed for survival and vital status information will be collected at 3 months intervals until death or the study cutoff date, whichever comes first.

8.15 TREATMENT ACCOUNTABILITY AND COMPLIANCE

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product (aflibercept/placebo). The investigational product (aflibercept/placebo) must be kept in a locked area with restricted access. The investigational product (aflibercept/placebo) must be stored and handled in accordance with the manufacturer's instructions.

Administration of the study drugs will be supervised by the investigator or subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of all study drugs. The labels of the aflibercept/placebo vials administered or dispensed to patients must be completed (patient number, and date of infusion, respectively). The packaging reference of investigational drug (aflibercept/placebo) and the lot number of docetaxel and prednisone or prednisolone must be recorded in the CRF/drug accountability form, as well as the total number of vials (docetaxel) or tablets (prednisone/prednisolone) per cycle.

The person responsible for drug administration to the patient will record precisely the date when the drug is administered to the patient. Interruption of the 1-hour aflibercept/placebo infusion or 1-hour infusion of docetaxel or of the prednisone or prednisolone will be recorded in the CRF.

The study monitor will periodically check the supplies of investigational product held by the investigator or pharmacist to verify accountability of all investigational product used. All unused investigational product and all medication containers will be returned to the sponsor unless other arrangements have been approved by the sponsor. The sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file.

9 ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 EFFICACY

9.1.1 Primary criteria

The primary endpoint is overall survival (OS) defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

Overall survival will be evaluated by collecting vital status information at 3 months intervals until death or the study cutoff date, whichever comes first.

9.1.2 Secondary criteria

The secondary efficacy parameters will be assessed as follows:

9.1.2.1 Progression Free Survival endpoint

Progression free survival (PFS) will be evaluated from the date of randomization to the date of disease progression or death due to any cause.

Disease progression is defined as the time of occurrence of the first documented among the following events:

- Radiological tumor progression on CT scan and /or X-ray ± MRI (RECIST).
- Occurrence of at least 2 new bone lesions, confirmed 6 weeks later by a bone scan showing at least 2 additional lesions.
- PSA progression (as defined in section 9.1.2.3)
- Pain progression (as defined in section 9.1.2.2)
- Radiotherapy for cancer related symptoms
- Occurrence of skeletal related events (SRE) (as defined in section 9.1.2.4)

9.1.2.2 Pain endpoints

Diaries will be utilized to collect analgesic consumption and pain scores in all patients (see Appendix F and Appendix H). The Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire will be utilized to assess pain [30]. Pain scores (AS and PPI) will be assessed in all patients at baseline, before each cycle, at the end of treatment and then every 3 weeks until pain progression is documented as defined below or study cut off, whichever comes first.

- Pain response is defined as a 2-point or greater reduction from baseline in median PPI score with no concomitant increase in AS, or a reduction of at least 50% in analgesic use from baseline mean AS (only in subjects with baseline mean AS ≥10) with no concomitant increase in pain. Either criterion has to be maintained for two consecutive evaluations at least 3 weeks apart. Pain response will be calculated among patients with baseline median present pain intensity score (PPI) ≥ 2 on the McGill-Melzack scale and/or baseline mean analgesic score (AS) ≥ 10 points and with stable analgesia at baseline. Stable analgesia will be derived from the 7-day baseline pain diary an defined as:
  - No change by more than one point in the daily PPI scores recorded over 7 consecutive days (data required for a minimum of 5/7 days)with an identical PPI score for the two last days and
  - No variation of the daily analgesic scores (AS) by more than 25% around the mean AS, i.e. the 7 daily AS should be within the range of values defined below:
    - the lowest value should be ≥ mean AS -25% mean AS.
    - the highest value should be ≤ mean AS +25% mean AS.

Increases in pain during the first 12 weeks should be ignored in determining pain response.

Pain progression, in patients with no pain or stable pain at baseline, is defined as an increase in the median PPI score of at least 1 point from the nadir, or an increase from baseline of at least 25% in the mean AS score, **due to cancer related pain**, confirmed by a second assessment at least 3 weeks later, or a requirement for palliative radiotherapy.

Early rise in pain (within the first 12 weeks) only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in pain beyond that time point or if it was associated with another sign of disease progression.

Pain progression-free survival is defined as the time interval between the date of randomization and the date of either first documented pain progression or death due to any cause, whichever is earlier.

9.1.2.3 PSA-derived endpoints

PSA-derived efficacy endpoints in this study will include PSA response and PSA progression-free survival. For each patient, PSA will be assessed at baseline, every 3 weeks until PSA progression as defined below or study cut off, whichever comes first. Two PSA determinations are needed to define PSA progression.

PSA response defined as a decline of serum PSA from baseline of ≥ 50% confirmed at least 3 weeks later. It will be calculated among patients with a baseline PSA≥ 10ng/mL. Increases (of any magnitude) in PSA during the first 12 weeks should be ignored in determining PSA response**.**

PSA progression, is defined as:

- An increase of 25% above the nadir (at least 2 ng/ml), confirmed by a second PSA value at least 3 weeks apart, in patients who have achieved a ≥ 50% decline of PSA.
- As an increase in PSA by 25 % above the baseline level (at least 2 ng/ml), confirmed by a second PSA value at least 3 weeks apart, in patients who have not achieved a ≥ 50% decline of PSA.

Early rise in PSA only indicates progression if it is associated with another sign of disease progression or if it continues beyond 12 weeks. Progression will only be dated prior to 12 weeks if there is continued increase in PSA beyond that time point or if it was associated with another sign of disease progression.

PSA progression-free survival defined as the time interval between the date of randomization and the date of either first documented PSA progression or death due to any cause, whichever is earlier.

9.1.2.4 Tumor-based and skeletal events endpoints

Tumor assessment will be performed by radiological evaluations.

For each patient, tumor assessments including bone scan will be performed at baseline,every 12 weeks or at any time in case of clinical suspicion of progression during study treatment, then at the end of study treatment (30 days after the last infusion) and then every 12 weeks until tumor progression is documented as defined below.

These evaluations will include thoracoabdominopelvic CT scan and bone scan. Other radiological evaluations may include bone-centered X-ray ± MRI, especially in case of a new lesions identified on bone scan.

Bone scan and chest/abdomen/pelvic CT scan or MRI will be carried out according to standard operating procedures by the respective laboratories or imaging centers.

SRE assessment will be performed by clinical evaluation.

Occurrence of SRE is defined as:

- Pathological fractures and / or spinal cord compression,
- Need for bone irradiation, including radioisotopes or bone surgery,
- Change of antineoplastic therapy (including introduction of biphosphonates in the face of increase in pain) to treat bone pain.

Tumor response defined as either a partial response (PR) or complete response (CR) according to the RECIST criteria (see Appendix B).

Tumor progression defined as:

- For measurable disease / Target lesions: Progression (PD) is defined according to RECIST
- For non-measurable disease/non-target lesions: Progressive Disease (PD) will be defined by any of the following:
  - When bone scan is the sole criterion to qualify progression:
    - Worsening bone scan as evidenced by the appearance of at least 2 new lesions not felt to be consistent with a tumor flare confirmed 6 weeks later by bone scan and at least the appearance of 2 new additional lesions.
    - Worsening of preexisting lesions (increase in intensity or size of a lesion) may be difficult to interpret, and therefore will not be considered evidence of PD ;

    Or

    - Appearance of new metastatic lesions outside the bone ;

    Or

    - Unequivocal progression of existing non-target lesions; Because a clear progression of "non-target" lesions only is exceptional, such circumstances should be discussed with the study chair.

9.1.2.5 Health-related quality of life outcomes

Health related quality of life evaluation will be performed using the "Functional Assessment of Cancer Therapy-Prostate" (FACT-P) questionnaire, version 4 (Appendix J) [42,43], a disease-specific instrument that measures the concerns of patients with prostate cancer. Data will be collected in a patient booklet separated from the CRF.

Instrument description

The FACT-P scale, developed by Cella et al. [40], consists of 5 (4 core + additional concerns) subscales:

- physical well-being (PWB): 7 questions
- social/family well-being (SWB): 7 questions
- emotional well-being (EWB): 6 questions
- functional well-being (FWB): 7 questions
- prostate-specific concerns (PSC): 12 questions

The FACT-P is summed to give a score in the range of 0-156, where higher values represent better HRQL.

The core questionnaire and prostate modules have been tested for reliability and validity [40,41] It will be assessed in countries where the questionnaire is available in the local language. Health Related-Quality of life is to be evaluated in a longitudinal design in all patients entered in the study. Questionnaires will be self-administered and takes approximately 10 minutes to complete. The recall period for this questionnaire is one week (7 days).

Timing of Assessment

Baseline assessment should be obtained from all patients. The questionnaire will be administered within 3 days prior to first infusion, but in any case before the patient is given the first dose. While on treatment, assessments should occur every 3 weeks, before administration of the treatment and at the end of treatment. During follow-up period, assessments will be performed every 3 weeks until disease progression or administration of further antitumor therapy, whichever comes first.

Questionnaires should be filled in at the center, at each cycle, prior to informing the patient about disease evolution and before the next infusion. It is mandatory that a key person (e.g., research nurse) at each center be responsible for questionnaire data collection, in order to optimize compliance of the patient and to ensure completeness of the data.

Health-Related Quality of Life (HRQL) will be assessed using the changes from baseline in score derived from the FACT P and its Trial outcome Index (TOI). The TOI combines the physical (7 items) functional (7items) and prostate specific concern (12 items).

