NCT number:NCT01571284

CLINICAL TRIAL PROTOCOL

COMPOUND: AFLIBERCEPT

A Multicenter, Single arm, Open Label Clinical Trial to Evaluate the Safety and Health-Related Quality of Life of Aflibercept in Patients with Metastatic Colorectal Cancer (mCRC) Previously Treated with an Oxaliplatin-Containing Regimen

STUDY NUMBER: AFLIBC06097

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NAMES AND ADDRESSES OF STUDY MANAGEMENT (Global Medical Affairs & Observational Studies)	Name: Address: Tel: E-mail: Name: Address: Tel: E-mail: Name: Address: Tel: E-mail:	[redacted]
ONCOLOGY DIVISION REPRESENTATIVE	Name: Address: Tel: E-mail:	[redacted]
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	Click here and type To be completed locally (Should be the contact person for the investigator (e.g.: in case of SAE), can be CRO Team according to what is delegated by Sanofi)
SPONSOR	Company: Address:	sanofi aventis Groupe 174 avenue de France 75013 Paris France

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1. SYNOPSIS

COMPOUND: AFLIBERCEPT **STUDY No.: AFLIBC06097**

TITLE	A multicenter, single arm, open label clinical trial to evaluate the safety and Health-Related Quality of life of aflibercept in patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen
TRIAL LOCATION	International Europe, North America, Asia and Latin America
STUDY OBJECTIVE(S)	Primary objective: * To provide mCRC patients (similar to the patients evaluated in the VELOUR phase III trial) and Investigators with access to aflibercept, prior to its marketing authorisation and/or commercial availability and to document the aflibercept overall safety in this patient population. Secondary objective: * To document the Health-Related Quality of Life (HRQL) of aflibercept in this patient population.
STUDY DESIGN	This is a prospective, phase IIIb/IV, International, Multicenter, Single Arm, Open-label Study. Each patient will be treated until disease progression, unacceptable toxicity, death, Investigator's decision or patient's refusal for further treatment (whichever come first). Patients will be followed-up during treatment and for at least 30 days after last treatment (either aflibercept or FOLFIRI) administration (for safety assessment).
STUDY POPULATION Main selection criteria:	<u>Inclusion criteria</u>: - Histologically or cytologically proven adenocarcinoma of the colon or rectum - Metastatic disease - Age ≥18 years - ECOG PS 0-1 - One and only one prior chemotherapeutic regimen for metastatic disease. This prior chemotherapy must be an oxaliplatin containing regimen. Patients must have progressed during or following the last administration of the oxaliplatin based chemotherapy. Patients relapsing within 6 months of completion of oxaliplatin adjuvant chemotherapy are also eligible. - Signed written informed consent obtained prior to inclusion.

	Exclusion criteria: - Prior therapy with irinotecan - Inadequate bone marrow function: • Absolute neutrophil counts (ANC) < 1.5 x 10^9/L • Platelet count < 100 x 10^9/L • Hemoglobin < 9.0 g/dL - Inadequate liver function tests: • Total bilirubin >1.5 x ULN • Transaminases >3 x ULN (unless liver metastasis are present, 5 x ULN in that case) • Alkaline phosphatase >3 x ULN (unless liver metastasis are present, 5 x ULN in that case) - Less than 4 weeks elapsed from prior radiotherapy or prior chemotherapy to the time of inclusion. Less than 4 weeks following major surgery to the time of inclusion or until the surgical wound is fully healed whichever came later (48 hours in case of minor surgical procedure or until wound full healing observed). - Treatment with any investigational drug within 30 days prior to inclusion. - Adverse events (with exception of alopecia, peripheral sensory neuropathy and those listed in specific exclusion criteria) from any prior anti cancer therapy of grade >1 (National Cancer Institute Common terminology Criteria [NCI CTCAE] v.4.0) at the time of inclusion. - History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease. - Other prior malignancy. Adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or any other cancer from which the patient has been disease free for > 5 years are allowed. - Any of the following within 6 months prior to inclusion: 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 inclusion: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive oesophagitis 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 inclusion.

	- Known 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 to interfere with interpretation of study results. - Known dihydropyrimidine dehydrogenase deficiency - Predisposing colonic or small bowel disorders in which the symptoms were uncontrolled as indicated by baseline of > 3 loose stools daily. - Prior history of chronic enteropathy, inflammatory enteropathy, chronic diarrhea, unresolved bowel obstruction/sub-obstruction, more than hemicolectomy, extensive small intestine resection with chronic diarrhea. - History of anaphylaxis or known intolerance to atropine sulphate or loperamide or appropriate antiemetics to be administered in conjunction with FOLFIRI. - Treatment with concomitant anticonvulsivant agents that are CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine), unless discontinued >7 days. - Patients with known Gilbert's syndrome. - Pregnant or breast-feeding women. Positive pregnancy test (serum or urine β-HCG) for women of reproductive potential. - Patients with reproductive potential (female and male) who do not agree to use an accepted effective method of contraception during the study treatment period and for at least 6 months following completion of study treatment. The definition of effective method will be left to the investigator's judgment. - For female patients enrolled in United Kingdom, the following methods of contraception are acceptable: oral contraceptives accompanied by the use of a second method of contraception, as it is not known how oral contraceptives interact with study medications or Intra Uterine Device (IUD) or women who are surgically sterile, or women who are post –menopausal or other reasons have no chance of becoming pregnant. <u>Exclusion criteria related to Aflibercept</u>: - Urine protein-creatinine ratio (UPCR) >1 on morning spot urinalysis or proteinuria > 500 mg/24-h. - Serum creatinine > 1.5 x upper limit of normal (ULN). If creatinine 1.0-1.5 x ULN, creatinine clearance, calculated according to Cockroft-Gault formula, < 60 ml/min will exclude the patient. - Uncontrolled hypertension (defined as blood pressure > 140/90 mmHg or systolic blood pressure >160 mmHg

	when diastolic blood pressure < 90 mmHg, on at least 2 repeated determinations on separate days, or upon clinical judgement) within 3 months prior to study inclusion. - Patients on anticoagulant therapy with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3) within the 4 weeks prior to inclusion. - Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g. INR>1.5 without vitamine K antagonist therapy), non-healing wound.
Total expected number of patients:	Approximately 900
Expected number of sites:	Approximately 150. All sites located in the US will be considered under IND obligations while all the other sites outside US will not be under IND.
INVESTIGATIONAL MEDICINAL PRODUCT/ NON INVESTIGATIONAL MEDICINAL PRODUCTS (BACKGROUND TREATMENTS) **Formulation(s):**	Aflibercept for IV administration supplied as a sterile, non-pyrogenic, colorless to pale-yellow colored, 25 mg/mL solution, packaged in a type 1, clear borosilicate glass vial closed with a flanged cap with tear-off lid and inserted sealing disc, Flurotec® (PTFE) coated. Two aflibercept drug product vial sizes available: - 100 mg/4 mL in a 5 mL vial - 200 mg/8 mL in a 10 mL vial The content of the vials must be diluted prior to infusion. Background treatments products (marketed formulation): - Irinotecan, Fluorouracil (5-FU) and Leucovorin (LV): see manufacturer's product information for handling, administration and storage. Commercially available products will be used.
Route(s) of administration:	Intravenous (I.V.) infusion
Dose regimen:	Aflibercept: 4 mg/kg over 1 hour on Day 1 followed by FOLFIRI, administered as follows: - dl-leucovorin: 400 mg/m² over 2 hours infusion on day 1 - Irinotecan: 180 mg/m² over 90-minute infusion, on day 1, followed by bolus 5-FU 400 mg/m² and 5-FU continuous infusion 2400 mg/m² over 46 hours infusion. Or as individualized by physician's clinical judgment.

	Treatment cycle to be administered every 2 weeks. Study treatment (aflibercept and FOLFIRI) has to be discontinued upon documentation of disease progression. If FOLFIRI (or either of its components) is permanently discontinued, then aflibercept should be continued until disease progression or unacceptable toxicity or patient's refusal of further treatment. If aflibercept is permanently discontinued, then FOLFIRI can be continued until disease progression or unacceptable toxicity or patient's refusal of further treatment. The end of treatment will be the date of the last treatment administration, either aflibercept or FOLFIRI whichever comes last. Patient treatment after aflibercept and FOLFIRI permanent discontinuation is at investigator discretion. Dose reduction and/or treatment delay and/or treatment discontinuation are planned in case of severe toxicity. Therapeutic use of Granulocyte Colony-Stimulating Factor (G-CSF) may be considered (if consistent with the local institutional treatment practice), upon occurrence of a first episode of grade $\geq$3 neutropenia and as secondary prophylaxis for subsequent cycles, in patients who may be at increased risk for neutropenia complications. The starting dose of irinotecan and/or 5-FU components of FOLFIRI regimen should take into consideration toxicities from prior regimens received by the patient and the patient characteristics (like UGT1A1*28 allele status, when known). In case drugs (5FU) administered during previous chemotherapy regimen were reduced due to toxicity, the decision to administer or not the full starting dose of FOLFIRI (irinotecan, 5FU continuous and/or bolus infusion) will be left to the investigator decision based on his/her clinical judgement of patient benefit at time of inclusion (provided all patient eligibility criteria are fulfilled). To start with a reduced dose of FOLFIRI may be considered.

PRIMARY STUDY ENDPOINT
 	
SECONDARY ENDPOINT
	<u>Primary endpoint:</u>
	- Safety:
	    o treatment-emergent adverse events (TEAEs) will be assessed: terminology (according to MedDRA - Medical Dictionary for Regulatory Activities), frequency and severity (according to NCI CTCAE V4.0), seriousness and relatedness;
	    o Laboratory abnormalities according to NCI-CTC V4.0.
	<u>Secondary endpoint:</u>
	- Health-Related Quality of Life (HRQL) assessed by

	using changes from baseline in scores derived from the following questionnaires: o EORTC QLQ-C30 (version 3); o EQ-5D™ (version 4) <u>Exploratory endpoint (optional):</u> - Health-Related Quality of Life (HRQL) assessed by using changes from baseline in scores derived from the following questionnaires: o EORTC QLQ CR29 (disease specific supplement to QLQ-C30).
SAFETY CRITERIA	Data collected for the assessment of safety: - Number of cycles administered, duration of dosing in weeks, cumulative dose received and reason for End of Treatment (EOT). Dose delays, omission and reductions will also be analyzed. - Adverse Events (AEs)/Serious Adverse Events (SAEs)
STATISTICAL CONSIDERATIONS	No formal sample size calculation is performed. The safety population (all included patients who received at least part of one dose of treatment) will be used to document safety. Only descriptive summaries will be provided. Interim analyses are planned during the course of the study, in order to obtain preliminary results on baseline characteristics, HRQL and safety data.
DURATION OF STUDY PERIOD	The study is planned to be initiated in the second quarter of 2012 in Europe and in the United States, simultaneously or sequentially in the other involved countries. In each country, patient recruitment will end when aflibercept (ZALTRAP) becomes commercially available (i.e. accessible to the patient as per each country regulation). Patients already included will continue to be treated until disease progression, death, unacceptable toxicity, Investigator's decision or patient's refusal of further treatment.

