AMENDED CLINICAL TRIAL PROTOCOL 02

POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS)

COMPOUND: ZALTRAP® (aflibercept or ziv-aflibercept in the US)

STUDY NUMBER: OBS13597

STUDY NAME: OZONE

(Observational study for ZALTRAP® in Europe and North America)

VERSION DATE / STATUS: 01 Feb 2016 / Final

Protocol Amendment 2	Version number: 1 (electronic 1.0)	Date: 01-Feb-2016
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Clinical Trial Protocol	Version number: 1 (electronic 2.0)	Date: 01-Jul-2013

EudraCT or IND number: 009948

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PROTOCOL AGREEMENT FORM

I, participating physician, have examined this protocol for the study

Entitled: ***Prospective international observational cohort non comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS)***

Date:

And I have fully discussed the objectives of this study and the contents of this protocol with the Sanofi representative(s).

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

I agree to keep confidential the content of the protocol, not to disclose it to any third party and to use it only for the purpose of conducting this study.

I understand that, should the decision be made by the COMPANY to terminate prematurely or suspend the study at any time for whatever reasons; such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate immediately such decision in writing to the COMPANY.

Data privacy policy:

I am informed that Sanofi and its affiliates collect, use and disclose to internal trials management personnel my personal and professional data I have provided. This data will be recorded in the database for the sole purpose of initiating study sites and conducting studies. I am informed that my data can be transferred to Sanofi affiliates bound by contractual agreements for the same purpose.

In accordance with the laws pertaining to the protection of personal information, I have a right to access, to rectify and to suppress any of my personal data held by Sanofi simply by requesting it to the Sanofi study team.

Participating Physician	**Study conducted by**
NAME**:**	NAME**:**
SIGNATURE**:**	SIGNATURE**:**
DATE: _____	DATE : _____

PASS INFORMATION

Title	Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS)
Protocol version identifier	Final version
Date of last version of protocol	12 Dec 2013
EU PAS register number	ENCEPP/SDPP/4836
Active substance	Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents aflibercept (or ziv-aflibercept in the US) ATC code: L01XX44
Medicinal product	ZALTRAP® 25mg/ml concentrate for solution for infusion The recommended dose of ZALTRAP®, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen, every 2 weeks.
Product reference	EU/1/12/814
Procedure number	EMEA/H/C/2532/MEA 002
Marketing authorisation holder(s)	sanofi-aventis groupe 54, rue La Boétie 75008 Paris France
Joint PASS	No
Research question and objectives	• To describe the long term safety, and clinical outcomes of ZALTRAP® in combination with FOLFIRI in patients treated in daily practice for a mCRC after failure of an oxaliplatin-based regimen; • To assess safety and effectiveness of ZALTRAP® in the following specific patient cohorts : - elderly patients (≥65 years old); - patients with renal or hepatic impairment (acknowledging the limits of irinotecan label); - non Caucasian patients. - Number and type of prior anti-cancer therapy (eg, prior bevacizumab) • To describe utilization of health resources in patients treated with a combination of ZALTRAP® and FOLFIRI.
Countries of study	Europe and US
Author	Françoise SILLAN, MD Sanofi EU-QPPV Head – sanofi-aventis R&D françoise.sillan@sanofi.com

MARKETING AUTHORISATION HOLDER(S)

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2 LIST OF ABBREVIATIONS

AE	adverse event
BOR	best overall response
CI	confidence interval
CRC	colorectal cancer
CR/PR/SD	complete response/partial response/stable disease
CVA	cerebro-vascular accident
DVT	deep vein thrombosis
e-CRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	emergency room
FOLFIRI	5-fluorouracil, leucovorin, irinotecan-(FOLFIRI regimen)
G-CSF	granulocyte colony-stimulating factor
GEP	good epidemiological practices
GPE	Global Pharmacovigilance & Epidemiology
ICF	informed consent form
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Market Authorization Holder
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MI	CVA
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	odds ratio
ORR	overall response rate
OS	overall survival
PASS	post-authorisation safety study
PE	pulmonary embolism
PFS	progression free survival
PS	performance status
QC	quality control
SAE	serious adverse event
SAS	statistical analysis system
SAP	statistical analysis plan
SmPC	summary of product characteristics
TEAE	treatment emergent adverse event

3 RESPONSIBLE PARTIES

3.1 RESPONSIBILITIES OF STEERING /PUBLICATION COMMITTEE

The Steering Committee/Publication committee will be composed of the study chairs and co chairs, and MAH representatives.