A HRQL analysis will be detailed in the SAP.

9.1.2.6 Pharmacokinetics and anti aflibercept antibodies

See details in section 9.3

9.2 SAFETY

Adverse event data will be collected by reporting at specified intervals throughout the study (see Sections 1.2 and 10.2.1). The results of weight, performance status and blood pressure will be recorded in the case report forms. Laboratory safety studies will be carried out according to standard operating procedures by the local laboratory. Abnormal, clinically significant results will be verified to rule out laboratory error. Persistent relevant abnormal values must be followed up until the cause is determined or until they return to the baseline value.

The study-specific and general safety criteria are developed in Section 10.1.

9.3 PHARMACOKINETICS AND IMMUNOGENICITY (IN SELECTED CENTERS)

Pharmacokinetics and immunogenicity evaluation are intended to be performed in all patients entered in selected centers.

Peak and trough levels of free and bound aflibercept will be measured and will permit to better understand the mechanism of action of aflibercept.

Free and bound aflibercept will be measured by validated ELISA methods. The ratio free aflibercept / bound aflibercept will be also estimated as an indicator of the presence of circulating endogenous VEGF.

Immunogenicity will be explored after exposure to aflibercept.

Venous blood samples for pharmacokinetic analysis and anti-aflibercept antibody measurements will be performed in approximately 300 patients.

In addition the impact of docetaxel/prednisone on the pharmacokinetics of aflibercept will be evaluated by estimating the clearance of free aflibercept(see section 13.4.6).

9.3.1 Sampling time and size

Plasma free and bound aflibercept concentrations will be estimated before the start and at the end of the first infusion (cycle 1) of aflibercept/placebo and then immediately prior to infusion of each every other cycle and then approximately 30 days and finally approximately 90 days after last dose of aflibercept/placebo administration and in the circumstances of specific adverse events**: adverse event driven evaluation (see section 8.5.1).**

Citrated plasma for measurement of endogeneous VEGF level, **4ml of whole blood** will be colleted before the start of the first infusion (cycle 1) **of aflibercept /placebo (only when equipment for sample preparation is available on site, i.e. 4°C centrifuge).**

Serum for detection of anti- aflibercept antibody will be collected at baseline (predose cycle 1), prior to infusion of study treatment of each every other cycle, then 30 days and finally 90 days after last dose of aflibercept /placebo administration, and in the circumstances of specific adverse events: **adverse event driven evaluation** (see section 8.5.1).

In case of adverse event driven evaluation, the first evaluation sampling (sampling for anti aflibercept antibodies and circulating free and bound aflibercept) will be done within 2 weeks following the occurrence of the event (when this timepoint is not covered with the prospective evaluation). Follow up will be prolonged up to 6 months following discontinuation of aflibercept/placebo with sampling repeated every 2-3 months.

Figure 6 - PK sampling during study treatment

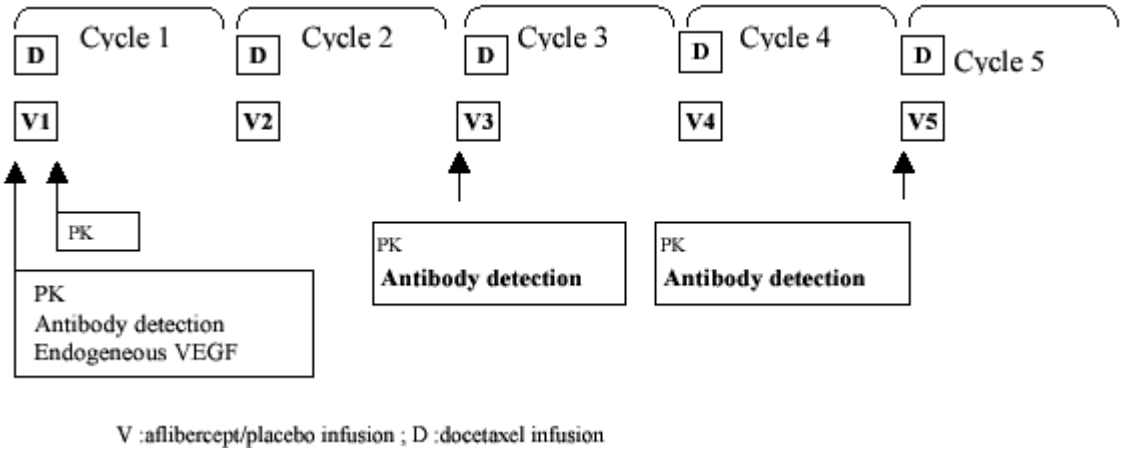
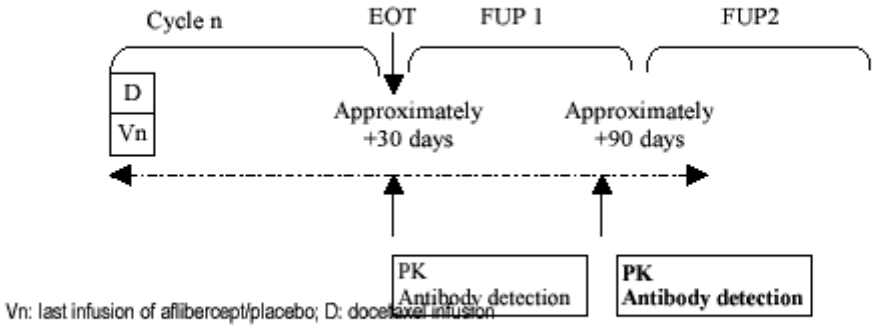


Figure 7 - PK sampling during follow-up



9.3.2 PK handling procedure

Vacutainer tubes will be used to collect 4 mL of whole blood from patients for plasma preparation: one tube for the determination of circulating free aflibercept and VEGF: aflibercept complex levels for pharmacokinetic analysis at the sampling times described in Section 0 above. Refer to Appendix C for detailed pharmacokinetic blood sample collection, handling, and shipping procedures. A total of 7 samples and 28 mL of whole blood will be collected for these evaluations.

Blood samples should not be taken at the infusion site.

Red-top vacutainer tubes will be used to collect 4 mL of whole blood from patients for serum preparation for the detection of anti-aflibercept antibody levels. Detailed anti-aflibercept antibody blood sample collection, handling, and shipping procedures are provided in Appendix C. A minimum of 3 samples and 12 mL of whole blood will be collected for these evaluations.

The analysis of free and bound aflibercept and anti-aflibercept antibody levels will be performed by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY).

ACD or CPD tubes will be used to collect blood sample for the analysis of free endogenous VEGF levels. A total of one sample per patient and 4 mL of whole blood will be collected for this evaluation. All specimens must be stored frozen at -20°C until shipped to sanofi-aventis. Refer to Appendix C for detailed pharmacokinetic blood sample collection, handling, and shipping procedures.

The plasma free VEGF concentrations will be determined at sanofi-aventis, GMPK Alfortville under the responsibility of [redacted] at Sanofi-aventis Recherche and développement, [redacted]

9.3.3 Bioanalytical methods

Free aflibercept concentrations in plasma will be measured by a validated ELISA method. The ELISA microplates are coated with human VEGF, which specifically binds functional aflibercept, while the detection antibody is directed against the receptor domains of the aflibercept. By requiring a vacant VEGF binding site, this ELISA specifically measures free aflibercept; it does not detect the VEGF: aflibercept complex.

The assay of VEGF: aflibercept complex will also be measured by a validated ELISA method. The ELISA captures the complex with an antibody selective for VEGF coated on a plate. The captured complex is detected with an antibody selective for the receptor domains of aflibercept.

Human antibodies selective for aflibercept will be detected with an enzyme-linked immunosorbent assay that uses microplates coated with extracellular receptor domains of aflibercept. Immobilized receptor domain-antibody complexes are detected using peroxidase conjugated mouse anti-human IgG, F(ab')2 fragment specific antibody. The calibration standard is a mouse monoclonal antibody specific for the R1 domain of aflibercept that is detected with a peroxidase-conjugated goat anti-mouse IgG Fc fragment-specific antibody.

9.4 MEASURES TO PROTECT BLINDING OF THIS TRIAL

Please also refer to Section 8.10 - Access to the randomization code during the study.

Patients, investigators, and other persons responsible for study conduct and data analyses will be blinded to treatment assignment.

All samples for PK evaluation will be assessed blindly (treatment arm and timing) and results will not be communicated to the study staff.

During the course of the study an external statistician (independent from the sponsor) will perform unblinded safety and efficacy (IA) analyses for the purpose of the DMC data review. Access to these data and analyses will be restricted to the DMC members, unless decision is made by the DMC to release results to the Executive Committee. Conditions to release unblinded results to the Executive Committee and processes to protect the integrity of the study are described in the DMC charter.

In case of a SAE that is unexpected and reasonably associated with the use of the study treatments the code will be broken by the global safety officer in charge of the study for the purpose regulatory reporting.

In case of an AE, the code can be broken at the investigator initiative only in exceptional circumstances, when knowledge of the investigational product is essential for treating the patient. The investigator or authorized person should follow the procedures outlined in Section 8.10.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

The NCI CTCAE v.3.0 will be used in this study (Appendix E) to grade clinical adverse events and laboratory data.