2. FLOW CHART

2.1 Study Flow chart

Evaluation	Baseline		Treatment		Post-treatment FUP
			Every cycle	End of Treatment (EOT) (30 days after last treatment)	
Informed consent	X	INCLUSION			
Inclusion/exclusion criteria	X				
Demography	X				
Prior Medical/Surgical History & Cancer History, Prior Medication History	X				
Clinical examination	X		X	X	
Hematology (a)	X		X		
Biochemistry (b)	X		X		
Urinalysis (c)	X		X		
Concomitant medication (d)			X	X	
Aflibercept + FOLFIRI (e)			Every 2 weeks (within 3 days from inclusion)		
AE / SAE (f)	X		X	X	X
Health-Related Quality of Life (g) EORTC- QLQ C30/ QLQ-CR29*/ EQ-5D™	X		X (every odd cycle starting from C3)	X	

a) Hematology (hemoglobin, WBC, ANC, platelet count); prothrombin time (expressed as INR) only for patients under VKA therapy
b) Biochemistry (sodium, chloride, potassium, calcium, blood urea nitrogen (BUN)/urea, creatinine, glucose, SGOT (AST), SGPT (ALT), alkaline phosphatase, LDH, total bilirubin, total protein, albumin.
c) Urinalysis: prior to inclusion perform UPCR/proteinuria to determine patient elegibility as per section 8.3. Following inclusion dipstick (WBC, RBC, urinary protein) will be assessed on morning urine spot before treatment administration. If urine protein on dipstick is ≥2+, perform UPCR before treatment administration. During study treatment, 24-hour urine collection should be performed to quantify proteinuria when

UPCR>1; in case UPCR >2 or in case a proteinuria from renal origin is associated with hematuria then a work-up for considering thrombotic microangiopathy should be considered.

d) Concomitant medications: G-CSF, pre-medications, antidiarrheal, Vitamin K antagonist, heparins, antihypertensive medications, SAEs corrective therapies, and any further anticancer treatment started within 30 days of last treatment administration (aflibercept/Folfiri), should be documented into e-CRF.

e) Treatment with aflibercept will start on Cycle 1 Day 1 just before FOLFIRI administration and then repeated every 2 weeks.

f) Adverse Events (AEs), regardless of seriousness or relationship to study treatment (aflibercept/Folfiri), will be collected from the time the patient signs the informed consent form up to 30 days after the last treatment administration (aflibercept or Folfiri). Following the 30 day EOT visit all ongoing SAEs (regardless of relationship with study treatment) as well as ongoing related AEs and new related SAEs will have to be collected and followed till resolution/stabilisation (stabilisation being defined as an event ongoing without any change for at least 3 months). Vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation/dose modification (reduction and/or delay) and/or fulfilling a seriousness criterion. Laboratories abnormalities are to be recorded as AE only if they are serious or leading to discontinuation/dose modification.

g) Health-Related Quality of Life (QoL questionnaires): to be self-administered by the patient at the center, prior to informing the patient about disease evolution, before the next study treatment and before any other assessment is performed. A key person (e.g., research nurse) at each center should 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 at baseline (before first treatment administration), before the treatment administration at the beginning (D1) of every odd cycle (cycle 3, 5, etc) and at the end of treatment visit.

* QLQ-CR29 as optional: if it is completed at baseline it should be collected at all further time-points as per EORTC-C30 questionnaire.

3. CLINICAL TRIAL PROTOCOL AGREEMENT FORM

I, ……, the investigator, have examined the above-referenced Sanofi clinical trial protocol and have fully discussed the objectives of this clinical trial and the content of this clinical trial protocol with the sponsor's team.

I agree to conduct the clinical trial according to this clinical trial protocol and to comply with its requirements, subject to ethical and safety considerations.

In understand that, should the decision be made by the sponsor to terminate prematurely or suspend the clinical trial at any time for whatever reason, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the clinical trial, I will communicate such decision in writing to the sponsor.

INVESTIGATOR

NAME:
DATE: _____ (e.g., 05 February 2010)

Signature: _____

FOR THE SPONSOR

NAME:
ADDRESS:

SIGNATORY

NAME:
DATE: _____ (e.g., 05 February 2010)

Signature: _____

4. LIST OF ABBREVIATIONS

5-FU	5-Fluorouracil
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT (SGPT)	Alanine Aminotransferase (or Serum Glutamate-Pyruvate Transferase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate Aminotransferase (or Serum Glutamate-Oxaloacetate Transferase)
BSA	Body Surface Area
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CNS	Central nervous system
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DRF	Discrepancy Resolution Form
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FUP	Follow-up
FOLFIRI	Irinotecan/bolus-infusion-5-Fluorouracil/Leucovorin
FOLFOX	Oxaliplatin/bolus-infusion-5-Fluorouracil/Leucovorin
GCP	Good Clinical Practices
HCG	Human Chorionic Gonadotrophin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
HSR	Hypersensitivity Reaction
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethical Committee
IFL	Irinotecan/5-Fluorouracil (weekly 4/6)/Leucovorin
Ig	Immunoglobulin
INR	International Normalized Ratio
IMP	Investigational Medicinal Product
IND	Investigational New Drug

IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
LDH	Lactate Dehydrogenase
LV	Leucovorin
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Package Insert
PlGF	Placental Growth Factor
PS	Performance Status
RBC	Red Blood Cell
RPLS	Reversible posterior Leuko-encephalopathy
ORR	Overall Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
SD	Standard Deviation
TMA	Thrombotic micro-angiopathy
ULN	Upper Limit of Normal
UPCR	Urinary Protein-Creatinine Ratio
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

5. INTRODUCTION AND RATIONALE

5.1 Colorectal cancer

Colorectal cancer is among the most frequent tumor types in the western countries, being the third most commonly diagnosed cancer in males (after lung and prostate) and the second most common in females (after breast cancer) with an increasing incidence in the low-risk area countries (Ref. 1). In 2008, the incidence of colorectal cancer was over 1.2 million cases, with mortality over 600,000 worldwide (Ref. 2). The end prognosis is dependent upon the extent of the disease. The five year survival rate in early localized stage of about 90% decreases to approximately 60-65% after spread to adjacent organ(s) or lymph nodes and is about 5-8% after spread to distant sites (Ref.3).

When diagnosed before nodal involvement, treatment is usually limited to surgical resection (and radiotherapy for patients with rectal cancer). Patients with nodal involvement are candidates for adjuvant chemotherapy following initial surgery in the attempt to prevent metastatic recurrence of the disease. Once spread to distant sites, treatment essentially consists of palliative chemotherapy.

Despite the fact that 75% to 80% of all the patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically removed, almost half of these patients will develop metastatic disease. Furthermore, typically 20% to 25% of the patients present with metastatic disease at diagnosis. Although mortality rates have been decreasing due to improved treatment options and early detection, once metastases are present median overall survival with available combination therapy is around 24 months (Ref. 4, Ref. 5, Ref. 6).

5.2 Metastatic colorectal cancer treatment

For many years, chemotherapy for colorectal cancer has been based on the use of the antimetabolite 5-fluorouracil (5-FU), administered with leucovorin (LV). Modifications in the administration schedules of this combination have yielded improvements in its use, with the fortnightly administration of bolus 5-FU and LV followed by 5-FU infusion, demonstrating improved activity (in terms of response rate and PFS) and safety over the so-called Mayo regimen (monthly 5-day bolus regimen) (Ref. 7). This combination, however, did not result in any improvement on survival (Ref. 8).
Improved survival in patients with colorectal cancer was not observed until the development of oxaliplatin and the topoisomerase I inhibitor irinotecan when phase 3 studies combining any of those agents with 5-FU and LV in a first-line metastatic setting showed median overall survival of 15 to 19 months (Ref. 9, Ref. 10, Ref. 11).

Currently, initial therapy in patients with mCRC is based on oxaliplatin-based chemotherapy (FOLFOX, capecitabine/oxaliplatin) or FOLFIRI (fortnightly leucovorin/bolus-infusional 5-FU/irinotecan). IFL, a previously used irinotecan-based regimen, is no longer used routinely due to safety concerns and has largely been replaced by FOLFIRI.
Therapy after first progression of the disease is based on a crossover from oxaliplatin treatment to irinotecan or vice-versa. The results from sequential therapy, reported by Tournigand et al, in a study in which patients with newly diagnosed mCRC were randomized to FOLFOX followed by FOLFIRI or the reverse sequence as first and second-line treatments support this approach (Ref. 5).

Todays standard treatments for mCRC have evolved to include the addition of targeted biologic therapies to the combination of 5-FU/LV with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI).

Targets for biologic therapies include vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR).

Anti-VEGF therapy
Several malignant tumors are dependent on angiogenesis (the growth of new blood vessels from existing vasculature) to maintain a source of nutrition and oxygen from the body to support their growth and metastasis. VEGF has become a major target for anti-angiogenic therapy because its overexpression in several tumor types (including tumors of the gastro-intestinal tract) has been associated with increased tumor vascularity, proliferation, progression, invasion, metastasis, and poor prognosis.
Furthermore, it has been shown that the level of VEGF is particularly elevated in patients with metastatic colorectal cancer, suggesting that the VEGF-induced increase in vascular permeability may contribute to the formation of malignant ascites.
mCRC is one of the first malignancy in which a clear benefit was demonstrated with an anti-VEGF treatment in randomized clinical trials.

Bevacizumab is a humanized monoclonal antibody that targets VEGF-A, a member of the VEGF-receptor activating ligands. It has demonstrated a survival benefit in the first-line [in combination with IFL, FOLFIRI and FOLFOX (Ref. 6, Ref. 12) and second-line (in combination with FOLFOX) treatment of mCRC (Ref. 13).
In a recent press release a statement was made that bevacizumab tested in combination with standard chemotherapy (either irinotecan or oxaliplatin based) as second line treatment following a first-line treatment with standard chemotherapy in combination with bevacizumab, met its primary endpoint of overall survival. More results are awaited (ML18147 study) and expected to be presented at an upcoming medical oncology conference.