The Steering Committee will be responsible for coordinating the conduct of this study. It will be involved in the preparation and approval of the protocol and its amendment(s), will assess the progress of the study at both global and site levels and is given full authority for presentation/publication of the results. The detailed responsibilities of the Steering Committee, its relationship with the other parties responsible for the management and conduct of the study, its membership, and the purpose and timing of its meetings are described in the Steering Committee Charter.

The Publication Committee will have to define the overall publication plan including the primary publications reporting new scientific findings/data from the study, to review and approve (or abstain) all other publications proposals and draft manuscripts regarding subsequent publications including local publications.

3.2 RESPONSIBILITIES OF STUDY CHAIR

The Study Chairs are international experts in oncology, specifically colorectal cancer, who are well recognized in the therapeutic area, will be responsible for scientific advice and recommendations on:

- Study conduct,
- Development of publication guidelines.

The detailed responsibilities of the Study Chairs, their relationship with the other parties responsible for the management and conduct of the trial, and the purpose and timing of the meetings are described in the Steering Committee Charter.

4 ABSTRACT

STUDY No.: OBS13597-OZONE

Title	Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP® administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS).
Location	Europe & US
Study chairman	Ian CHAU, MD, Chairman Royal Marsden Hospital, Department of Medicine, Downs Road, Sutton, Surrey SM2 5PT - UK
Objectives	The objectives of this observational study are: • To describe the long term safety, and clinical outcomes of ZALTRAP ® in combination with FOLFIRI in patients treated in daily practice for a mCRC after failure of an oxaliplatin-based regimen; • To assess safety and effectiveness of ZALTRAP® in the following specific patient cohorts: - elderly patients (≥65 years old); - patients with renal or hepatic impairment (acknowledging the limits of irinotecan label); - Non Caucasian patients. - Number and type of prior anti-cancer therapy (eg, prior bevacizumab) • To describe utilization of health resources in patients treated with a combination of ZALTRAP® and FOLFIRI.
Study design & duration	• Prospective, international, multicenter observational (non-interventional on the therapeutic strategy) cohort study. • Each patient will have data collected prospectively for 24 months from the first dose of ZALTRAP® or until death, whichever comes first. As this is an observational study, no pre-defined visit schedule is planned, and visits will take place according to routine clinical practice. However, physicians will be asked to record data for study endpoints assessment every 3 months (±15 days) from ZALTRAP® treatment start. It is expected that the data collected will represent a realistic characterization of the patient population treated with ZALTRAP®and a rational evaluation of clinical outcome measures related to effectiveness and safety as assessed by the physicians in routine clinical practice.
Population	This prospective observational cohort non comparative study will enroll patients treated with ZALTRAP®in combination with FOLFIRI for metastatic colorectal cancer after failure of an oxaliplatin-based regimen as per the approved indication. Treatment related decisions will be made solely by the treating physician. • Inclusion Criteria - All patients planned to be treated with ZALTRAP®in combination with a 5FU plus irinotecan regimen (FOLFIRI) for metastatic colorectal cancer (mCRC) after failure of an oxaliplatin based regimen (including bevacizumab pretreated patients), according to physician decision. - Age ≥18 years. - Availability of a written informed consent. • Exclusion criteria: - Patients concurrently participating in any clinical study. - Patients receiving concomitant anti-VEGF agents and/or receiving ZALTRAP®through an investigational clinical study or through any compassionate use program. - Patients receiving ZALTRAP® in combination with chemotherapy regimens other than FOLFIRI.