Information on the following parameters will be collected by the investigator and reported in the CRF:

- Clinical examination, including body weight, blood pressure and ECOG PS.
- Laboratory data
  - Complete blood count and clinical chemistry (see study flowchart footnote 'i' in Section 1.2)
  - Other tests as clinically indicated (e.g., 12-lead ECG)
- Adverse events and serious adverse events
- Concomitant medications and treatments
- Reason of treatment withdrawal and date of last administration
- Adverse events encountered before the start of study treatments will be summarized separately. Pre-treatment and treatment-emergent adverse events will be summarized with respect to the type as assessed by the Medical Dictionary for regulatory activities(current version or immediate previous version), frequency, cycle, severity according to the NCI CTCAE v.3.0., seriousness, and relatedness. Laboratory abnormalities will be assessed according to the NCI CTCAE v.3.0.

Please also refer to Section 11.

10.2 SAFETY INSTRUCTIONS

10.2.1 Physical examination

Physical examination will include, but not limited to the examination of major body systems:

- Blood pressure
- Height (baseline only), body weight
- ECOG PS (Appendix D).

If abnormal findings emerge or worsen from the baseline assessment, then the adverse event page of the CRF should be completed for these findings. If a finding meets the criteria for a serious adverse event, then the appropriate procedures for reporting such events should be followed as described in Section 10.5. Height will be recorded at baseline only. Body weight and ECOG PS will be recorded prior to the start of each treatment cycle and every 3 months during follow-up period until death or cut-off date whichever comes first.

Every attempt should be made to have the same study personnel to perform the assessment throughout the study for any given patient for consistency of grading.

10.2.2 Laboratory variables

Hematology panel, blood chemistry profile as well as urinalysis (refer to section 8.5.1) will be performed by a local laboratory. Baseline results must be available for eligibility determination. At the start of each new treatment cycle, results must be available prior to treating the patient with the study drug.

10.3 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.4 DEFINITIONS OF ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENT (SAE)

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A priori, efficacy endpoints will not be considered as Aes.

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

These should also usually be considered serious.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions or asymptomatic ALT increase ≥ 10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse Events

The period of safety observation starts from the time the patient gives informed consent.

During baseline period (i.e. even in the absence of any administration of study treatments), all signs and symptoms will be recorded as adverse event only if they are still present at the time of first study drug administration or if they are serious, are to be recorded on the corresponding page(s) included in cycle 1 in the Case Report Form.

During the treatment period (i.e.until 30 days after the last administration of study drugs), all adverse events, regardless of seriousness or relationship to study treatments, are to be recorded on the corresponding page(s) included in the Case Report Form.

For follow-up period, refer to Section 10.5.3.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the study treatments.

Vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to study treatment discontinuation/study drugs dose modification and/or fulfilling a seriousness criterion.

Laboratory are to be recorded as Adverse Events only if they lead to study treatment discontinuation/study drugs dose modification and/or fulfills a seriousness criterion.

10.5.2 Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately:

- SEND (within 1 working day) by email (automatic sending activated by ticking "save complete" (for the initial report) or "save" (for follow-up reports) the electronic Adverse Event/Serious Adverse Event notification (html format) to the representatives of the Monitoring Team in the Clinical Research Unit (Clinical Safety Officer and Clinical Research Associates) who then forwards to Global Pharmacovigilance and Epidemiology and the Clinical Study Director. Before sending, please verify relationship to study drug has been indicated and treatment number is provided on the SAE complementary form.
- APPROVE the Adverse Event/Serious Adverse Event page in the electronic CRF immediately after automatic sending of the electronic Serious Adverse Event notification by entering, for a second time, "username and password";
- If the mail connection is not functional or in case of any technical issue, SEND (within 1 working day, preferably by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and fax number appear on the Clinical Trial Protocol;
- ATTACH AND FAX photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges;
- Follow-up of any Serious Adverse Event that is fatal or life threatening should be provided within one additional calendar week.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any related Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition.
- In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- In case of any Adverse events or Serious Adverse Event brought to the attention of the Investigator at any time after cessation of study treatment and considered by him/her to be caused by the study treatment with a reasonable possibility, should be reported to the Monitoring Team.

10.6 PREGNANCY OF FEMALE PARTNER

In the event of pregnancy is confirmed in the female partners during the treatment or within 3 months after the last dose of study medication, follow-up of the pregnancy will be mandatory until the outcome has been determined.

10.7 OVERDOSAGE

No cases of aflibercept overdose, defined as any administered dose at least 1 dose level higher than the highest explored dose level, have been reported to date. The highest doses administered of aflibercept are 7 mg/kg iv every 2 weeks and 9 mg/kg iv every 3 weeks.

For safety reporting purposes, in this protocol, an overdose for docetaxel is defined as any doses administered above 100mg/m² every 3 weeks.

10.8 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study treatments, to the Authorities, IECs / IRBs as appropriate and to the Investigators. The determination of the expectedness for SAEs, for regulatory reporting purposes, will be defined by the current Investigator's brochures of aflibercept and of docetaxel (Taxotere® Injection concentrate) in force at the moment of the event occurrence.

In addition, the Sponsor may report in an expedited manner all SAEs that are expected and at least reasonably related to the study treatments to the Authorities, according to local regulations.

In this study, the SAEs considered related to the underlying condition such as disease progression or lack of efficacy) will not be considered unexpected unless their course, intensity or other specific features are such that the Investigator, according to his/her best medical judgment, considers these events as exceptional in the context of this medical condition.

Any other AE not consistent with SAEs listed in the Investigator's Brochure of aflibercept and of docetaxel and reference safety information for prednisone/prednisolone on file in the department of pharmacovigilance will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

11 HANDLING OF PATIENT DEFINITIVE TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

11.1 DEFINITIVE TREATMENT DISCONTINUATION

11.1.1 List of criteria for definitive treatment discontinuation

The patients may withdraw from study treatment (either aflibercept/placebo or docetaxel) under the following circumstances but will continue to be assessed and followed in the study unless the patient refuses:

- The patients may withdraw from treatment if they decide to do so, at any time and irrespective of the reason (consent's withdrawal) or at the request of their legally authorized representative. "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research.
- If, in the investigator's opinion, continuation of the treatment would be detrimental to the patient's well being, such as:
  - Disease progression as defined in section 9.1.2.1
  - Unacceptable adverse event(s) not manageable by symptomatic therapy, dose delay or dose modification (see sections 8.5, 8.4)
  - Intercurrent illness that prevents further administration of study treatment
  - Non compliance to the study protocol or logistic consideration
- Patient is lost to follow-up
- Of note, any investigational treatment unblinded by the Investigator will lead to permanent investigational agent discontinuation.

In all cases, the reason for and date of withdrawal must be recorded in the CRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in Section 10.5.

11.1.2 Handling of patients after definitive treatment discontinuation

All definitive treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

Patients will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of a followed-up AE, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the Investigational Product, including antibody and pharmacokinetics measurement.

11.2 PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

The patients may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision:

- All study withdrawals should be recorded by the Investigator in the appropriate pages when considered as confirmed;
- If possible, the patients are assessed using the procedure normally planned for the end-of-study visit as described in Section 12.1.

The investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter). Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up. The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

11.3 CONSEQUENCE

Patients who have been withdrawn from the study cannot be reincluded in the study. Their inclusion and treatment number must not be reused.

12 STUDY PROCEDURES:

12.1 VISIT SCHEDULE

12.1.1 Pretreatment evaluation (Baseline)

Each potential patient will be examined before the start of the study to determine his/her eligibility for participation.

- The **written informed consent** will have to be signed by the patient before any protocol specific procedures.

The following examinations will be performed within 21 days prior to randomization:

- **Demographics**: age (date of birth), gender, and race
- **Medical, surgical and oncological history** including significant prior and concurrent illnesses, existing signs and symptoms, primary diagnosis and prior antitumor therapy.
- **Prior medications** will be recorded from 21 days prior to the start of the study treatment.
- **Tumor assessment**: Chest, abdomen, and pelvic spiral CT or MRI and bone scan (bone scan dated less than 6 weeks prior to randomization is allowed) and all other exams as clinically indicated (e.g. brain CT-Scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and non measurable).
  When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition. If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.
- **Serum Testosterone Measurement.**

The following examinations will be performed within 8 days prior to randomization:

- **Inclusion/Exclusion criteria**
- **Clinical examination** including major body systems exam, height and weight for BSA determination, ECOG PS, SRE and blood pressure.
- **Serum for Measurement of PSA Tumor Marker at baseline.** In case of rising PSA alone, 2 sequential increases above a previous lowest reference value obtained at least 1 week apart, are required. A PSA value at study entry of at least 2 ng/mL is required (See section 7.2).

- **Laboratory safety studies:**
    - **Hematology**: WBC, ANC, hemoglobin, platelet count.
    - **Blood Chemistry** sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, creatinine clearance (calculated with Cockroft-Gault formula for patient <65 years or aMDRD formula for patients ≥65 years, see Appendix A) if creatinine >ULN, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose.
    - **Coagulation tests**: prothrombin time expressed as INR in patients under antivitamin K
    - **Urinalysis**: dipstick (WBCs, RBCs) and UPCR on morning urine spot or 24 hour urine collection must be performed.
- **12-lead ECG.**

The following examinations will be performed within 3 days prior to first administration of study treatments:

- **Pain evaluation** using the PPI see Appendix H and the analgesic consumption assessment see Appendix F for 7 days.The last daily evaluation must be obtained within 3 days prior to first administration of study treatments.
- **HRQL** using the FACT P questionnaire see Appendix J.
- Other investigations if clinically indicated.