Anti-EGFR therapies
Both cetuximab and panitumumab (respectively a chimeric and a fully human monoclonal antibody binding to EGFR) demonstrated activity in patients with refractory mCRC (Ref. 14, Ref. 15). After early indications that cetuximab could improve efficacy when combined with irinotecan in mCRC (Ref. 16), the phase 3 CRYSTAL study of FOLFIRI with or without cetuximab in first-line patients was able to demonstrate a significant improvement in PFS (the primary objective) and response rate in patients treated with cetuximab and FOLFIRI (Ref. 17), but showed no statistically significant improvement in overall survival. Post-hoc analysis, performed to evaluate the impact of KRAS status on the effect of adding cetuximab to FOLFIRI, demonstrated that patients with KRAS mutations received no benefit from cetuximab (Ref. 18). Similar results in the same patient setting were reported with the combination of cetuximab with the FOLFOX regimen (Ref. 19). Recently, a phase 3 trial with panitumumab combined to FOLFOX in the first-line setting and to FOLFIRI in the pre-treated setting, failed to demonstrate a significant survival advantage over FOLFOX and over FOLFIRI, respectively, even in wild type KRAS mCRC patients (Ref. 20, Ref. 21).

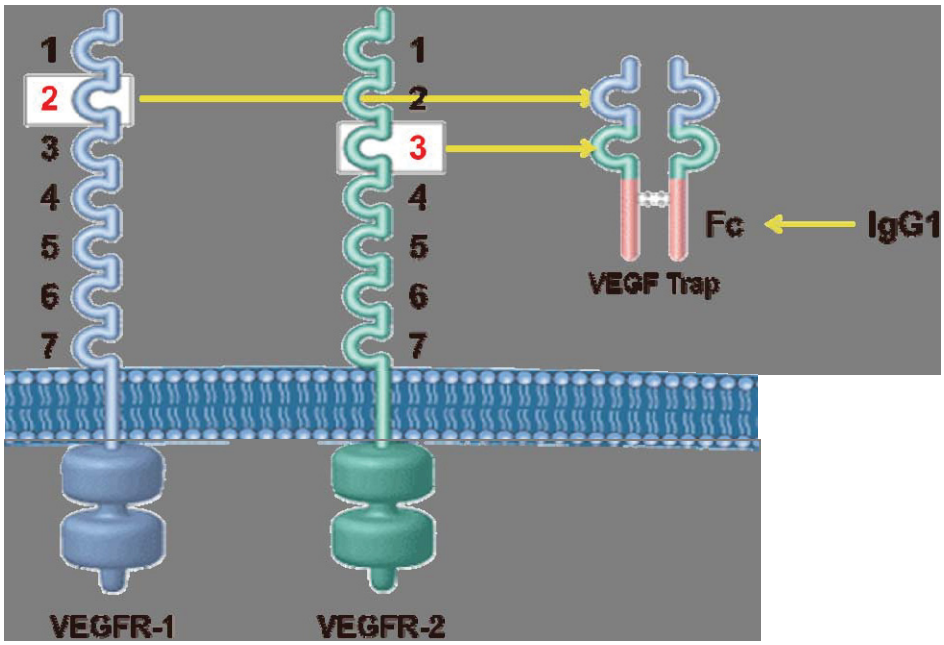
Initial therapy in patients with mCRC is actually based on oxaliplatin/5-FU/LV or on irinotecan/5-FU/LV chemotherapy combined with bevacizumab followed by the alternate sequence in second line setting, either with or without biologics.

Cetuximab and panitumumab are palliative options for patients whose tumors harbor wild-type KRAS, but their addition to chemotherapy has not yet shown a significant improvement in overall survival.

5.3 Aflibercept background

Aflibercept (referred also as VEGF-Trap or AVE0005) is a novel antiangiogenic agent. It is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains (from both VEGFR1 and VEGFR2) fused to the F_c portion of human IgG_1 (Immunoglobulin G1).

Figure 1 – Aflibercept schematic representation (VEGF Trap)



Aflibercept interferes with the biological actions of VEGF by complexing VEGF in the blood stream and extravascular space and preventing it from interacting with its receptors on endothelial cells. The molecule functions as a soluble decoy receptor for VEGF with high affinity to all VEGF-A isoforms (i.e. binds more tightly to aflibercept than to native receptors), VEGF-B and placental growth factor (PlGF1 and PlGF2) and with a long circulating half life.

Aflibercept was designed to prevent the growth of primary and metastatic tumors by blocking tumor angiogenesis and vascular permeability.
In preclinical studies aflibercept inhibited tumor growth, either as single agent or in combination with chemotherapy, in a variety of mouse tumor models and acted synergistically when combined with standard chemotherapeutic agents, 5-fluorouracil and irinotecan included.

Phase I and early phase II clinical trials demonstrated activity in a range of tumor types with increased responses when used in combination with chemotherapy, including also 5-fluorouracil and irinotecan (phase I trial TCD6118).

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, reaching a plateau thereafter between 2 and 7 mg/kg, suggesting that free aflibercept is present in sufficient amount to bind all endogenous VEGF at these higher dose levels.
The 4 mg/kg dose, administered once every 2 weeks, was selected for development, as it appeared to provide an adequate aflibercept free/bound ratio at the end of a q2 week dosing interval, at the steady state.

The preliminary activity observed in the dose escalation Phase I (TCD6118) with standard doses of irinotecan/5FU/LV together with the above mentioned preclinical activity were the basis for the conduction of the pivotal phase III study EFC10262/VELOUR in mCRC patients.

The VELOUR phase III double-blind clinical trial has been conducted in 1.226 patients with metastatic colorectal cancer (mCRC) who progressed during or after the completion of treatment with an oxaliplatin-based regimen. Patients were randomised either to receive aflibercept 4 mg/kg in combination with FOLFIRI (n=612) every 2 weeks or FOLFIRI every 2 weeks (n=614) alone. Primary endpoint was overall survival (target hazard ratio (HR) was 0.8 with 90% power and a 2-sided type I error of 0.05); secondary endpoints included Progression-free survival (PFS), overall response rate (ORR), safety and pharmacokinetic. Stratification factors were prior bevacizumab therapy (that was permitted) and ECOG PS. Approximately 28% of patients in each arm received prior bevacizumab as part of their initial treatment.
The median number of cycles delivered was 9 in the aflibercept arm compared to 8 in the placebo one. OS was based on 863 death events out of 1216 treated patients.
The median OS was significantly longer in the aflibercept arm (13.5 months) compared to placebo (12.06 months) with an HR= 0.817 [95% CI, 0.71-0.94], p = 0.0032. The survival curves separated early and continued to separate throughout the follow-up period. The clinical benefit of aflibercept treatment is further observed by the increase in the 2-year survival rate. Median PFS was significantly higher in the aflibercept arm, with an absolute increase of 2.23 months over the placebo arm (6.9 months versus 4.67 mo; HR=0.76 [95%CI, 0.58-0.99], p=0.00007), representing approximately a 25% reduction in the risk of disease progression. The ORR (evaluable population) in the aflibercept arm was significantly higher than in placebo (19.8% versus 11.1%, p=0.0001).
Pre-specified subgroup analyses (accounting for stratification factors and patient characteristics) supported consistency and robustness of the efficacy results (OS and PFS) across all domains, including prior treatment with bevacizumab, with no evidence of interaction between treatment and prior bevacizumab exposure. A significant interaction was observed between treatment arm and the presence of liver metastases only, indicating a greater treatment effect in this group of patients, as compared with patients with disease not confined to the liver or no liver disease. Adverse events (AEs) were similar to the safety profile of FOLFIRI chemotherapy. Grade 3-4 adverse events (AEs) with > 2% higher incidence in aflibercept arm *vs* placebo were diarrhea, asthenia/fatigue, stomatitis/ulceration, infections, hypertension, GI/abdominal pain, neutropenia/neutropenic complications and proteinuria. AEs leading to treatment discontinuation occurred in 26.6% and 12.1% of patients in aflibercept and placebo arm respectively. For aflibercept the most common causes were asthenia/fatigue, infections, diarrhea, hypertension and venous thromboembolic events. The incidence of grade 3-4 adverse events were as expected with the anti-VEGF class of agents, and were similar among patients with and without prior bevacizumab exposure. Grade 3-4 hypertension occurred in 16.6% and 20.5% of these groups, respectively. Prior treatment with bevacizumab did not appear to significantly impact the safety profile of aflibercept (Ref. 22, Ref. 23).

Further details on preclinical, clinical safety and preliminary efficacy are provided in the Investigator's Brochure, which contains comprehensive information on aflibercept (Ref. 24).

5.4 Study rationale

Treatment options for patient with previously treated metastatic colorectal cancer are limited and, prior to the public presentation of the VELOUR study results, no biological therapies have been shown to provide a survival benefit in the second-line setting in patients who are being treated with FOLFIRI. This still remains to be the case and at need to add another treatment option to the current battery of therapies.

Aflibercept is the first therapeutic agent in combination with FOLFIRI to demonstrate survival benefit in non-selected patients with mCRC who had progressed following an oxaliplatin-based regimen.

Aflibercept in the oncology setting is an investigational agent and has not been approved for marketing by any Regulatory Authority to date. VELOUR results will serve as basis of worldwide marketing authorization dossier filings.

The use of a non-registered product within a pre-approval access program (i.e. before marketing authorisation is released) may be a treatment option for patients with an unmet medical need for which no suitable or clinically satisfactory similar alternative is currently available or when similar alternative treatments failed.

The results of the VELOUR trial are expected to generate significant interest and increase demand for accessing aflibercept because of the medical need, among the 2L mCRC patients.

This study is therefore required to allow patients and physicians access to aflibercept for the management of mCRC patients having progressed after an oxaliplatin-based regimen.

This study will permit collection of data from the VELOUR target patient population in the real-life setting and across different geographical areas with the aim to capture utility values derived from Quality of Life (QoL) instruments and everyday practice safety data in order to raise awareness of the anticipated toxicities typical of the anti-angiogenic class and to further extend understanding of recently reported benefit patient showed from VELOUR.

Investigators who had previous experience with aflibercept (i.e., who have had at least one patient treated in the VELOUR trial) or have extensive experience in administering anti-angiogenic agents will be invited to participate in this study.
Investigators who have not previously participated in the VELOUR trial will be specifically trained on the use of aflibercept and the management of its adverse events.

6. STUDY OBJECTIVES

6.1 Primary

To provide mCRC patients (similar to the patients evaluated in the VELOUR phase III trial) and Investigators with access to aflibercept, prior to its marketing authorisation and/or commercial availability and to document the aflibercept overall safety in this patient population.

6.2 Secondary

To document the Health-Related Quality of Life (HRQL) of aflibercept in this patient population.

7. STUDY DESIGN

7.1 Description of the protocol

This is a phase IIIb/IV, international, multicenter, single arm, open-label study.

7.2 Duration of study

The study will be initiated in the second quarter of 2012 in Europe and in the United States, simultaneously or sequentially in the other involved countries.

In each country patient recruitment will end when aflibercept (ZALTRAP) becomes commercially available (i.e. accessible to the patient as per each country regulation).

Patients already on study will continue to be treated until disease progression, death, unacceptable toxicity, Investigator's decision or patient's refusal of further treatment, whichever comes first.