	• Expected number of patients: - Approximately 750 patients overall, in order to have an adequate number of elderly (≥65 years old) patients (expected 40%, ie, approximately 300) and non-Caucasian patients (expected 10% to 15%, ie, approximately 75-112) and patients with renal and hepatic impairment (expected 30% and 18%, ie, approximately 225 and 135) • Expected number of countries - Approximately 14 • Expected number of sites - Approximately 170
Recruitment modalities	• Selection of physicians: oncologists and gastroenterologists with a recognized competency in oncology who prescribe ZALTRAP® in combination with FOLFIRI after failure of an oxaliplatin-based regimen. The physicians will be randomly selected based on physicians lists in each participating countries. • Selection of patients: all patients planned to be treated with ZALTRAP® in combination with FOLFIRI for mCRC following an oxaliplatin-based regimen will be approached for potential enrollment. A screening form will capture why an eligible patient is not included.
Main evaluation criteria	<u>Study Endpoints</u> • Safety (Treament Emergent Adverse Event [TEAE] and serious TEAE); • Effectiveness (Overall Survival [OS], Progression Free Survival [PFS], and Best Overall Response [BOR]); • Health resource utilization (Emergency room visits, number of days and type of hospitalization).
Main data collected	Data collection: Adverse events (AEs), serious adverse events (SAEs) both as per NCI CTCAE version 4.03), including laboratory abnormalities. Patients and disease information: patient demographics, physical exam, prior medical/surgical history, primary tumor site, primary site tumor pathology including molecular information (eg, KRAS or BRAF status) if available, date of initial diagnosis and stage of the disease, prior surgery, prior chemotherapy, prior other anticancer therapies, date of mCRC diagnosis and sites, date of last disease progression before ZALTRAP®-FOLFIRI combination start, laboratory data at baseline, treatment other than anticancer treatments at baseline. Effectiveness: best response to the ZALTRAP®-FOLFIRI combination and date of disease progression (based on the treating physician judgment), survival status up to 2 years or date of death whichever comes first.. ZALTRAP® pattern of use: date of administration of ZALTRAP®and FOLFIRI, doses (intended and actual for ZALTRAP®and FOLFIRI), the doses reduction, doses delay for both ZALTRAP® and FOLFIRI, the reason for treatment discontinuation and the premedication administered. The cumulative dose, the duration of exposure and the total number of infusions for both ZALTRAP®, 5FU and irinotecan will be calculated. Concomitant medications: diarrhea prophylaxis and treatment including hydration, G-CSF, biphosphonate use and all other treatment administered data will be collected as well as their intent (prophylaxis, treatment of a (S)AE etc). Health resource utilization during treatment with ZALTRAP®: data concerning emergency room visits , hospitalization (related to mCRC management and/or adverse events due to ZALTRAP® and/or FOLFIRI administration) including number of days of hospitalization, and type of hospitalization (intensive care unit versus standard ward versus palliative units). If the hospitalization is due to an AEs, the recovery status will be collected as well as the event duration. At the end of the follow-up period or at death (whichever comes first), the date and reason for completing study, the disease status and the date of death will be collected. The outcome of any potentially related AEs or ongoing SAEs regardless of relationship will be collected as well.

Statistical methodology

The analyses of this study will be descriptive in nature and the sample size has been chosen to permit collection of sufficient data to address the post authorization measures. Consequently, the sample size has not been determined in terms of statistical power, but rather in terms of precision (95% CI) associated to event rate estimations.

The study is planned to enrol approximately 750 patients; Based on epidemiological data, the study population is expected to be comprised of:

Approximately 40% of patients in the elderly (≥65 years old) group.

Approximately 10% to 15% of patients in the non-Caucasian group.

Approximately 30% of patients in renal impairment group.

Approximately 18% of patients in hepatic impairment group.

A subset of 40% (300), respectively 10%-15% (75-112), 30% (225) and 18% (135) of patients in each subgroup will allow the following precision:

For safety/health resources event rates:

Sample Size	Expected 95%CI for various event rates					
	5%	10%	20%	30%	40%	50%
300	[2.5% - 7.5%]	[6.6% - 13.4%]	[15.5% - 24.5%]	[24.8% - 35.2%]	[34.5% - 45.5%]	[44.3% - 55.7%]
75	[1.0% - 9.9%]	[3.2% - 16.8%]	[10.9% - 29.1%]	[19.6% - 40.4%]	[28.9% - 51.1%]	[38.7% - 61.3%]
112	[1.0% - 9.0%]	[4.4% - 15.6%]	[12.6% - 27.4%]	[21.5% - 38.5%]	[30.9% - 49.1%]	[40.7% - 59.3%]
225	[2.2% - 7.8%]	[6.1% - 13.9%]	[14.8% - 25.2%]	[24.0% - 36.0%]	[33.6% - 46.4%]	[43.5% - 56.5%]
135	[1.3% - 8.7%]	[4.9% - 15.1%]	[13.3% - 26.7%]	[22.3% - 37.7%]	[31.7% - 48.3%]	[41.6% - 58.4%]