12.1.2 Randomization

Randomization will take place once the consented patient has completed all the necessary baseline procedures and is deemed eligible for study entry by the investigator or designee. All eligible patients must be randomized by contacting the IVRS (see section 8.7).

The results of the baseline examinations will be recorded in each randomized patient's CRF. Source documentation to support the screening results must be maintained in the patient's medical record. Treatment should begin within 3 days after randomization.

12.1.3 During study treatment period

The Study treatment period begins when the patient receives the initial dose of study drugs (Cycle 1 Day 1). Each cycle consists of 21 days and assessments are scheduled on a every 3 weeks basis (Day 1 of each cycle) but may be repeated more often, as clinically indicated. Cycle length may be extended if additional time is required for resolution of study drug-related toxicities or other adverse events, but cycle shortening to less than 19 days is not permitted. A maximum 2-week delay for resolution of study-drug related toxicities is allowed. Beyond this, the sponsor should be contacted for guidance.

Each randomized patient will be treated with aflibercept or placebo every 3 weeks.

The following examinations will be performed every cycle:

- **Clinical exam** before each cycle: ECOG PS, examination of major body systems, assessment of SRE as defined in section 9.1.2, blood pressure, weight. In addition the BP will be measured and recorded at least once in between treatment visits, preferably during week 2 of each cycle.
- **Concomitant medications**
- **Pain evaluation** before each cycle, using the PPI see Appendix H and the analgesic consumption assessment see Appendix F for 7 days.
- **HRQL** using the FACT P questionnaire see Appendix J.
- **Serum for PSA Tumor Marker Measurement** (i.e., on pre dose of day 1 of each cycle).
- **All adverse events** will be assessed before each cycle.
- **Laboratory safety studies:**
    - **Hematology**: WBC, ANC, hemoglobin, platelet count.
    - **Blood Chemistry** sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, creatinine clearance (calculated with Cockroft-Gault formula for patient <65 years or aMDRD formula for patients ≥65 years, see Appendix A) if creatinine >ULN, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose
    - **Coagulation tests**: prothrombin time expressed as INR in patients under **antivitamin K**
    - **Urinalysis**: dipstick (WBCs, RBCs) and UPCR on morning urine spot. If UPCR is >1 then 24 hour urine collection must be performed.
    - -During study treatment, if proteinuria from renal origin (according to urine protein electrophoresis) is occuring please refer to Table 10 and section 8.5.1 for management. A urine microscopy examination should be also considered.
- **Other investigations if clinically indicated.**

The following examinations will be performed every 4 cycles:

- **Tumor assessment**, every 12 weeks from first cycle or at any time in case of clinical suspicion of progression, to follow target and /or not target lesion present at baseline. To ensure comparability, the imaging should be performed *using identical techniques throughout the study* period (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

Intended for all patients treated in selected centers:

- **Blood samples for Pharmacokinetics** will be collected as follow:
  - just before the start of the first infusion aflibercept/placebo and at the end of this infusion
  - prior to infusion of aflibercept/placebo of each every other cycle
  - and in the circumtances of specific adverse events (see section 8.5.1).
- **Blood samples for determination of endogeneous VEGF level** just before the start of the first infusion of aflibercept /placebo **(only when equipment for sample preparation is available on site, i.e. 4°C centrifuge).**
- **Anti-aflibercept antibody detection**, just before the start of the first infusion aflibercept/placebo**,** prior to the infusion of each every other cycle and in the circumtances of specific adverse events (see section 8.5.1).

In case of adverse event driven evaluation: the first samplings for anti aflibercept antibodies and circulating free and bound aflibercept will be done within 2 weeks following the occurence of the event (when this time point is not covered with the prospective evaluation). Follow up will be prolonged up to 6 months following discontinuation of aflibercept/placebo with sampling repeated every 2-3 months.

12.1.4 End of treatment

All patients must continue to be observed for at least 30 days after the final dose of study treatment (either aflibercept/placebo or docetaxel /prednisone or prednisolone).

The following procedures should be performed approximately 30 days following the final dose of study treatment:

- **Clinical exam**:
  ECOG PS, examination of major body systems, assessment of SRE as defined in section 9.1.2, blood pressure and weight.
- **Concomitant medications**
- **Tumor assessment**: To ensure comparability, the imaging should be performed *using identical techniques throughout the study* period (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). For patients with measurable disease the objective response achieved during the treatment period will be assessed by the investigators using the RECIST criteria and reported in the e CRF.
- **HRQL** using the FACT P questionnaire see Appendix J.
- **Serum for PSA Tumor Marker Measurement**
- **All adverse events**

- **Laboratory safety studies:**
    - **Hematology**: WBC, ANC, hemoglobin, platelet count.
    - **Blood Chemistry** sodium, potassium, calcium, phosphorus, BUN, magnesium, creatinine, creatinine clearance (calculated with Cockroft-Gault formula for patient <65 years or aMDRD formula for patients ≥65 years, see Appendix A) if creatinine >ULN, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, glucose.
    - **Coagulation tests**: prothrombin time expressed as INR in patients under antivitamin K
    - **Urinalysis**: dipstick (WBCs, RBCs) and UPCR on morning urine spot. If UPCR is >1 then 24 hour urine collection must be performed.

    -During study treatment, if proteinuria from renal origin (according to urine protein electrophoresis) is occuring please refer to Table 10 and section 8.5.1 for management. A urine microscopy examination should be also considered.
- **Other investigations** if clinically indicated.

Intended for all patients treated in selected centers:

- **Blood samples for Pharmacokinetics:** approximately 30 days after the last infusion of aflibercept/placebo.
- **Anti-aflibercept antibody**: approximately 30 days after the last infusion of aflibercept/placebo.

12.1.5 Post treatment Follow-up period

The first follow up visit will occur approximately 90 days after the final dose of study treatment (i.e., 60 days after the end of treatment visit).

- **Clinical exam**:
  ECOG PS, examination of major body systems, blood pressure, assessment of SRE as defined in section 9.1.2.
- **Concomitant medications**
- **Tumor assessment (if applicable – if tumor progression has not yet been documented)**:
  To ensure comparability, the imaging should be performed using identical techniques throughout the study period (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
- **Pain evaluation (if applicable – if pain progression has not yet been documented)** using the PPI see Appendix H and the analgesic consumption assessment see Appendix F for 7 days.
- **HRQL (if applicable – if disease progression has not yet been documented**) to be assessed every 3 weeks using the FACT P questionnaire see Appendix J.

- **Serum for PSA Tumor Marker Measurement (if applicable – if PSA progression has not yet been documented)**
- **All adverse events related to study treatment ongoing** at the end of the study treatment, or new related AE and related SAE which occur during the follow-up period will be recorded until recovery, or until progression has been stabilized or initiation of any further anticancer therapy.

Intended for all patients treated in selected centers:

- **Blood samples for Pharmacokinetics:** approximately 90 days after the last infusion of Aflibercept/Placebo.
- **Anti-aflibercept antibody**: approximately 90 days after the last infusion of Aflibercept/Placebo.

Subsequent Follow up visits:

No further antitumor therapy should be administered before disease progression (except prednisone - or equivalent dose of glucocorticosteroids - which may be continued) unless the patient requests further antitumor therapy, or the investigator deems it necessary.

The following evaluations should be performed every 12 weeks until progression is documented or study cutoff, whichever comes first:

- **Survival status, ECOG PS,** assessment of SRE as defined in section 9.1.2
- **Post medications** if correspond to treatment of related adverse events
- **Tumor assessment**: **(if applicable – if tumor progression has not yet been documented)** To ensure comparability, the imaging should be performed using identical techniques throughout the study period (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

The following evaluations should be performed every 3 weeks until progression is documented or study cutoff, whichever comes first:

- **Pain evaluation (if applicable – if pain progression has not yet been documented)** using the PPI see Appendix H and the analgesic consumption assessment see Appendix F for 7 days, until **pain** progression, or study cutoff, whichever comes first.
- **HRQL (if applicable – if disease progression has not yet been documented)** using the FACT P questionnaire see Appendix J.
- **Serum for PSA Tumor Marker Measurement (if applicable – if PSA progression has not yet been documented**)until PSA progression, or study cutoff, whichever comes first.

In addition, adverse events and further anticancer therapy will be collected as follows:

- **All adverse events related to study treatment ongoing** at the end of the study treatment, or new related AE and related SAE which occur during the follow-up period will be recorded until recovery, or until progression has been stabilized.
- **Further anticancer therapy** if any (name doses and duration), which is at the discretion of the investigator. No further antitumor therapy should be administered before disease progression (except prednisone - or equivalent dose of glucocorticosteroids - which may be continued) unless the patient requests further antitumor therapy, or the investigator deems it necessary.

Once progression is documented, all patients will be followed for survival and vital status information every 3 months until death or the study cutoff date, whichever comes first. Further anticancer therapy will be collected.

12.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within a CRF.

The results of certain examinations or evaluations recorded in the CRF may be considered to be source data (such as patient's PPI, AS diary….).

13 STATISTICAL CONSIDERATIONS

The statistical considerations presented in this section forms the basis for the Statistical Analysis Plan (SAP), which will provide accurate definitions and detailed specifications for the analyses to be performed on the data collected from this study. A final SAP will be issued prior to database lock for the first interim analysis to be performed.