8. SELECTION OF PATIENTS

8.1 Number of patients planned

It is planned to include a total of approximately 900 patients in this study, from around 150 investigational sites, over about 20 months of accrual.

Global study accrual will be terminated when the anticipated number of patients has been achieved across all study sites.

Actively treated patients from VELOUR (EFC10262) study who will be still under treatment with aflibercept at the time of initiation of this study will be allowed to rollover on to this study if according to their treating Investigator's opinion they are continuing to derive benefit from treatment with aflibercept.

No confirmation of entry criteria will be required for these patients provided they meet the criteria to initiate a subsequent cycle of therapy.

A new patient number will be assigned to these patients, however the patient number from the VELOUR study and the new study number will be annotated on a specific form to be able to track individual patients from the parental protocol to this study.

8.2 Inclusion criteria

I01 Histologically or cytologically proven adenocarcinoma of the colon or rectum

I02 Metastatic disease

I03 Age ≥18 years

I04 ECOG PS 0-1

I05 One and only one prior chemotherapeutic regimen for metastatic disease This prior chemotherapy must be an oxaliplatin containing regimen. Patients must have progressed during or following the last administration of the oxaliplatin based chemotherapy. Patients relapsing within 6 months of completion of oxaliplatin adjuvant chemotherapy are also eligible.

I06 Signed written informed consent

8.3 Exclusion criteria

E01 Prior therapy with irinotecan

E02 Inadequate bone marrow function as follow**:**

- Absolute neutrophil count (ANC) < 1.5 x 10^9/L
- Platelet count < 100 x 10^9/L
- Hemoglobin < 9.0 g/dL

E03 Inadequate liver function tests:

- Total bilirubin >1.5 x ULN
- Transaminases >3 x ULN (unless liver metastasis are present, 5 x ULN in that case)
- Alkaline phosphatase >3 x ULN (unless liver metastasis are present, 5 x ULN in that case)

E04 Less than 4 weeks elapsed from prior radiotherapy or prior chemotherapy to the time of inclusion. Less than 4 weeks following major surgery to the time of inclusion or until the surgical wound is fully healed, whichever came later (48 hours in case of minor surgical procedure or until wound full healing observed) (ref to section 9.1.3 for examples of minor surgeries).

E05 Treatment with any investigational drug within 30 days prior to inclusion.

E06 Adverse events (with exception of alopecia, peripheral sensory neuropathy and those listed in specific exclusion criteria) from any prior anti cancer therapy of grade >1 (National Cancer Institute Common terminology Criteria [NCI CTCAE] v.4.0) at the time of inclusion.

E07 History of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease.

E08 Other prior malignancy. Adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or any other cancer from which the patient has been disease free for > 5 years are allowed.

E09 Any of the following within 6 months prior to inclusion: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, stroke or transient ischemic attack.

E10 Any of the following within 3 months prior to inclusion: Grade 3-4 gastrointestinal bleeding/hemorrhage, treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event.

E11 Occurrence of deep vein thrombosis within 4 weeks, prior to inclusion.

E12 Known acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.

E13 Any severe acute or chronic medical condition, which could impair the ability of the patient to participate to the study or to interfere with interpretation of study results.

E14 Known dihydropyrimidine dehydrogenase deficiency

E15 Predisposing colonic or small bowel disorders in which the symptoms were uncontrolled as indicated by baseline of > 3 loose stools daily.

E16 Prior history of chronic enteropathy, inflammatory enteropathy, chronic diarrhea, unresolved bowel obstruction/sub-obstruction, more than hemicolectomy, extensive small intestine resection with chronic diarrhea.

E17 History of anaphylaxis or known intolerance to atropine sulphate or loperamide or appropriate antiemetics to be administered in conjunction with FOLFIRI.

E18 Treatment with concomitant anticonvulsivant agents that are CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine), unless discontinued >7 days.

E19 Patients with known Gilbert's syndrome.

E20 Pregnant or breast-feeding women. Positive pregnancy test (serum or urine β-HCG) for women of reproductive potential.

E21 Patients with reproductive potential (female and male) who do not agree to use an accepted effective method of contraception during the study treatment period and for at least 6 months following completion of study treatment. The definition of effective method will be left to the investigator's judgment.

E22 For female patients enrolled in United Kingdom, the following methods of contraception are acceptable: oral contraceptives accompanied by the use of a second method of contraception, as it is not known how oral contraceptives interact with study medications or Intra Uterine Device (IUD) or women who are surgically sterile, or women who are post –menopausal or other reasons have no chance of becoming pregnant.

Exclusion criteria related to aflibercept:

E23 Urine protein-creatinine ratio (UPCR) >1 on morning spot urinalysis or proteinuria > 500 mg/24-h.

E24 Serum creatinine > 1.5 x upper limit of normal (ULN). If creatinine 1.0-1.5 x ULN, creatinine clearance, calculated according to Cockroft-Gault formula, < 60 ml/min will exclude the patient.

E25 Uncontrolled hypertension (defined as blood pressure > 140/90 mmHg or systolic blood pressure >160 mmHg when diastolic blood pressure < 90 mmHg, on at least 2 repeated determinations on separate days, or upon clinical judgement) within 3 months prior to study inclusion.

E26 Patients on anticoagulant therapy with unstable dose of warfarin and/or having an out-of-therapeutic range INR (>3) within the 4 weeks prior to inclusion.

E27 Evidence of clinically significant bleeding diathesis or underlying coagulopathy (e.g. INR>1.5 without vitamine K antagonist therapy), non-healing wound.

No waiver, prospective or retrospective, to deviate in any way from the inclusion/exclusion criteria can be granted to investigators.

9. TREATMENTS

9.1 Investigational Medicinal Product

9.1.1 Description of aflibercept

AVE0005, 25mg/ml concentrate for solution for infusion.
INN: aflibercept.

[redacted]

9.1.2 Preparation, reconstitution and administration for aflibercept

Sealed, sterile, single-use vials at a concentration of 25 mg/mL will be supplied by the Sponsor.

Two aflibercept drug vial size presentations will be available:

- 100 mg/4 mL in a 5 mL vial
- 200 mg/8 mL in a 10 mL vial

with a withdrawable content of 4 mL and 8 mL, respectively.

The content of the vials must be diluted prior to infusion directly into infusion bags of 0.9% sodium chloride solution or 5% dextrose. The concentration of the diluted solution can range between 0.6 and 8 mg/mL. The pH of the diluted solution is about 6.2.

The dilution must be carried out under aseptic conditions. Any unused portion left in a vial must be discarded as the drug product does not contain any preservatives.

Diluted aflibercept 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 solution of aflibercept should be administered using infusion tubing made of the following materials:

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

The infusion sets must contain a 0.2 µm polyethersulfone inline filter. PVDF or Nylon filters should not be used.

Multiple vials may be required in the preparation of each dose depending on the patient's weight and aflibercept intended dose.

The volume of aflibercept to be administered to each patient, and hence the rate of infusion, will be based on each patient's weight. The pharmacist or designee will prepare the dosing solution as follows:

- Calculate the number of aflibercept vials needed according to the patient's body weight, and the aflibercept intended dose.

Then:

- Withdraw the exact volume of aflibercept needed, according to body weight and intended dose, from vials,
- And dilute directly into the infusion bag (0.9% NaCl or 5% dextrose) to obtain a final concentration for the diluted solution ranging from 0.6 mg/ml 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 listed materials.

Aflibercept IV dose should be infused over 1 hour. The infusion should not exceed 2 hours at ambient temperature (approximately 25°C).

9.1.3 Precautions

All IMP 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 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 Medicinal Product can start and for a minimum of 1 hour following the completion of the infusion:

Immediate access to appropriate resuscitative equipment.

Appropriately qualified and trained personnel must be on site.

Aflibercept 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. Aflibercept may be administered peripherally via peripheral venous catheter inserted prior to and removed immediately following peripherally administered doses.

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 3). In case of severe reaction (grade $\geq$ 3) aflibercept should be permanently discontinued.

9.2 Non Investigational Medicinal Products (Background treatments)

Marketed formulation of irinotecan, 5-FU and leucovorin will be used. For all these products refer to package insert or summary of product characteristics for details on description, preparation, administration, warnings and precautions for use.
The Sponsor will not provide these products.

9.3 Dosage and schedule of administration

On day 1 of each cycle patients will receive aflibercept followed by irinotecan, 5-FU and leucovorin (FOLFIRI regimen). This treatment will be repeated every 2 weeks.

Aflibercept: 4 mg/kg will be administered IV over 1 hour on Day 1, every 2 weeks, prepared and administered as described in Section 9.1.2.

FOLFIRI administration will immediately follow the aflibercept one. The dosage and schedule used in the VELOUR trial are described hereafter, for reference.

- Irinotecan 180 mg/m2 IV infusion in 500 mL D5W over 90 minutes and dl leucovorin* 400 mg/m² IV infusion over 2 hours, at the same time, in bags using a Y-line, followed by:
- 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by:
- 5-FU 2400 mg/m² continuous IV infusion in 500 mL D5W (recommended) over 46-hours.

The starting dose of irinotecan and/or 5-FU components of FOLFIRI regimen should take into consideration toxicities from prior regimens received by the patient and the patient characteristics (e.g. UGT1A1*28 allele status, when known). In case drugs (5FU) administered during previous chemotherapy regimen were reduced due to toxicity, the decision to administer or not the full starting dose of FOLFIRI (irinotecan, 5FU continuous and/or bolus infusion) is left to the investigator's decision based on his/her clinical judgement of patient benefit at time of inclusion in this trial. Reduced doses of 5-FU to those that were tolerable when used with the previous regimen would be acceptable. Similar consideration and clinical judgement should be used when determining the initial starting dose of irinotecan.

**400 mg /m² of leucovorin expressed in dl racemic. When the l-isomer form is used the dose should be divided by 2, i.e. 200 mg/m²*
Doses should be based upon actual body weight measured before each administration.

In case BSA > 2.0 m², the actual doses of irinotecan and 5-FU should be adjusted to a maximum BSA of 2.0 m², for safety reasons.

9.3.1 Premedication

Cholinergic adverse effects (including early diarrhea): unless contra-indicated, 0.25 -1mg intravenous or subcutaneous atropine may be given.

Antiemetic: appropriate prophylactic anti-emetic therapy is left to current hospital practices.

Granulocyte-colony stimulating factor (G-CSF): therapeutic use of Granulocyte Colony-Stimulating Factor (G-CSF) may be considered (if consistent with the local institutional treatment practice), upon occurrence of a first episode of grade ≥3 neutropenia and as secondary prophylaxis for subsequent cycles, in patients who may be at increased risk for neutropenia complications.