For overall survival:

Assuming an exponential distribution of the overall survival and a median survival of 12 months, the survival rate would be 50% at 12 months, 35% at 18 months and of 25% at 24 months. The precision (Greenwood's formula) around the overall survival rates (Kaplan-Meier estimates) at these time points is provided in the following table (SAS simulations performed on 5000 replicates - Lost to follow up are simulated using an exponential distribution, a 5% rate at 12 months is assumed).

Sample size	Expected 95%CI for various survival time points		
	OS rate at 12 months	OS rate at 18 months	OS rate at 24 months
	50%	35%	25%
300	[44.1% ; 55.6%]	[29.5% ; 40.5%]	[20.1% ; 30.2%]
75	[38.1% ; 60.7%]	[24.3% ; 46.0%]	[15.7% ; 35.6%]
112	[40.3% ; 58.9%]	[26.1% ; 44.0%]	[17.2% ; 33.6%]
225	[43.2% ; 56.4%]	[28.6% ; 41.4%]	[19.4% ; 31.0%]
135	[41.1% ; 58.1%]	[26.9% ; 43.2%]	[17.8% ; 32.8%]

	Statistical analyses All statistical analyses will be descriptive using 2-sided 95% confidence intervals. Population characteristics will be summarized into count of non-missing data, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean for quantitative variables and count and frequencies with 95% confidence interval for categorical data. For the time to event outcomes, the Kaplan-Meier estimates (including curves) will be computed and the 95% confidence interval for the median survival times / survival rates at given time points will be provided. The following subgroups analyses will be performed (each of the subgroups vs. the rest of the population): • Elderly, • Hepatic or renal dysfunction, • Non Caucasian, • Number and type of prior anti-cancer therapy (eg, prior bevacizumab). These subgroups analyses will include multivariate analyses adjusting for any potential confounding prognostics variables.
Timelines	Estimated enrolment duration: 28 months Follow-up duration per patient: 24 months

5 FLOW CHART

Evaluation	INCLUSION*	Post initiation of ZALTRAP® treatment ([0])	End of Study
Informed Consent Form	X		
Inclusion/exclusion criteria	X		
Demographics	X		
Medical/surgical history	X		
Colorectal cancer history	X		
Colorectal Cancer prior treatments	X		
Physical examination (height/weight/ECOG PS/race)	X		
ZALTRAP® /FOLFIRI treatment pattern ([a])		X	
AEs/SAEs, laboratory, vital signs, ECG abnormalities ([b])	X	X	X
Concomitant medication ([c])		X	
Health resource utilization/ER visits/hospitalisations		X	
Physician assessed best overall response		X	
Date of disease progression		X	
Subsequent therapies for mCRC		X	
Patient vital status		X	
Reason for completing study			X

*Inclusion should be as close as possible and prior to the first administration of ZALTRAP® (ideally within one week).

a ZALTRAP®/FOLFIRI treatment pattern including line of therapy, dose, dose reductions, dose delays, reason for treatment discontinuation, pre-medications and G-CSF support.

b **AE (including SAE)** assessment extends from patient's ICF signature date till 30 days after last ZALTRAP®and/or FOLFIRI administration. After this 30 days period only AEs (including SAE) considered by physician to be related to ZALTRAP® and/or FOLFIRI will be collected**. Laboratory, vital signs or ECG abnormalities** are to be recorded in the AE pages only if they are medically relevant: symptomatic, leading to treatment modification (delay, reduction or discontinuation) and/or fulfilling a seriousness criterion.

c Diarrhoea prophylaxis and treatment including hydration and all other treatment administered data will be collected as well as their intent (prophylaxis, treatment of a (S)AE,etc) a (S)AE,etc) , from first administration of Zaltrap up to 30 days after last dose of the components of the Zaltrap/ FOLFIRI combination. Beyond 30 days, all treatments given to treat ongoing related non-serious AE and SAE(s) regardless of relationship will be collected until resolution or stabilization of the SAE (s).