13.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint for the study is overall survival. The median survival for patients treated with docetaxel/prednisone is estimated to be 19.0 months based on a recently completed study (TAX 327, [5]) comparing docetaxel/prednisone with mitoxantrone/prednisone in patients with MAIPC. A 20% risk reduction (median survival improvement from 19.0 months in the docetaxel/prednisone arm to 23.75 months in the aflibercept/docetaxel/prednisone arm, corresponding to a hazard ratio of 0.8) is expected to be demonstrated. Assuming that survival times are exponentially distributed in both treatment arms and taking into account the planning of two interim analyses on O.S. using a group sequential approach, with stopping boundaries based on a gamma(-5) β-spending function for futility, when approximately 50% of the events have been observed and on an O'Brien-Fleming α-spending function at 75% of events (for efficacy), a total of 873 deaths would be required to provide 90% power to detect a 1.25-fold increase in median survival utilizing a one-sided log-rank test at a significance level of 0.025. Based on an anticipated uniform accrual rate over a period of 36 months and a minimum 24-month follow-up period, a total of approximately 1200 patients (600 patients per treatment arm) would need to be enrolled in order to achieve the required number of deaths by the end of the minimum follow-up period.

13.2 ANALYSIS VARIABLES

13.2.1 Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age, race, height and weight), medical history, cancer diagnosis and prior anticancer therapy will be collected at baseline. Baseline efficacy variables e.g. tumor assessment, pain evaluation, PSA and other prognostic variables will be assessed as well, baseline value being defined as the last value or measurement taken up to the first dose in the study.

13.2.2 Efficacy variables

13.2.2.1 Primary efficacy variable

The primary efficacy endpoint is overall survival defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

13.2.2.2 Secondary efficacy variables

PSA response as defined in section 9.1.2.3 will be calculated among patients with a baseline PSA≥ 10ng/mL. Increases (of any magnitude) in PSA during the first 12 weeks should be ignored in determining PSA response**.**

Pain response as defined in section 9.1.2.2 will be calculated from patient reported PPI and calculated AS scores among patients with baseline pain and with stable analgesia at baseline (eg for a minimum of 5/7 consecutive days prior to randomization). Increases in pain during the first 12 weeks should be ignored in determining pain response.

Time to occurrence of SRE is defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SRE or death due to any cause, whichever occurs first. Date of skeletal related events (SRE) will be the earliest date between:

- date of pathological fractures and / or spinal cord compression,
- date of bone irradiation including radioisotopes or date of bone surgery,
- date of change of antineoplastic therapy (including biphosphonates in the face of increase in pain) to treat bone pain.

Progression-free survival defined as the time interval between the date of randomization and the date of the first documented event defining disease progression (see section 9.1.2.1) and death due to any cause, whichever occurs first.

Tumor response defined as either a partial response (PR) or complete response (CR) according to the RECIST criteria (see Appendix B).

PSA progression-free survival defined as the time interval between the date of randomization and the date of either first documented PSA progression or death due to any cause, whichever is earlier. **PSA progression** is defined in section 9.1.2.3

Pain progression-free survival defined as the time interval between the date of randomization and the date of either first documented pain progression or death due to any cause, whichever is earlier. **Pain progression** is defined in section 9.1.2.2.

Health-Related Quality of Life using the FACT-P (version 4.0) questionnaire will be used and scored. The Trial Outcome Index (TOI) that combines the physical (7 items), functional (7 items) and prostate-specific concerns (12 items) domains will be the primary endpoint in the HRQL assessment for this study. It is the most focused and sensitive indicator of the physical aspects of HRQL [41]. The other subscale scores (including the Total FACT-P and the prostate-specific concerns) will also be analyzed. HRQL analyses will be detailed in the SAP.

Specific data handling conventions defined for the questionnaire analysis will be documented and appended to the Statistical Analysis Plan.

13.2.3 Safety variables

The safety variables include:

- **AE**
  - On-treatment period: On-treatment period is the period from the first dose to 30 days after the last dose.
  - Treatment-emergent AEs (TEAEs): A TEAE is defined as an AE that is reported during the on-treatment period defined above.
  - Post-treatment AEs: A "post-treatment AE" is defined as an AE that developed, worsened or became serious after completion of the on-treatment period.
- **Discontinuation**
  - Treatment discontinuation and reasons.
  - Treatment discontinuation due to AEs.
- **Vital signs** blood pressure and ECOG performance status
- **Major laboratory safety parameters**
  - **Hematology**: WBC, ANC, platelets, and hemoglobin.
  - **Selected Blood chemistry**: total bilirubin, alkaline phosphatase, SGOT (AST), and SGPT (ALT), Creatinine.
  - **Renal function and urinalysis**: Dipstick (WBC, RBC), Urinary Protein-to-creatinine Ratio (UPCR), and 24-hour protein.

13.2.4 Pharmacokinetic variables

Sparse population PK sampling for aflibercept is planned. It is not planned to study the pharmacokinetics of docetaxel/prednisone.

Free and bound aflibercept plasma concentrations are to be measured before the start of the first aflibercept/placebo infusion (cycle 1, day 1), at the end of this first infusion, then prior to every other cycle (i.e. pre-dose of aflibercept/placebo infusion cycle 3, cycle 5, cycle 7, etc…), then approximately 30 days and 90 days after last aflibercept/placebo administration.

For the purpose of exploratory analyses, endogenous VEGF will be measured at baseline in all patients who are randomized at study sites equipped with a 4°C centrifuge (needed for preparation of the samples).

The pharmacokinetic variables will include:

• C_{VEGF}, concentration of VEGF at baseline

• Cmax of free aflibercept at the end of infusion on cycle 1. Plasma concentration obtained from patients in the aflibercept treatment group will be classified Cmax if sampling occurs within end of infusion +/- 20%.

• Ctrough of free and adjusted bound aflibercept measured prior to each cycle. Plasma concentration obtained from patients in the aflibercept treatment group will be classified Ctrough if sampling occurs before the next dose and if time interval before the next dose is <24h.

• Ratio of free / adjusted bound aflibercept if feasible. Of note, adjusted bound is obtained using the bound concentrations multiplied by 0.717 (in order to be expressed in equivalent free aflibercept).

Drug-drug interaction between aflibercept and docetaxel/prednisone:

Aflibercept clearance, measured using apopulation PK will be used to explore the impact of docetaxel/prednisone on aflibercept.

13.2.5 Immunogenicity variables

Anti- aflibercept antibody levels will be categorized as negative and positive. A patient will be considered to have positive anti-body levels if antibodies were detected above the quantification limits.

13.3 ANALYSIS POPULATIONS

13.3.1 Efficacy population

13.3.1.1 Intent-to-treat (ITT) population

The intent-to-treat (ITT) population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number through the study treatment allocation system. Patients will be included in a treatment arm as randomized, regardless of whether patients received any study drug or received a different study drug from which they were randomized. Analysis of the primary efficacy endpoint will be performed using the ITT population. Secondary efficacy endpoints will also be analyzed in the ITT population, and in evaluable patients whenever applicable.

13.3.1.2 Clinical Trial Protocol deviations

Determinations of protocol deviations will be primarily based on the inclusion and exclusion criteria and actual patient experience during the conduct of the trial. Dosing utility and compliance will be assessed based on parameters specified in Section 13.4.2. Specifics on determination of protocol deviations will be detailed in the statistical analysis plan (SAP).

13.3.2 All treated population

The all treated population is the subset of the ITT population that received at least part of one dose of study drug. All analyses using this population will be based on the treatment actually received. Treatment compliance/administration and all clinical safety data will be summarized using the all treated population.

13.3.3 Other analysis populations

Some patients may be excluded from secondary analyses as a result of missing data. Specifically, patients who are not evaluable for a specific secondary endpoint will be excluded from the analyses of the corresponding endpoint. Following subpopulations will be defined:

- **ITT population evaluable for PSA response**: PSA response will be assessed only among patients with a baseline PSA ≥ 10ng/mL.
- **ITT population evaluable for Tumor response**: Tumor response will be calculated among patients with measurable disease according to RECIST criteria.
- **ITT population evaluable for Pain response**: Pain response is to be applied only to patients with baseline present pain intensity score (PPI) ≥ 2 on the McGill-Melzack scale and/or baseline mean analgesic score (AS) ≥ 10 points and stable analgesia at randomization (eg for a minimum of 5/7 consecutive days prior to randomization). Stable analgesia will be derived from the 7-day baseline pain diary an defined as:
  - No change by more than one point in the daily PPI scores recorded over 7 consecutive days with an identical PPI score for the two last days and
  - No variation of the daily analgesic scores (AS) by more than 25% around the mean AS, i.e. the 7 daily AS should be within the range of values defined below:
    - the lowest value should be ≥ mean AS -25% mean AS.
    - the highest value should be ≤ mean AS +25% mean AS.
- **Pharmacokinetics population**: The pharmacokinetic analysis will be performed based on the all treated population with evaluable blood samples (drawn from all patients in selected centers at pre and post-dose cycle 1 and pre-dose cycle 3, cycle 5 and every other cycle and then approximately 30 and 90 days after the last infusion of aflibercept/placebo) e.g. whom had a pre-dose and at least one post dose assessment performed. Peak analysis will be performed at cycle 1 and through analysis will be performed at cycle 2, at cycle 4 and every other cycle. The same population will be used in the analysis of anti- aflibercept antibody measurement.

- **Health-related Quality of life** will be assessed in the ITT population for patients who complete at least a baseline FACT-P questionnaire and at least one post baseline questionnaire.

13.3.4 Disposition of patients

Summary of patient populations will be presented with counts (n) and percentages (%).

Rates of study drug discontinuation will be calculated for treatment arm and overall among the ITT patients.