9.3.2 Schedule modification

Cycle length is 2 weeks (± 2 days). Delays of up to 2 weeks in case of unresolved toxicity at the time of planned re-administration are permitted (note that in some circumstances, administration of aflibercept could be omitted for one cycle as indicated in Table 2 and Table 3 and). Doses may be modified or infusion delayed for toxicity as described in Section 9.3.3. New cycles of therapy may not begin until any drug-related toxicity has been adequately resolved. The treatment will continue until a definitive treatment discontinuation criterion is met (see Section 12.2.1).

9.3.3 Dosage modification

Dose adjustment and/or cycle delay are planned in case of toxicity. Dose adjustments will be made according the worst grade toxicity. Toxicities will be graded according the NCI-CTC AE V. 4.0 scale (Ref. 30) (Appendix C). 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.

In case of toxicity from treatment, administration should be delayed until:

- neutrophil count is ≥ 1.5 X 109/L and platelet count is ≥ 75 X 109/L
- recovery to grade ≤ 1 for other toxicities (except alopecia and if otherwise specified).

The maximum delay allowed is of 2 weeks.

If FOLFIRI (the whole regimen or any of its components) is permanently discontinued, then aflibercept should be continued until disease progression or unacceptable toxicity or patient's refusal of further treatment.

If aflibercept is permanently discontinued, then FOLFIRI can be continued until disease progression or unacceptable toxicity or patient's refusal of further treatment.

The end of treatment will be the date of the last treatment administration, either aflibercept or FOLFIRI whichever comes last**.**

9.3.3.1 Aflibercept

Aflibercept dose reduction is described in the Table 1. Only one dose reduction is allowed.

Sponsor should be contacted by Investigator for discussion on a case by case basis if deemed appropriate, upon clinical judgment.

Table 1 – Aflibercept dose reduction level

	Initial dose (mg/kg)		Dose reduction, level – 1 (mg/kg)
Aflibercept	4	→	2

Actions considered for aflibercept according to the type of toxicity, are described in Table 2 and Table 3.

Table 2 – Dose modifications for aflibercept

Toxicity	Grade	Action
Hypertension	Grade ≤ 2	Initiate antihypertensive drug therapy (see recommendation below) and close monitoring of blood pressure for further adjustment, as needed. No dose modification and no delay. Modify antihypertensive drug therapy (see recommendation below).
	Grade 3 (requiring more than one drug or more intensive therapy than previously)	Delay the administration of both FOLFIRI **and** aflibercept for a maximum of 2 weeks, until recovery to blood pressure (BP) ≤ 140/90 or to systolic BP < 160 if diastolic BP < 90 for patients with known history of isolated systolic hypertension: • If BP is controlled within 2 weeks delay: - First episode: re-administer FOLFIRI **and** aflibercept at the same dose. - Second episode: re-administer FOLFIRI **and** aflibercept, with aflibercept reduced to dose level -1. -Third episode, discontinue aflibercept. • If BP is still uncontrolled despite appropriate anti hypertensive treatment and after 2 weeks delay: Administer FOLFIRI **and** discontinue aflibercept for 1 cycle; the reintroduction of aflibercept at a dose reduced to dose level – 1 will be reconsidered at the time of the administration of the subsequent cycle (in combination with FOLFIRI), only if BP is controlled at the time of re-administration. • In case of re-occurrence of grade 3 BP, in presence of maximal/optimal antihypertensive therapy despite dose reduction of aflibercept, or if BP is still uncontrolled despite 1 omission of administration of aflibercept, the patients will be permanently discontinued from aflibercept. FOLFIRI will be continued if the investigator thinks the patient is benefiting from it.
	Grade 4	Seek cardiologist opinion, and permanently discontinue aflibercept.

Toxicity	Grade	Action to be taken
Arterial thromboembolic events (e.g.: myocardial infarction, or stroke, etc) **documented by appropriate tests**	Any Grade	Permanently discontinue aflibercept
Hemorrhage	Grade 3-4	Permanently discontinue aflibercept
GI perforation/ fistula formation	Any Grade	Permanently discontinue treatment.

Toxicity	Grade	Action to be taken
Reversible posterior Leuko-encephalopathy syndrome documented with appropriate tests	Any grade	Permanently discontinue treatment.
Venous Thromboembolic Event documented by appropriate tests	Grade 3 (DVT)	First episode: Treat DVT with heparins **and** continue treatment [a] Second episode despite appropriate anticoagulation: Permanently discontinue aflibercept
	Grade 4 (PE)	Permanently discontinue aflibercept [b]

[a] Based on investigator's judgement in assessing potential risk of extension and/or embolization.
[b] Continuation of aflibercept may be considered, depending on individual patient benefit/risk assessment in case of incidental discovery of asymptomatic pulmonary embolism.

Hypertension therapy recommendations:

- *For patients without prior antihypertensive therapy*, at the time of the hypertensive episode a close monitoring of the BP (every 2 weeks is recommended) should be initiated for adjustment in treatment, as needed. Ultimately, antihypertensive treatment must be individualized based on the presence of comorbidity factors such as diabetes, cardiovascular or renal disease, additionally taking into account the safety and the efficacy of any prior antihypertensive therapy received. Oral and/or intravenous sodium intake should be carefully monitored in these patients.
- *For patients already under anti-hypertensive therapy*, efforts should be done to optimize the existing therapy before adding other agents as required to control the BP.

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 morbidity or central nervous system (CNS) morbidity, aflibercept should be interrupted.

Proteinuria:

Determination and management of proteinuria:
Prior to each administration of aflibercept perform a urine dipstick for WBC, RBC and protein (morning spot urine).
If proteinuria is < 2+ on the dipstick in absence of hematuria, aflibercept should be administered as planned.
If the proteinuria is ≥ 2+ on the dipstick, UPCR (Urinary Protein/urinary Creatinine Ratio) should be performed prior to administration of aflibercept.

Urinary protein creatinine ratio (UPCR) corresponds to the ratio of urinary protein and urinary creatinine concentrations (expressed in mg/dL). There is a high correlation between morning UPCR and 24-hour proteinuria in patients with normal or reduced renal function. This ratio provides an accurate quantification of 24-hour urinary protein excretion (Ref. 25).

UPCR to detect proteinuria, should be done on morning urine spot. If UPCR > 1, 24-hour urine collection to grade proteinuria will be performed. In addition, in case UPCR is greater than 2 or in

case of proteinuria of renal origin (according to urinary protein electrophoresis and/or nephrologist judgement) is associated with hematuria (microscopic or macroscopic), then a work up for considering thrombotic microangiopathy should be initiated and a nephrologist consultation be considered.

Delay in availabilty of the results should not delay consultation wth a nephrologist.

Actions with regard to aflibercept dosing will depend on the presence of hematuria and the level of 24-hour proteinuria results. Only one dose level reduction for aflibercept is foreseen.

Aflibercept administration should be suspended for ≥2 grams of proteinuria/24 hours and restarted when proteinuria is <2 grams/24 hours. If there is recurrence, the administration should be suspended until <2 grams/24 hours and then the dose reduced to 2 mg/kg.

Aflibercept treatment should be discontinued in patients who develop nephrotic syndrome or TMA.

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

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 BP and interruption of the offending drug, which are important in order to prevent progression to irreversible tissue damage.

Gastro-intestinal perforation:

Patients should be monitored for signs and symptoms of GI perforation as this has been reported with anti-VEGF agents as a class.

Hypersensitivity reaction:

In case of hypersensitivity reaction, institutional treatment guidelines for this type of AEs, or the following proposed guideline in Table 3 can be applied. Pre-treatment with corticosteroids and/or antihistamines may be considered in subsequent cycles.

Table 3 – 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 infusion; Give diphenhydramine 50 mg IV and/or IV dexamethasone 10 mg; Resume aflibercept infusion after subject recovery.
Severe e.g., symptomatic bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema, anaphylaxis	Stop aflibercept infusion; Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg and/or epinephrine as needed; Permanently discontinue aflibercept.

Wound healing complications/surgery

The half-life of bound aflibercept is approximately 20 days. Suspend aflibercept for at least 4 weeks prior to elective surgery.
Aflibercept therapy should not be administered for at least 4 weeks following major surgery and not until the surgical wound is fully healed.
For minor surgery such as central venous access port placement, biopsy and tooth extraction, aflibercept may be initiated/restarted once the surgical wound is fully healed. Aflibercept should be permanently discontinued in patients who develop wound dehiscence or compromised wound healing requiring medical intervention.

9.3.3.2 FOLFIRI

In addition to optimizing supportive care, irinotecan and 5-FU dose adjustments based on the worst toxicity encountered during the previous cycle, may be recommended. These are at investigator's discretion considering the current local prescribing information and the standard clinical practice.

The following tables describe recommended chemotherapy dose modifications on Day 1 of a new cycle. These are minimum standards but more stringent/significant dose modifications can be instituted upon clinical judgment.

Table 4 – FOLFIRI dose reduction level

	Initial dose (%)		Dose Reduction, level – 1 (% of initial dose)		Dose Reduction, level – 2 (% of initial dose)
Irinotecan	100	→	85-80	→	70-60
Bolus 5-FU	100	→	80	→	60
Infusional 5-FU	100	→	80	→	60

Note: in general a dose reduction of irinotecan by 15-20% and of 5-FU, bolus and infusion, of 20% may be considered.

Table 5 - Chemotherapy dose modifications for hematologic toxicity

Hematologic Toxicity	Grade 2	Grade 3-4	Associated measure
Isolated neutropenia	NA	No dose reduction, except if grade 4 neutropenia >7 days.	∗ Administer G-CSF upon occurrence of first event of grade ≥3 neutropenia ∗ Administer prophylactic G-CSF in subsequent cycles
Febrile neutropenia and neutropenic sepsis	NA	∗ First episode: reduce irinotecan by 1 dose level*. ∗ Second episode: reduce 5-FU bolus by 1 dose level. ∗ Third episode: discontinue chemotherapy.	
Thrombocytopenia	Full dose	∗ First episode: reduce 5-FU (bolus and infusion) by 1 dose level. ∗ Second episode: reduce irinotecan by 1 dose level. ∗ Third episode: discontinue chemotherapy.	