Visit frequency according to local clinical practice: data recording every 3 months (± 15 days) from ZALTRAP® initiation up to maximum of 2 years., except for AE (see Section 12).

6 AMENDMENTS AND UPDATES

- ***Amendment 1 dated 12 Dec 2013***

  Main reason: The prolongation of the period for the reporting of non-serious adverse event to the MAH.

  Rationale: The Sanofi internal policy for adverse event reporting in prospective observational cohort studies has been changed on 28-Nov-2013.

- ***Amendment 2 dated 15 Oct 2015***

  Main reason: Decrease the study sample size

  Rationale: Due to ZALTRAP® usage below expectation, the initial target of 1000 patients to be recruited over 2 years (Last Patient In: Q3-4 2015) cannot be achieved. Therefore, the initial sample size is decreased from 1000 patients up to 750 patients, corresponding to real life exposure over approximatively 2 years recruitment period. Patient recruitment will be stopped once Sanofi has granted the Pharmacovigilance Risk Assessment Committee (PRAC) agreement on the revised targeted sample size. The Last Patient In is therefore planned for 1Q16.

7 MILESTONES

Milestone	Estimated Planned date
First Patient In	Q3-4 2013
Last Patient In	Q1 2016
Last Patient out	Q1 2018
Database lock	Q1 2018
Study progress report	Provided in RMP updates and/or periodic safety update reports (PSUR)
Final report of study results	Q3 2018

8 RATIONALE AND BACKGROUND

8.1 BACKGROUND

Colorectal cancer is a major worldwide health problem. It is the third most common cancer amongst men (behind lung and prostate cancer) accounting for 10% of the total, and the second most common cancer in women (behind breast cancer), accounting for 9.4% of the total. Incidence rates are higher in men (1.4 to 1) (1). In 2008, the incidence of colorectal cancer was over 1.2 million cases, with mortality over 600,000 worldwide (2); in the US, the incidence of colorectal cancer was over 153,000 and in Europe (including Central and Eastern Europe) the incidence was over 450,000. Approximately half of all patients develop metastasis (3).
The five year survival rate in early localized stage is about 90%, decreasing to approximately 60-65% after spread to adjacent organ(s) or lymph nodes, and to less than 10% after spread to distant sites (1).

For patients with metastatic Colorectal Cancer (mCRC) having failed a prior oxaliplatin-based regimen for first-line treatment of mCRC, the preferred treatment is an irinotecan based regimen (most often irinotecan combined with bolus/infusional 5-fluorouracil and leucovorin: FOLFIRI).

Recently, the randomized Phase III pivotal study EFC10262/VELOUR study in second-line metastatic colorectal cancer comparing ZALTRAP® versus placebo in patients treated with irinotecan /5-FU combination (FOLFIRI) after failure of an oxaliplatin based regimen demonstrated a statistically and clinically significant improvement in OS, progression free survival (PFS) duration and a significantly higher overall response rate (ORR) in patients treated with ZALTRAP®/FOLFIRI over those treated with placebo/FOLFIRI and demonstrating for the first time an overall survival benefit of a targeted therapy in combination with FOLFIRI in second line chemotherapy (4). Therefore, ZALTRAP®provides an important new treatment option for the treatment of second-line mCRC patients in combination with FOLFIRI, and is the only agent to demonstrate an OS benefit in this setting.

Table 1 – VELOUR, Main efficacy endpoints[a] – ITT population

	Placebo/FOLFIRI (N=614)	ZALTRAP® /FOLFIRI (N=612)
Overall Survival		
Number of death events, n (%)	460 (74.9%)	403 (65.8%)
Median overall survival (95.34% CI) (months)	12.06 (11.07 to 13.11)	13.50 (12.52 to 14.95)
Stratified Hazard ratio (95.34% CI)	0.817 (0.713 to 0.937)	
Stratified Log-Rank test p-value	0.0032	
Progression Free Survival (PFS)[b]		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (99.99% CI) (months)	4.67 (4.07 to 5.55)	6.90 (5.88 to 7.85)
Stratified Hazard ratio (99.99% CI)	0.758 (0.578 to 0.995)	
Stratified Log-Rank test p-value	0.00007	
Overall Response Rate	(N=530)	(N=531)
(CR+PR)[d] (95% CI) (%)[c]	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p-value	0.0001	

a Stratified on ECOG Performance Status (0 versus 1 versus 2) and Prior Bevacizumab (yes versus no)
b PFS (based on tumor assessment by the IRC): Significance threshold is set to 0.0001
c Overall objective response rate by IRC
d CR (complete response) PR (partial response)