13.4 STATISTICAL METHODS

Continuous data will be summarized for each treatment group using the number of non-missing observations (N), mean, SD (standard deviation), median, minimum and maximum. Quantitative discrete variables will also be presented using counts and percentages when specification of relevant groupings of variable values is provided. Categorical data will be summarized for each treatment group using counts (n) and percentages (%). The number of subjects with missing data may be mentioned, but will never be included in the denominator for the calculation of percentages unless otherwise specified.

Descriptive summary of the variables will be provided by treatment arm. Time-to-event (or event-free survival) data will be analyzed using means of Kaplan-Meier method. Median time-to-event (or event-free survival) and its 95% confidence intervals by treatment arm will also be provided

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by visit will be provided on observed cases, i.e. the inclusion of only subjects having non-missing assessments at a nominal visit. In addition, the tables summarizing the change from baseline will include only subjects having both a baseline and a post-baseline evaluation.

13.4.1 Demographic and baseline characteristics

13.4.1.1 Patients demographic characteristics, medical history and diagnoses

All patient demographic characteristics, medical history, and diagnoses will be tabulated based on the ITT population. Continuous variables (such as age, weight, and height) will be summarized as described above Qualitative characteristics (such as race) will be summarized by counts (n) and percentages (%).

13.4.1.2 Previous medications

Previous anticancer therapies (e.g., prior hormonal therapy, prior surgery, prior radiotherapy, etc.) will be summarized by frequencies.

13.4.2 Extent of study treatment exposure and compliance

13.4.2.1 Investigational Product

Extent of exposure will be assessed in the all treated population. In general, first day of each cycle will be defined as the day of aflibercept/placebo administration.

It will consist in summarizing the number of cycles administered to the patients. Cumulative dose and dose intensity of study treatment will be calculated for all patients, where cumulative dose is the sum of all doses (in mg/kg) from Cycle 1 to the last cycle, and dose intensity (in mg/kg/wk) is the cumulative dose divided by the number of weeks on study (the last cycle considered as 3-week duration). Any dose reductions or dose interruptions will be documented. In addition, the relative dose intensity will be calculated during the treatment period, as well as the number (n) and percentage (%) of cycles delayed and the corresponding reasons for treatment delay.

13.4.2.2 Docetaxel administration

Number of cycles administered to patients will be summarized. Cumulative dose and dose intensity of docetaxel (in mg/m^2 and in mg/m^2/wk, respectively) will be presented in each treatment arm.

Relative dose intensity will be calculated, as well as the number of dose reductions, the number (n) and percentage (%) of cycles delayed (authorized up to 2 weeks) and associated reasons for treatment modifications will be presented.

13.4.2.3 Concomitant medication/therapy

Concomitant medication and therapy while on study will be summarized by counts (n) and percentages (%). Medications of specific interest will be described in the SAP.

13.4.3 Analysis of primary efficacy variable

A total of approximately 1200 patients with MAIPC will be randomized to 1 of 2 treatment arms (i.e., 600 patients per treatment arm): aflibercept plus docetaxel / prednisone or placebo plus docetaxel / prednisone.

The primary efficacy endpoint is overall survival. In the primary analysis, overall survival will be analyzed by means of Kaplan-Meier method, with log-rank comparison stratified by baseline performance status (0-1 vs 2).

The null hypothesis is that aflibercept plus docetaxel / prednisone or placebo plus docetaxel / prednisone have equal overall survival in this population. Two interim looks are planned of OS for the purpose of futility when approximately 437 (50%) of deaths have been observed and for the purpose of early demonstration of efficacy when 655 (75%) of deaths have occurred. Type I and type II errors of the design and the integrity of the trial will be protected by the means of a group sequential approach with an O'Brien Fleming α-spending function and a gamma(-5) β-spending function. Interim analyses timing and statistical operational characteristics are described in section 13.6.

Median overall survival and its 95% confidence interval by treatment arm will also be provided. Hazard ratio and 95% confidence interval will be calculated after adjustment for baseline ECOG PS based on the Cox proportional hazard model. Non stratified logrank will be also performed as sensitivity analysis.

13.4.4 Analysis of secondary efficacy variables

The analysis of the secondary endpoints will be performed at the time of the final analysis of overall survival.

13.4.4.1 Analysis of main secondary efficacy variables

Main secondary endpoints are PSA response, pain response,time to occurence of SRE and progression-free survival. PSA response, pain response and occurrence of SRE will be summarized by means of count (n) and percentage (%) and presented with 95% confidence intervals. Progression-free survival will be analyzed by means of Kaplan-Meier method. Medians and its 95% confidence intervals by treatment arm will also be provided. Hazard ratios and 95% confidence interval will be calculated after adjustment for baseline ECOG PS based on the Cox proportional hazard model.

Hypothesis testing of the main secondary efficacy variables will be carried out. A closed test procedure will be used to control the type I error rate meaning that not further testing will be performed unless the significance level had been reached on OS. The hierachical procedure will be then carried out at the two tailed 5% significance level in the following order:

- PSA response will be tested first,
- Pain response, if test on PSA response is statistically significant,
- Time to occurrence of SRE, if test on pain response is statistically significant,
- PFS, if test on time to ccurrence of SRE is statistically significant

The tests to be performed are Cochran-Mantel-Haenszel test (Pain, PSA response) and log-rank test (progression-free survival, time to occurrence of SRE) stratified by ECOG performance status.

13.4.4.2 Analysis of other secondary efficacy variables

Analysis of the following secondary endpoints will be descriptive only as specified in section 13.4. Any testing procedure carried out on these endpoints will be considered as exploratory. Tumor response, pain progression-free survival, and PSA progression-free survival will be summarized and presented as planned in section 13.4.

The comparison of health-related quality-of-life scores between treatment arms will be performed by means of mixed linear models. The covariates to be included in the mixed linear models include treatment group (aflibercept vs. placebo), baseline ECOG PS (0-1 vs 2).

HRQL Specific data handling conventions and analyses will be documented in the SAP.

13.4.5 Analysis of safety data

Analysis of adverse events, vital signs, ECG, and laboratory data will be descriptive and conducted on the all treated population by treatment group as defined in Section 13.3.2. Summary of safety data will also be performed by cycle (where applicable). For each of the safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study.

13.4.5.1 Adverse Events

Adverse events will be collected from the time informed consent is signed until 30 days after the last study treatment administration. Adverse events will be summarized with the number and percentage of patients with adverse events, classified by MedDRA preferred term and intensity as graded by the NCI CTCAE, v. 3.0.

Tables of treatment-emergent adverse events (TEAE) will be provided.

SAEs and treatment-emergent SAEs will be summarized using MedDRA classification up to the preferred term. SAEs will be also presented by worst NCI grade by patients.

Adverse events will be analyzed regardless of their relationship to the study drug. However, summaries will be done for specific subsets of adverse events, such as those potentially related to study drug.

13.4.5.2 Laboratory safety data

Hematological toxicities will be assessed from laboratory parameters. Worst NCI CTCAE grades of leukopenia, neutropenia, thrombocytopenia, and anemia will be determined.

Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst NCI CTCAE grade) will be summarized by cycle and by patient.

Biochemistry and urinalysis will be analyzed using the worst NCI CTCAE grade, whenever applicable (laboratory normal ranges, otherwise) calculated from laboratory values. Specific attention will be given to incidence of proteinuria.

13.4.5.3 Vital signs

By visit descriptive analyses of vital signs will be provided for observed values and change from baseline. Vital signs will be collected at each visit and once in between treatment visits as per protocol.

13.4.6 Pharmacokinetic analysis

The pharmacokinetic analysis will be performed based on the PK population.

Descriptive statistics (number of observations, median, arithmetic and geometric means, standard deviations, coefficient of variation, minimum and maximum) will be presented in aflibercept treatment group for C_{VEGF} at baseline (prior to the first infusion), Cmax (at the end of the first infusion), Ctrough (i.e., pre-dose of aflibercept infusion 3-cycle 3, infusion 5-cycle 5, infusion 7-cycle7) of free and adjusted bound aflibercept and ratio of free / adjusted bound aflibercept.

A population pharmacokinetic analysis is currently ongoing investigating the pharmacokinetic of aflibercept administered as monotherapy in the Phase I and II studies. Data analysis will be performed by the NONMEM program using a stepwise approach. Once a pharmacokinetic model will be obtained, covariates effect will be assessed on pharmacokinetic parameters and then individual pharmacokinetic parameter will be estimated. The model will be then evaluated using visual predictive check. Patients characteristics such as age, gender, tumor type, hepatic and renal function will be investigated. As ethnicity also represents an important factor in determining the response of patients, exploration of race will be part of this analysis.

This population PK model will be used to estimate the pharmacokinetics of aflibercept in patients included in this study.

<u>Drug-drug interaction between aflibercept and docetaxel/prednisone:</u>

Aflibercept clearance estimated in this study will be compared to that obtained in studies with aflibercept single agent and aflibercept in combination with docetaxel only. Descriptive statistics of aflibercept clearance estimated in each study will be tabulated. The associated 90% confidence interval for the mean of aflibercept clearance ratio estimated in EFC6546 versus clearance estimated in aflibercept single agent or aflibercept/ docetaxel studies will be calculated.

13.4.7 Anti- Aflibercept antibodies measurement

Blood samples for systematic prospective detection of anti-aflibercept antibody levels are collected at the same timepoints as blood samples for PK parameters, except at the end of first infusion.

Sampling for anti-aflibercept antibody detection is also performed on an adverse event driven basis (See section 8.5.1).