Notes:

- Depending on institution guidelines decision to reduce the dose could be postponed to after initiation of G-CSF

Table 6 – Chemotherapy dose modifications for non-hematologic toxicity

Non-Hematologic Toxicity	Grade 2	Grade 3	Grade 4
Diarrhea	Full dose	∗ First episode: reduce irinotecan by 1 dose level ∗ Second episode: reduce 5-FU (bolus and infusion) by 1 dose level. ∗ Third episode: discontinue chemotherapy.	
Stomatitis	Full dose	Reduce 5-FU (bolus and infusion) by 1 dose level.	Reduce 5-FU (bolus and infusion) by 2 dose levels.
Palmar-Plantar Erythrodysesthesia	Full dose	Reduce 5-FU (bolus and infusion) by 1 dose level.	NA
Bilirubin increase	Delay next infusion until recovery to grade ≤ 1 (bilirubin ≤ 1.5 x ULN): ∗ First episode, no dose reduction ∗ Second episode, reduce irinotecan by 1 dose level ∗ Third episode, reduce irinotecan by a second dose level ∗ Fourth episode, permanently discontinue irinotecan. Persisting grade 2 (bilirubin >1.5 x ULN and ≤ 3 x ULN) after 2 weeks delay: ∗ First episode, reduce irinotecan by 2 dose levels ∗ Second episode, permanently discontinue irinotecan.	Delay next infusion until recovery to grade ≤ 2 (bilirubin ≤ 3 x ULN). Persisting grade 3 (bilirubin >3.0 x ULN and ≤ 10 x ULN) after 2 weeks delay, permanently discontinue irinotecan.	Permanently discontinue FOLFIRI.
Transaminases increase	No dose reduction	Delay next infusion until recovery to grade ≤ 2. Persisting grade 3 after 2 weeks delay, permanently discontinue irinotecan.	Permanently discontinue FOLFIRI.
Alkaline Phosphatase (ALP) increase	No dose reduction	Delay next infusion until recovery to grade ≤ 2. Persisting grade 3 after 2 weeks delay, permanently discontinue irinotecan.	Permanently discontinue FOLFIRI.
Hypersensitivity reaction	Discontinue irinotecan if related to irinotecan		

9.3.3.3 Other toxic effects

Any other dose modification 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 12.2.1, have not been met. Chemotherapy should be held for a maximum of two weeks from the planned date of reinfusion until resolution to ≤ grade 1, and then reinstituted, if medically appropriate. A dose reduction of subsequent doses will be considered. These patients will be withdrawn from study treatment if >2 dose reductions for FOLFIRI or greater than 1 dose reduction for aflibercept are needed.

9.4 Packaging and labeling

This is an open-label Study and the treatments will not be blinded.

Packaging number and quantity of vials dispensed to each patient will be recorded in the electronic Case Report Form (e-CRF)/Drug accountability form.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

9.5 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. Vials should be stored according to their labeling and kept in their box until use.

For irinotecan, 5-FU and leucovorin refer to the respective package insert or summary of product characteristics.

9.6 Responsibilities

The investigator, the hospital pharmacist, or other personnel allowed to store and dispense Investigational Medicinal Product is responsible for ensuring that the Investigational Medicinal Product used in the clinical trial is securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.

All Investigational Medicinal Product shall be dispensed in accordance with the investigator's prescription and it is the investigator's responsibility to ensure that an accurate record of Investigational Medicinal Product issued and returned is maintained.

Any quality issue noticed with the receipt or use of an Investigational Medicinal Product (deficient IMP 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 shall the investigator supply Investigational Medicinal Product to a third party, allow the Investigational Medicinal Product to be used other than as directed by this clinical trial protocol, or dispose of Investigational Medicinal Product in any other manner.

9.7 Retrieval and/or destruction of treatments

9.7.1 Partially used or unused treatment

All used treatment vials (IMP) will be destroyed by the study site after an accurate accountability has been performed and countersigned by the investigator (or pharmacist).

All unused vials of aflibercept will be destroyed on site or retrieved by the Sponsor, depending on local requirements.

The Investigator will not destroy the unused Investigational Medicinal Product unless the Sponsor provides written authorization.

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

9.7.2 Potential recall

A potential defect in the quality of Investigational Medicinal Product 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 Investigational Medicinal Product and eliminate potential hazards.

9.8 Concomitant treatment

During the Study, the Investigator may prescribe concomitant medications as deemed necessary. Supportive treatment as medically indicated for the patient's well-being, consistent with optimal patient care (including hyper-alimentation, blood transfusion, heparins and anti-coagulation medications, erythropoietin, treatment for pain relief) and unlikely to interfere with the Investigational Medicinal Product may be prescribed at the Investigator's discretion (except for those contraindicated for any component of FOLFIRI regimen as per local prescribing information).

Antihypertensive medications: some recommendations are described in section 9.3.3.1.

Antidiarrheal medications: in case of occurrence of late diarrhea loperamide 4 mg at onset of diarrhea, then 2 mg q2h until the patient is diarrhea free for 12 hours (and octreotide in case of loperamide failure) can be considered.

Granulocyte-colony stimulating factor (G-CSF): therapeutic use of Granulocyte Colony-Stimulating Factor (G-CSF) may be considered (in agreement with the local institutional treatment practice), upon occurrence of a first episode of grade $\geq$3 neutropenia and as secondary prophylaxis for subsequent cycles, in patients who may be at increased risk for neutropenia complications.

During treatment with aflibercept the Vitamin K antagonists should be used with caution.

The following concomitant treatments are not allowed during the study:

- Other anticancer therapies, investigational therapies or devices
- Concomitant radiotherapy
- Anticonvulsivant agent that are CYP 3A4 inducers: phenytoin, phenobarbital, carbamazepine as well CYP 3A4 inhibitors: e.g. ketoconazole

Patient with reproductive potential should be advised to adhere to an accepted and effective method(s) of birth control while on treatment and for at least 6 months after its last administration.

9.9 Post-Study treatment

Patients will continue to be treated as long as they are benefiting from the study treatment and they have nor met study withdrawal criteria as defined in section 12.2.1. After withdrawal from study treatment the patient will be switched to any appropriate therapy as per Investigator clinical decision.

9.10 Treatment accountability and compliance

The Hospital Pharmacist or authorized person will inventory and acknowledge of receipt of all shipments of the IMP (aflibercept). Any discrepancies or quality issue upon receipt should be notified to the Sponsor. Administration of the study drug in accordance with the protocol will be supervised by the Investigator or delegate.

The Investigator (or delegate) or pharmacist will keep accurate records of the quantities of the IMP dispensed (with the corresponding batch numbers) to each patient and will fill in the Treatment Log Forms. All these data will be also reported in the e-CRF.

The monitor in charge of the study will ensure that the Treatment Log Form is filled in on an ongoing basis and will check the e-CRF by comparing the recorded data with the treatment Log Form.
The person responsible for drug administration to the patient will record precisely the date and time when drug is administered to the patient.

10. ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

10.1 Efficacy

Efficacy will not be assessed.

10.2 Safety

Safety profile will be determined by the incidence of adverse events (AEs) including serious adverse events (SAEs). AEs will be collected from the time the patient signs the informed consent form through 30 days after the last administration of the treatment (either aflibercept or FOLFIRI). Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v 4.0) and summarized using MedDRA terminology.

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

- Clinical examination, including body weight, ECOG PS (Appendix B) and BP.
- Laboratory data:
  - Complete blood count and clinical chemistry
  - Urinalysis
- AEs and SAEs.

Laboratory safety work-up will be carried out by local laboratory according to standard operating procedures.

Note: Any abnormal laboratory value or medical investigation result must be immediately rechecked for confirmation before making a decision of permanent discontinuation of Investigational Medicinal Product for the concerned patient

The study-specific and general safety criteria are developed in Section 11 - Patient Safety.

10.3 Health-related quality of life outcomes

Health related quality of life evaluation will be performed using the following questionnaires (Appendix A):

- EORTC QLQ-C30 (version 3);
- EORTC QLQ CR29 (disease specific supplement to QLQ-C30) - optional;
- EQ-5D™

Data will be collected in a patient booklet separated from the e-CRF.

Instruments description

- EORTC QLQ-C30 (version 3).

The EORTC-QLQ-C30 is a cancer-specific instrument that contains 30 questions and provides a multi-dimensional assessment of Patient Reported Outcomes (PRO). The validity and reliability of the EORTC-QLQ-C30 has been established in various types of cancers (Ref. 26).
The EORTC-QLQ-C30 is one of the standard instruments used in oncology for the evaluation of new chemotherapies and provides a comprehensive assessment of the principal PRO dimensions identified as relevant by cancer subjects (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global QOL, impact of symptoms and of toxicities).
The first 28 questions of the QLQ-C30 V3.0 questionnaire use a 4-category response system (not at all/a little/quite a bit/very much) that correspond to numeric values 1, 2, 3, 4, respectively. Then for each item a high score represents a high level of symptomatology/problem. The last 2 questions represent patient assessment of overall health and quality of life. These items are coded on a 7-point response category scale, 1 being very poor and 7 excellent, with no label between. The recall period is the past week.

- EORTC QLQ CR29 (disease specific supplement to QLQ-C30) – optional.

The EORTC QLQ-C30 can be supplemented by a module specific to colorectal cancer, the EORTC QLQ-CR29 colorectal cancer module (Ref. 27) which includes four scales (urinary frequency, faecal seepage, stool consistency and body image) and 19 single items assessing other common problems following treatment for colorectal cancer.

- EQ-5D™ questionnaire

The EQ-5D™ is a standardized health-related quality of life questionnaire developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Ref. 28. EQ-5DTM essentially consists of 2 pages: the EQ-5DTM descriptive system and the Visual Analogue Scale (VAS). The EQ-5DTM is a well-validated and researched assessment tool which has been widely used and supported in QOL assessment across a range of disease areas, including oncology.
The EQ-5DTM descriptive system comprises 5 dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problem, some problems,

and severe problems. The 5 dimensional 3-level system can be converted into a single index utility score. Values for the 243 theoretically possible health states defined by the EuroQOL classification were calculated using a regression model and weighted according to the social preferences of the UK population (Ref. 29). The minimum value for the single index utility score is -0.594, which corresponds to a level 3 (severe problems) for the 5 dimensions. The maximum value for this index is 1.0, which corresponds to a full health (level 1, no problem) for the 5 dimensions.
The VAS records the respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

Timing of Assessment
The above described questionnaires have been designed for self-completion.
Baseline assessment should be obtained from all patients. All the questionnaires will be administered within 3 days prior to the first treatment administration, but in any case before the patient is given the first dose. While on treatment assessments should occur before the treatment administration at the beginning of every odd cycle (day 1 of cycle 3, 5, etc) and at the end of treatment visit.
Questionnaires should be self-administered by the patient at the center, prior to informing the patient about disease evolution, before the next study treatment and before any other assessment is performed.
For the quality of life questionnaires it is mandatory that a key person (e.g., research nurse) at each center should be responsible for questionnaire data collection, in order to optimize compliance of the patient and to ensure completeness of the data.

A HRQL analysis will be detailed in the SAP.

11. PATIENT SAFETY

11.1 Safety instructions

Adverse Events (AEs), regardless of seriousness or relationship to study treatment, will be collected from the time the patient signs the informed consent form up to 30 days after the last administration of treatment (either aflibercept or FOLFIRI).
Details and schedule of requested evaluations are given in Sections 2 and 13.

If a finding meets the criteria for a SAE, then the appropriate procedures for reporting such events should be followed as described in Section 11.4.2.

After the 30 day FUP period all ongoing SAEs (regardless of relationship with study treatment) as well as ongoing related AEs and new SAEs, that are considered to be related to study treatment, will have to be collected and followed till resolution/stabilization (stabilization being defined as an event ongoing without any change for at least 3 months).

11.2 Adverse Events monitoring

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

11.3 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 **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.

Elective hospitalizations for the administration of the treatment or due to social circumstances or hospitalizations for surgeries that were planned before the enrollment into the study (e.g. planned surgery for metastases resection after treatment discontinuation) will not be considered SAEs (unless there is complication from surgery [e.g. hemorrhage or wound infection or wound healing difficulties etc.]) in which case the complication should be reported as AE(s)/SAE(s).

Note: The following medical important events intend to serve as a guideline for determining which condition has to be considered as a medically important event. It is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - allergic bronchospasm,
  - blood dyscrasias (i.e., agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - convulsions (seizures, epilepsy, epileptic fit, absence, etc.)
- Development of drug dependency or drug abuse,
- ALT > 3 ULN + total bilirubin > 2 ULN or asymptomatic ALT increase > 10 ULN ,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study or aggravated during the study (only if judged as unusual/significant by the investigator),
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

11.4 Obligation of the investigator regarding safety reporting

11.4.1 Adverse Events

All Adverse Events regardless of seriousness or relationship to the treatment (either aflibercept or FOLFIRI), spanning from the signature of the informed consent form until the 30 days after the last administration of the treatment,(aflibercept/FOLFIRI) are to be recorded on the corresponding page(s) included in the Case Report Form.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The investigator should specify the date of onset, intensity, action taken with respect to Investigational Medicinal Product and Non Investigational Medicinal 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 Investigational Medicinal Product and/or Non Investigational Medicinal Product.

Signs/symptoms that are present or occurred from the time the patient signed the informed consent to first study treatment administration (i.e. even in the absence of any administration of Investigational Medicinal Product), will be recorded as Adverse Event only if they are still present at the time of first study treatment administration or if they are serious.

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

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

11.4.2 Serious Adverse Events

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

- ENTER (within 1 working day) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or by e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of Sanofi monitoring team whose name, address and fax number appear on this Protocol. 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
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status ..) should be sent (by fax or e-mail) to the monitoring team within 1 working day of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening as soon as information is available and anyway within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the e-CRF system does not work.

11.4.3 Safety Observations

The investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any 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 beyond the 30 days follow-up period and that additional investigations may be requested by the monitoring team;
- In case of any Serious Adverse Event brought to the attention of the investigator at any time after cessation of the treatment and considered by him/her to be caused by the treatment with a reasonable possibility, this should be reported to the monitoring team.

11.4.4 Pregnancy

Pregnancy should be recorded as an AE in all cases. It should be qualified as an SAE only if it fulfills SAE criteria.

In the event of pregnancy, the treatment should be discontinued and the sponsor informed immediately (i.e. within 1 working day), even not fulfilling a seriousness criterion, using the AE form together with the SAE complementary form to be sent to the representative of the monitoring team whose name, address and fax number appear on the clinical trial protocol.

Follow-up of the pregnancy is mandatory until the outcome has been determined.

11.4.5 Overdose

A symptomatic overdose (accidental or intentional) even not fulfilling a seriousness criterion, is to be reported to the sponsor immediately (within 1 working day) using the SAE complementary form to be sent to the representative of the monitoring team whose name, address and fax number appear on the clinical trial protocol.

An overdose of study treatment is defined as:

FOLFIRI:
For the purpose of safety reporting (as described above) dosing of 30% above the intended/planned dose of either irinotecan or 5-FU should be considered as an overdosage.

Aflibercept:

The highest doses of aflibercept that have been administered so far are 7 mg/kg IV every 2 weeks and 9 mg/kg IV every 3 weeks. No overdoses have been reported so far.

In this protocol an aflibercept overdose is defined as 30% above the intended/planned dose.

The circumstances (i.e., accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms. Based on investigator’s best clinical judgment, patients experiencing overdose should be monitored for the onset of known anti-VEGF toxicities (e.g. hypertension, proteinuria, etc.).

11.5 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 IMP (SUSAR), to the competent/ health

authorities, ethics committee(s) as appropriate and to the investigators in accordance with local regulatory timelines.

In addition, the sponsor should report in an expedited manner all SAEs that are expected and at least reasonably related to the IMP to the competent/ health authorities, according to local regulations.

Any AE not consistent with events listed as expected in the most current Investigator's Brochure of aflibercept and/or contained within the reference safety information for irinotecan, 5-FU and leucovorin on file in the Pharmacovigilance Department will be considered as unexpected.

The sponsor should report all safety observations made during the conduct of the trial in the CSR.

12. HANDLING OF PATIENT TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

12.1 Temporary treatment discontinuation with Investigational Medicinal Product

Re-initiation of treatment with the IMP should be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (ref to Sections 8.2 and 8.3).

All temporary treatment discontinuation and date of treatment re-initiation should be recorded by the Investigator in the e-CRF when considered to be confirmed.

12.2 Permanent treatment discontinuation

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the investigator or the patient not to re-expose the patient to the treatment at any time.

12.2.1 List of criteria for permanent treatment discontinuation

The patients may withdraw from the treatment if they decide to do so, at any time and irrespective of the reason, or this may be due to the investigator's decision if, in his/her opinion, continuation of the study treatment would be detrimental to the patient's well being, such as:

- Disease progression (as per investigator assessment)
- Unacceptable AE(s) not manageable by symptomatic therapy, dose delay or dose modification (see Section 9.3.2 and Section 9.3.3)
- Intercurrent illness that prevents further administration of study treatment

All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

12.2.2 Handling of patients after permanent treatment discontinuation

Patients should be followed up to 30 days after the last administration of the treatment (either aflibercept or FOLFIRI).

Following the 30-day follow-up visit, ongoing SAEs (regardless of causality), ongoing related AEs and new related SAEs should recorded/followed as described in Section 11.

All permanent treatment discontinuation should be recorded by the investigator in the appropriate pages when considered to be confirmed.

12.3 Procedure for withdrawal of patients from study

The patients may withdraw from the study, 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 30 day follow-up visit.

For patients who fail to return to the site the investigator should make every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status.

Patients who did not complete the study and for whom no endpoint data are available should 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.

12.4 Consequence

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

13. STUDY PROCEDURES

13.1 Visit schedule

Data will be collected at baseline, at each cycle and at the end of treatment. Each cycle consists of 14 days (± 2 days). Cycle length may be extended if additional time is required for resolution of study treatment-related toxicities or other adverse events.

Each patient will be treated until disease progression, death, unacceptable toxicity, Investigator's decision or patient refusal of further treatment.

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 procedure is performed.

13.1.1 Pre-treatment assessment (Baseline)

The following data will be collected as baseline:

- Informed Consent
- Demography: age, gender and race

- Vital signs (height, weight, ECOG performance status, BP and other signs and symptoms, if medically relevant), within one week of first treatment infusion)
- Colon Cancer History (diagnosis including primary site and histopathology)
- Prior anticancer therapies (surgery, radiotherapy and chemotherapy)
- Prior Medical/Surgical History (including cardiovascular risk factors and prior vascular events if any)
- Prior medications will be recorded, if medically relevant (i.e. VKA, antihypertensive medications, etc), from 1 week prior to the start of the study treatment
- Most recent laboratory evaluations (within one week of first treatment infusion):
    - Hematology: hemoglobin, white blood cells (WBC), ANC, platelet counts.
    - Blood Chemistry: sodium, chloride, potassium, calcium, blood urea nitrogen (BUN)/urea, creatinine (if creatinine 1.0-1.5 x ULN then creatinine clearance, calculated according to Cockroft-Gault formula), total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH, glucose.
    - Coagulation tests: prothrombin time expressed as INR only in patients under treatment with Vitamine K antagonist.
    - Urinalysis: dipstick [WBCs, red blood cells (RBCs)] and UPCR on morning urine spot or proteinuria assessed on 24-hour urine collection.
    - Pregnancy test in women of reproductive potential: serum or urine β-hCG.
- Health-Related Quality of Life (before first treatment infusion):
    - EORTC QLQ-C30;
    - EORTC QLQ CR29 (optional);
    - EQ-5D™.

Patient inclusion will take place once the consented patient has completed all the necessary baseline assessment and is deemed eligible for study entry by the investigator or designee. The results of the baseline examinations will be recorded in each included patient's CRF. Source documentation to support the baseline results must be maintained in the patient's medical record.

Treatment should begin as soon as possible after inclusion (possibly within 3 days).

13.1.2 During study treatment period

Data collection:

- Vital signs: ECOG PS, body weight, BP (before each study treatment dosing)
- Concomitant medications if medically relevant (see also the flow chart, Section 2.1).
- Laboratory evaluations (performed before each study treatment dosing)
    - Hematology: hemoglobin, WBC, ANC, platelet counts.
    - Blood Chemistry: sodium, chloride, potassium, calcium, BUN/urea, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH, glucose.
    - Coagulation tests: prothrombin time expressed as INR for patients under treatment with VKA
    - Urinalysis: dipstick (WBCs, RBCs, urinary protein) and UPCR on morning urine spot and/or the 24-hour urine collection (see Section 9.3.3.1).

- Study treatment (aflibercept/FOLFIRI) administration (including dose delays and dose reductions)
- AEs/SAEs (from signature of informed consent up to 30 days after last administration of treatment)
- Health-Related Quality of Life: before treatment administration at the beginning of every odd cycle (on D1 of cycle 3, 5, etc.)
    - EORTC QLQ-C30;
    - EORTC QLQ CR29 (optional);
    - EQ-5D™.

13.1.3 End of treatment (30-day Follow-up visit)

All patients have to continue to be observed for at least 30 days after the final dose of the treatment (either aflibercept or FOLFIRI).

Data collection:

- Date and reason for aflibercept discontinuation
- Date of last FOLFIRI administration and reason for discontinuation
- Vital signs: ECOG PS, BP
- Concomitant medications if medically relevant (including further anticancer treatment started within 30 days of last treatment administration, if any. See also the flow chart, Section 2.1)
- AEs/SAEs
- Patient's status
- Health-Related Quality of Life: EORTC QLQ-C30, EORTC QLQ-CR29 (optional) and EQ-5D™.

13.1.4 Post treatment Follow-up period

The following data will be collected:

- Related AEs and all SAEs, ongoing at the end of the study treatment, or new related SAEs will be recorded until recovery, or until progression has been stabilized.

13.2 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 study. 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.

14. STATISTICAL CONSIDERATIONS

14.1 Statistical and analytical plans

The material of this Section is the basis for the Statistical Analysis Plan for the study. This plan may be revised during the study to accommodate clinical trial protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analysis. Thus a final plan should be issued before database lock.