Anti- aflibercept antibody levels will be described categorically as negative (below detection limits), and positive (titer based) by treatment arm and treatment period as appropriate.

13.5 DATA HANDLING CONVENTIONS

13.5.1 General rules for handling of missing, unused or inconsistent data

The following approaches are default methods for missing data handling. Some exploratory analyses can be planned with different strategies for treating missing outcomes. The details will be provided in the SAP.

- Binary data: When a proportion is calculated for a binary variable, the denominator is based on the total number of patients in the analysis population used for the summary. There can be 3 observations: Yes, No, and Non-evaluable (or missing). For the patients with non-evaluable outcomes, the default rule is that the patients will be treated as “no events”.
- Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only. However, the number of patients with missing observations will be provided.
- Time-to-event data: Missing outcomes due to different reasons will be handled using different censoring rules. The censoring rules are specified as part of the definition of the analysis variables.

13.5.2 Censoring in event-free survival analyses

Censoring techniques will be used in the analysis of event-free survival endpoints (e.g. pain progression free survival, PSA progression-free survival, tumor progression-free survival and disease progression-free survival).

- Progression-free survival will be censored on the date of assessment among components of the criteria documenting absence of progression on all components (e.g. radiological tumor progression or occurrence of skeletal related events, or requirement of radiotherapy for cancer related symptoms, or death due to any cause), for patients without progression who are either still on study at the study cut off date or withdrawn from study prior to documentation of disease progression.

- Pain progression-free survival will be censored on the date of last pain assessment documenting absence of pain progression (as described in section 13.2.2) for patients without pain progression for those still on study by the cutoff date for the analysis or withdrawn from study prior to documentation of pain progression
- PSA progression-free survival will be censored on the date of last PSA assessment documenting absence of PSA progression (as described in section 13.2.2) for patients without PSA progression for those still on study by the cutoff date for the analysis or withdrawn from study prior to documentation of PSA progression.
- Time to occurrence of SRE will be censored on the date of last assessment documenting absence of SRE (as described in section 13.2.2) for patients without occurrence of SRE who are either still on study by the cutoff date for the analysis or withdrawn from study prior to documentation of any SRE.

13.6 INTERIM ANALYSIS

The objective of the interim analyses is to provide a methodological rationale and decision rules to the members of the DMC to either recommend to continue the study as planned or to stop earlier the study because of already demonstrated efficacy given the pre-specified α-spending O'Brien Fleming boundaries or because of futility boundaries crossing.

Assuming that the first interim look will actually be carried out on 437 events (50% information fraction e.g. of the total expected deaths), futility boundary will be crossed if the hazard ratio is ≥1.01 in favor of the placebo arm at this time. Although there is no intention to stop the trial for positive outcome at 50% information time, a conservative alpha (0.0015) is allocated at the first interim look using O-F spending function to protect the integrity of the trial as a single pivotal study for registration. At the second interim analysis with 655 deaths observed (75% information fraction), the nominal critical p-value for the one-sided log rank test to declare superiority of aflibercept plus docetaxel / prednisone compared to placebo plus docetaxel / prednisone will be 0.0092.

The final OS analysis will be conducted when 873 deaths have been observed. The one-sided nominal significance level to be used at the final analysis is 0.022.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP).

14.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

14.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator’s Brochure, Investigator’s CV, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigators undertake to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. During these monitoring visits, the following non-exhaustive list of points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to source data which support the data on the Case Report Forms (e.g., patient's medical file, appointment books, original laboratory records, etc.). Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation.

In this study an electronic CRF will be used to collect part of the requested information for all enrolled patients. All CRFs should be completed in their entirety to ensure accurate interpretation of data.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned.

A separate manual will describe in detail the procedures for using the electronic CRF. The sponsor is responsible for ensuring that appropriate material is available at the investigative sites for completion of the electronic CRFs or for providing this material, if needed.

15.5 USE OF COMPUTERIZED SYSTEMS

Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls shall include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, time-stamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination that person who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution of or use of documentation for system operation and maintenance, and revision and change control procedures which document time-sequenced development and modifications of systems documentation.

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

An updated copy in English of the curriculum vitae limited to the experience, qualification and training for each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

16.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

17 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential. The Investigator and any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

18 PROPERTY RIGHTS

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

19 DATA PROTECTION

- The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

20 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy which covers the liability of the Investigator. This insurance policy is in accordance with local laws and requirements.

An insurance certificate will be provided to the Investigator in countries requiring this document.

The insurance of the Sponsor does not relieve the Investigator and the collaborators of any obligation to maintain their own liability insurance policy as required by applicable law.

21 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

22 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

22.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
- If the total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

22.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed.

23 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a Clinical Study Report;

- When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigators.

24 PUBLICATIONS AND COMMUNICATIONS

Once the study has been completed, it is expected that the chair and co-chairs of the study, together with the sponsor, prepare a publication that will be submitted to a peer-reviewed journal.

The investigator undertakes not to make any publication or release pertaining to the Study and/or results of the Study without the sponsor's prior written consent, it being understood that the Sponsor will not unreasonably withhold its approval.

If the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, the first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this Study, subsequent to the procedure set forth hereafter.

The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least thirty (30) days in advance of any presentation or submission for publication. In addition, if requested by the sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or other such measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

If the study is conducted with the support of the main investigators, the latter may define specific rules for publication.

The Investigator shall not use the name(s) of the sponsor and/or its employees in advertising or promotional material or in publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the investigator and/or the collaborators in advertising or promotional material or in publication without having received his/her and /or their prior written content(s).

The Sponsor has the right to publish the results of the study at any time.

For the main publication, authors' ranking will be based on their contribution to design and management of the study and to the number of eligible patients included by centers (only 1 author per center) and the principal investigator will be at least the last author. Other investigators will be acknowledged in the publication.

25 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Clinical Trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

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27 APPENDICES

Appendix A creatinine clearance calculation Formulas

For patients <65 years:

Cockroft-Gault Formula [38]

$$\text{Creatinine Clearance} = \frac{(140 - \text{Age [yrs]}) \times \text{Body Mass (kg)}}{\text{Plasma Creatinine (mg/dL)} \times 72} \times \text{Gender Correction Factor (male : 1.00; female : 0.8 5)}$$

The result obtained is in ml/min

For patients ≥ 65 years:

abbreviated Modification of Diet Renal Disease formula (aMDRD) [44]

Creatinine Clearance (ml/min) =

[186 x (serum creatinine in mg/dL) $^{-1.154}$ x (age in yrs) $^{-0.203}$ (x 0.742 if female) (x 1.21 if african descent)] x BSA/1.73

Appendix B Response evaluation criteria in solid tumors (RECIST) quick reference [39]

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to quality for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response / Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions[1]

[1] Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician. Should prevail and the progression status should be confirmed later on by the review panel (or study chairmen).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

Appendix C Specialized blood sample collection, handling and shipping

Recommended methods for pharmacokinetic, the assay of free endogenous VEGF and anti-aflibercept antibody blood sample collection and handling

Since study treatment is administered intravenously, blood samples for pharmacokinetic analysis should not be collected from the arm where study treatment is infused, or from a central line used for study treatment administration. For samples collected through a catheter, 1 mL of blood should be withdrawn and discarded at each sampling time to ensure that the solution used to maintain catheter patency does not dilute the blood sample.

It is extremely important to collect all blood samples as close to the protocol-specified times as possible. The reasons for any missed or lost blood samples should be documented. Both the scheduled and actual dates/times of blood collection should appear on the blood collection record at the study site. The times of aflibercept or placebo administration should also be precisely recorded.

Blood collection for aflibercept pharmacokinetic analysis in CTAD plasma

At the protocol-specified intervals indicated in Sections 9.3, "CTAD" vacutainer tubes (containing 1 mL of citrate buffer, sodium citrate, and 4.2 mg of citric acid) will be used to collect 4 mL of whole blood from patients for plasma preparation for the determination of circulating free aflibercept and VEGF: aflibercept complex levels for pharmacokinetic analysis.

Because platelet lysis can release VEGF into the serum and possibly affect aflibercept measurements, it is important to carefully follow the steps outlined below:

1. Draw blood slowly, using the largest-bore catheter that is feasible for the patient and transfer blood to a CTAD vacutainer tube (B-D Hemogard, sedimentation rate determination 4.5 mL tubes), being careful to minimize agitation of the sample.
2. gently mix tube by inverting 4 times.
3. Centrifuge at 2000 x g for 15 minutes at room temperature within 1 hour of blood draw.
4. Within 30 minutes after centrifugation, draw off plasma very slowly with transfer pipette to within 0.5 cm of the buffy coat, taking great care not to disturb the buffy coat (any contamination may invalidate the assay).
5. Pipette the plasma specimen into two separate plastic cryovials.
6. Complete corresponding lines for each blood draw on the shipping log. Include patient identification number, initials, and date of specimen collection.
7. All specimens must be stored frozen at -20°C (or colder) in a freezer that is not frost-free until shipped to Regeneron.

8. The Regeneron Specimen Log Sheets must be completed and included along with all shipments to Regeneron.
9. Only the primary samples of each patient should be sent with the first shipment to ensure that duplicates are available at the site for backup in case of damage during shipment.
10. On the day specimens will be shipped, please notify Regeneron to expect arrival.

Sufficient dry ice is to be included for samples to remain frozen for at least 48 hours (recommend at least 14 lbs. of dry ice).