14.2 Determination of sample size

No formal sample size calculation has been done. The Safety analyses of this study will be descriptive in nature, and the table below provides the precision (95% CI) associated to a variety of AE event rates for a targeted sample size of 900 patients:

Table 7 : Expected 95% CI for various event rates

Overall sample size	p=10%	p=20%	p=30%	p=40%	p=50%
900	[8.0%; 12.0%]	[17.4%; 22.6%]	[27.0%; 33.0%]	[36.8%; 43.2%]	[46.7%; 53.3%]

14.3 Analysis variables

14.3.1 Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age, gender, race, height and weight), medical and surgical history, cancer diagnosis and prior anticancer therapy will be summarised at baseline.

Baseline safety variables will also be assessed. These variables include vital signs and main laboratory parameters.

Baseline value is defined as the last value or measurement taken before the first dose of treatment.

14.3.2 Efficacy variables

Not applicable.

14.3.3 Safety variables

Analysis of safety will be performed by summarizing AEs and laboratory data.

The safety variables include:

- AEs
    - On-treatment period: On-treatment period is the period from the first dose of treatment to 30 days after the last dose of treatment (either aflibercept or Folfiri).

- 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 or worsened or became serious more than 30 days after the last dose of treatment (aflibercept or Folfiri).

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

- Discontinuation (including reason for discontinuation and discontinuation due to AEs)
- Blood pressure and ECOG performance status
- Major laboratory safety parameters
  - Hematology: WBC, neutrophil, platelets, and hemoglobin.
  - Blood chemistry: sodium, chloride, potassium, calcium, BUN/urea, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, LDH, glucose.
  - Urinalysis: Dipstick (WBCs, RBCs and protein), Urinary Protein-to-creatinine Ratio (UPCR).

14.3.4 Health economic/ Health-Related Quality of life variables

Health Related Quality of Life:

- EORTC QLQ-C30 questionnaire: change from baseline for the Global health status (scoring of items 29 & 30), the five functional scales (Physical, Role, Emotional, Cognitive and Social), the three symptom scales (Fatigue, Nausea/vomiting and Pain) and the other single items
- EQ-5D™: change on health-related QoL and utility.

Exploratory endpoint:

- EORTC QLQ-CR29 questionnaire (specific colorectal module - optional): change from baseline for the four scales (urinary frequency, faecal seepage, stool consistency and body image) and the other single items.

HRQL analysis will be detailed in the SAP.

14.4 Analysis populations

Patients previously treated with aflibercept (i.e. the patients participating to VELOUR/EFC10262 trial that were allowed to rollover into this study) will not be included in any analysis population and their data will be listed separately.

14.4.1 Efficacy populations

Not applicable.

14.4.2 Safety population

The safety population will consist of the patients who have signed the informed consent form and who have received at least part of one dose of study treatment.

14.4.3 HRQL analysis population

Health related quality of life analysis will be performed in the patients who completed the questionnaires at baseline and at least one assessment post baseline and who have received at least part of one dose of study treatment.

14.4.4 Disposition of patients

The number of patients in the safety population will be provided.
In addition, reasons for treatment discontinuation as well as reasons for withdrawal from the study will be summarized.

14.5 Statistical methods

All statistical analyses will be descriptive (no formal statistical tests will be performed).

The following information will be provided for continuous variables: number of patients (N), mean, standard deviation, median, 25^{th} and 75^{th} percentiles, as well as minimum and maximum.

Number and percentage of patients will be provided for categorical variables.

All statistical analyses will be based on the Safety population. Health-related quality of life variables will be summarized on the HRQL analysis population.

Sub group analyses per country or region will also be provided as appropriate.

Final analysis will be performed after the global Data Base Lock.

14.5.1 Demographics and baseline characteristics

All patient demographic characteristics, medical and surgical history, cancer diagnosis and prior anticancer therapy will be tabulated.

14.5.2 Extent of study treatment exposure and compliance

Extent of exposure will be assessed as follows:
Number of patients treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg/kg for aflibercept and mg/m² for FOLFIRI regimen compounds) and dose intensity (mg/kg/week for aflibercept and mg/m²/week for FOLFIRI regimen compounds) will be summarized. Dose delays, omissions and dose reductions will also be analyzed.

14.5.3 Analysis of efficacy variables

Not applicable.

14.5.4 Analysis of safety data

Summary of safety data will also be performed by cycle (when 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 of treatment.

14.5.4.1 Analysis of adverse events

The following frequency distributions of adverse events (incidence tables presented by SOC and PT and worst intensity as graded by the NCI CTCAE, version 4.0) will be provided for the Safety population: TEAE, possibly related TEAE, Serious TEAE, TEAE leading to death, TEAE leading to permanent treatment discontinuation.

The number and percentage of patients who die will be presented.

14.5.4.2 Laboratory variables analysis

Hematological toxicities will be assessed from laboratory parameters.
Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst NCI CTCAE grade) will be summarized 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 and impairment of renal function.

14.5.4.3 Analysis of vital sign variables

By visit descriptive analyses of vital signs (ECOG PS, BP) will be provided for observed values and change from baseline.

14.5.5 Analysis of health economics / Health-Related Quality of life variables

The compliance profile over time will be summarized (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected).

- EORTC QLQ-C30 questionnaire
  A descriptive summary by assessment and change from baseline to each assessment for the Global health status (scoring of items 29 & 30), the five functional scales (Physical, Role, Emotional, Cognitive and Social), the three symptom scales (Fatigue, Nausea/vomiting and Pain) and the other single items will be described.

- EQ-5D™ questionnaire
  The responses to each EQ-5D™ item will be presented at each assessment. This will contain information on the frequency and proportion with its 95% CI of the population reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) per item. Descriptive summary statistics (size, mean, standard deviation, median, range) will be provided for the single index utility score and the VAS at each assessment. Change from baseline will be also described.

Exploratory endpoint:
- EORTC QLQ-CR29 questionnaire (specific colorectal module - optional)
  A descriptive summary by assessment and change from baseline to each assessment for the four scales (urinary frequency, faecal seepage, stool consistency and body image) and the other single items will be described.

14.6 Interim analysis

It is planned to perform interim analyses during the course of the study, in order to obtain preliminary results on baseline characteristics, HRQL and safety data.

Details will be provided in the SAP.

15. ETHICAL AND REGULATORY STANDARDS

15.1 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.

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in a public registry website before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

15.2 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.

15.3 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. 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 and any other local applicable documents in accordance with local laws and regulations, 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 must 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 for approval/favorable opinion.

15.4 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The investigator or the sponsor must submit this clinical trial protocol to the appropriate Ethics Committee, and is required to forward to the sponsor a copy of the written and dated approval/ favorable opinion signed by the chairman with ethics committee(s) 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.), the list of voting members and their qualifications and the date of the review should be clearly stated on the written ethics committee approval/favorable opinion.

Investigational Medicinal Product will not be released at the study site and the clinical trial will not start until a copy of this written and dated approval/ favorable opinion has been received by the sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Ethics Committee. 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 should be sent to the ethics committee(s).

If requested, a progress report is sent to the ethics committee(s) annually and a summary of the clinical trial's outcome at the end of the clinical trial.

16. STUDY MONITORING

16.1 Responsibilities of the investigator(s)

The investigator(s) undertake(s) 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 e-Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

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 should be supervised by and under the responsibility of the investigator. The investigator should provide them with a copy of the clinical trial protocol and all necessary information.

16.2 Responsibilities of the sponsor

The sponsor of this clinical trial is responsible to competent/ health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial 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 but not exhaustive list of points should be scrutinized with the investigator: patient informed consent, patient eligibility, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, Investigational Medicinal Product allocation, patient compliance with the clinical trial protocol and the Investigational Medicinal Product regimen, Investigational Medicinal Product accountability, concomitant therapy use and quality of data.

16.3 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(s), and the competent/ health 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).

16.4 Use and completion of Case Report Forms (CRFs) and additional request

Data will be collected using an electronic Case Report Form (e-CRF). All CRFs should be completed in their entirety to ensure accurate interpretation of data.

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.

For each patient, baseline data will be reviewed by Sanofi in order to ensure the patient is eligible for this study.

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

16.5 Use of computerized systems

Computerized systems will be used to create, modify, maintain, archive, retrieve or transmit data (monitoring tool, data entry and statistical analysis).

17. ADMINISTRATIVE RULES

17.1 Curriculum Vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each investigator and sub-investigator should be provided to the sponsor prior to the beginning of the clinical trial.

17.2 Record retention in study site(s)

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, unless otherwise specified in the investigator Agreement in line with national standards and/or local laws.

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.

18. 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 agree 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(s) is expressly permitted, the ethics committee(s) 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.

19. PROPERTY RIGHTS

All information, documents and Investigational Medicinal 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 Investigational Medicinal Product in any application for a patent or for any other intellectual property rights.

All the results, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the 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.

20. 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.

21. INSURANCE COMPENSATION

The sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance obtained by the sponsor does not relieve the investigator and his/ her collaborators from maintaining their own liability insurance policy. A copy of the insurance certificate will be provided to the ethic committees and/ or competent/ health authorities in countries requiring this documentation.

22. 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 should not disclose any personal identity or personal medical information.
The investigator should 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 should 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.

23. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

23.1 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 Medicinal 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;
- If the aim of the clinical trial has become outdated or is no longer of interest;
- 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;

In any case the sponsor will notify the investigator of its decision by written notice.

23.2 Decided by the investigator

The investigator must notify (at least 30 days prior to discontinuation) 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) and competent/ health authorities should be informed.

24. 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 investigator(s).
Regardless of the study outcome the sponsor is committed to publishing the results.

25. PUBLICATIONS AND COMMUNICATIONS

The sponsor recognizes the investigator's right to utilize data derived from the clinical trial for teaching purposes, communication at congresses and scientific publications. Nevertheless, in order to ensure the accuracy and scientific value of the information, while preserving the independence and accountability of the investigator, and the confidentiality of the information, only checked and validated data will be used. To that effect, it is essential that the parties exchange and discuss, prior to any publication or communication, any draft publication or communication made by the investigator.

The investigator shall send to the sponsor a copy of the manuscript for review and possible comments at least forty-five (45) calendar days in advance of the date of submission to the journal and at least twenty (20) days in advance for abstracts. The publication shall be delayed until a written response is received by the sponsor, not to exceed ninety (90) days. The sponsor can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein, it being understood that the sponsor cannot refuse its consent without reasonable cause. The investigator agrees to include the modifications requested by the sponsor, provided they do not jeopardize the accuracy and/or the scientific value of the publication.

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

The sponsor has the right at any time to publish the results of the clinical trial.

26. 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 written approval/ favorable opinion from the ethics committee(s) 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 shall be recorded in writing, the written amendment must be signed by the investigator and by the sponsor and the signed amendment be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/ favorable opinion by the ethics committee(s) 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 ethics committee approval/ favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

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