For free aflibercept and VEGF: aflibercept complex assays, the transport of plasma samples from the clinical site to Regeneron Pharmaceuticals, Inc. will take place in containers of solid CO2 and be coordinated with:

Sample Analysis Group
Regeneron Pharmaceuticals, Inc.
[redacted]

Blood collection for Anti- aflibercept antibody analysis

At the protocol-specified intervals indicated in Sections 9.3, red-top vacutainer tubes without clot activator will be used to collect 4 mL of whole blood from patients for serum preparation for the analysis of anti- aflibercept antibodies formation. The following procedures should be followed:

1. Complete the pre-printed labels with Investigator's name, patient identification numbers, initials and date of specimen collection.
2. Allow serum to clot for 30 minutes. Spin at 2000 x g for 15 minutes to separate clot from serum.
3. Pipette the serum specimen into two separate plastic cryovials (supplied by Regeneron Pharmaceuticals, Inc.).
4. Complete corresponding lines for each blood draw on the shipping log. Include: patient identification number, initials, date of specimen collection.
5. All specimens must be stored frozen at -20°C (or colder) until shipped to the laboratory designated by Regeneron Pharmaceuticals, Inc.
6. The Specimen Log Sheet must be completed and included along with all shipments.
7. Only the primary samples of each patient should be sent with the first shipment. This is to ensure that in case of damage during shipment there are duplicates at the site for backup.
8. On the day you will be shipping specimens, please notify Stacy Valluzzo or designee at Regeneron to expect arrival of the package.

Sufficient dry ice is to be included for samples to remain frozen for at least 48 hours (recommend 14 lbs. of dry ice).

For the analysis of anti-aflibercept antibodies, the transport of serum samples from the clinical site to Regeneron Pharmaceuticals, Inc. will take place in containers of solid CO2 and be coordinated with:

Sample Analysis Group
Regeneron Pharmaceuticals, Inc.
[redacted]

Blood collection for the assay of free endogenous VEGF

Blood samples (4 ml) will be collected in **CPD or ACD tubes** and centrifuged at +4°C, at 2000 g for 20 minutes. The plasma will be transferred into two polypropylene screw caps tubes (500 µL in each tube as a minimum) and frozen immediately at -**20**°C in the upright position within 1 hour after the puncture.
All specimens must be stored frozen at -**20°**C until shipped to sanofi-aventis
The Specimen Log Sheet must be completed and included along with all shipments.
One week before specimen shipment, please notify Viviane Letonnelier to expect arrival of the package.

The plasma free VEGF concentrations will be determined at sanofi-aventis, GMPK Alfortville under the responsibility of [redacted] at the following address:

Sanofi-aventis Recherche and développement
[redacted]

Appendix D ECOG performance status scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix E National Cancer Institute Common Terminology Criteria for Adverse Events

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. The evaluator must attempt to discriminate between disease / treatment and related signs / symptoms.
4. An accurate baseline prior to therapy is essential.

See [35]

Appendix F Analgesic scores

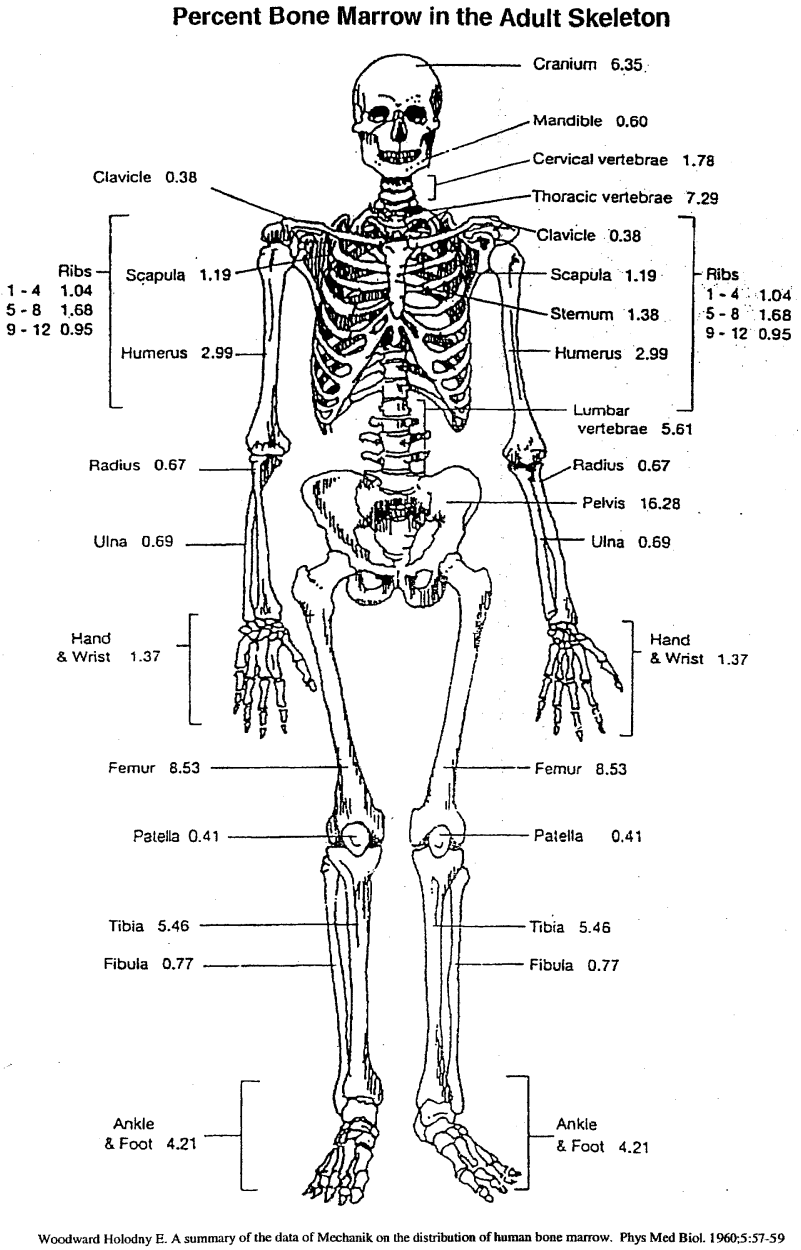
Analgesic use will be recorded in the patient's diary and on the appropriate CRF page. The sponsor or sponsor's designee will convert the analgesic dose to the analgesic score utilizing the table below.

Analgesic score based on analgesic type and dose

Non-narcotic medications (1 point) Any route of administration		Narcotic medications (4 points) Oral or rectal route		Narcotic medications (4 points) Intravenous, intramuscular, or subcutaneous routes	
Generic name	**Dose (mg)**	**Generic name**	**Dose (mg)**	**Generic name**	**Dose (mg)**
Aceclofenac	100	Anileridine	25		
Acemetacin	90	Buprenorphine	0.8	Buprenorphine	0.8
Acetaminophen / paracetamol	325			Butorphanol	1
Aminophenazone	500	Codeine	60		
Aspirin	325	Dextropropoxyphene	50		
Celecoxib	100	Dihydrocodeine	30		
Clonixin	250				
Dexibuprofen	200				
Diclofenac	25	Fentanyl[a]	100 µg	Fentanyl[a]	50 µg
Diflunisal	250	Hydrocodone	10	Hydrocodone	5
Dipyrone / metamizole	500	Hydromorphone	2	Hydromorphone	1
		Ketobemidone	5		
Etodolac	200	Levorphanol	2	Levorphanol	2
Fenoprofen	200	Meperidine / pethidine	100	Meperidine / pethidine	50
Flurbiprofen	50	Methadone	10		
Ibuprofen	200	Morphine	10	Morphine	5
Indomethacin	25	Oxycodone	5	Oxycodone	2.5
Ketoprofen	25	Oxymorphone (rectal)	2.5		
Ketorolac	10			Papaveretum	15.4
Lornoxicam	8				
Mefenamic acid	250	Pentazocine	50	Pentazocine	30
Meloxicam	7.5				
Nabumetone	500	Piritramide	15		
Naproxen	250	Propoxyphene	50		
Nefopam	20	Tilidine	50		
Nimesulide	100	Tramadol	50	Tramadol	50
Phenacetin	180				
Propyphenazone	250				
Rofecoxib	12.5				
Tenoxicam	20				

[a] Fentanyl patch (TTS): 36 points/day for 25µg/hour patch.
The information in this table was adapted from Tannock et al., *J Clin Oncol* 1996;14(6):1756-1764 and Martindale 1996; 31st Edition, London Royal Pharmaceutical Society.

Appendix G Percent bone marrow in the human skeleton



Woodward Holodny E. A summary of the data of Mechanik on the distribution of human bone marrow. Phys Med Biol. 1960;5:57-59

Appendix H Present pain intensity score

The patient will answer the question, "How much pain have you experienced during the previous 24 hours," by choosing from the possibilities in the possibilities below.

0 ☐ No pain

1 ☐ Mild

2 ☐ Discomforting

3 ☐ Distressing

4 ☐ Horrible

5 ☐ Excruciating

Each result will be recorded in the patient's diary and on the appropriate CRF page.

Appendix I New York Heart Association Classification

Functional Class	Description
0	No cardiac disease or limitations
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina.
III	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present event at rest. With any physical activity, increased discomfort is experienced.

Appendix J Health Realated Quality of life questionnaire FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea (I feel sick)	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain areas of my body where I experience significant pain.....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my current level of physical comfort	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating (passing water)	0	1	2	3	4
BL2	I urinate more frequently than usual.....	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4