On the basis of these study results, in August 2012, the US Food and Drug Administration (FDA) after a priority review, granted approval for ZALTRAP® (ziv-aflibercept) with the following indication: ZALTRAP®in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

In November 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorization of aflibercept (ZALTRAP®) in combination with irinotecan/5 fluorouracil/folinic acid (FOLFIRI) chemotherapy in the treatment of adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin containing regimen.

The recommended dose of ZALTRAP®, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen, every 2 weeks.

For details, please consult the most recent ZALTRAP® EU SmPC or US Package Insert or local Product Information.

8.2 RATIONALE

Following the EMA evaluation, the Applicant was requested to conduct a post-authorisation safety study (PASS) in real life to assess safety and effectiveness of ZALTRAP® administered in the approved indication. The sponsor proposes to conduct an observational cohort non comparative study, of which primary objective will be to better characterize the safety and effectiveness of ZALTRAP® in the real life setting, particularly in subpopulations such as elderly patients or patients with hepatic or renal impairment (within the limits of the irinotecan label) or non Caucasian patients. This study will prospectively collect safety and effectiveness data in patients treated with ZALTRAP® in clinical practice, including long-term safety data.

9 RESEARCH QUESTION AND OBJECTIVES

The objectives of this observational study are:

9.1 PRIMARY OBJECTIVE

To describe the long term safety, and clinical outcomes of ZALTRAP® in combination with FOLFIRI in patients treated in daily practice for a mCRC after failure of an oxaliplatin-based regimen.

To assess safety of ZALTRAP® in the following patient cohorts:

- Elderly patients (≥65 years old);
- Patients with renal or hepatic impairment (within the limits of irinotecan label);
- Non Caucasian patients.
- Number and type of prior anti-cancer therapy (eg, prior bevacizumab).

9.2 SECONDARY OBJECTIVES

To describe effectiveness of ZALTRAP® and FOLFIRI in combination (eg, PFS, OS, RR) in subgroups mentioned in Section 9.1.

To describe utilization of health resources in patients treated with a combination of ZALTRAP® and FOLFIRI.

10 RESEARCH METHODS

Study Endpoints:

- Safety (TEAE and serious TEAE),
- Effectiveness (OS, PFS, and BOR) as per physician,
- Health resource utilization (Emergency Rooms visits, days and type of hospitalisation).

10.1 STUDY DESIGN

This is a prospective, international, multicenter observational (non-interventional on the therapeutic strategy) cohort non-comparative study. It will include a cohort of patients treated with ZALTRAP® in the clinical setting (not as part of an interventional clinical trial) and followed for 24 months after initiation of ZALTRAP® The design of the study will mirror real life management of these patients. It is expected that the data collected will represent a realistic characterization of the patient population treated with ZALTRAP® and a rational evaluation of clinical outcome measures related to effectiveness and safety as assessed by the physicians in routine clinical practice.

There will be no fixed study visit schedule. The study visits will occur according to the treating physician's clinical practice and judgement. However, physicians will be asked to record data for study endpoint assessments every 3 months.

10.2 SETTING

10.2.1 Duration of the study

Each patient will have data collected prospectively for 24 months from the first dose of ZALTRAP® or until death, whichever comes first. As this is an observational study, no pre-defined visit schedule is planned, and visits will take place according to routine clinical practice. However, physicians will be asked to record data for study endpoints assessment every 3 months (± 15 days) from ZALTRAP® treatment start.

10.2.2 Eligibility criteria

10.2.2.1 Inclusion criteria

I 01. Patient planned to be treated with ZALTRAP® in combination with a 5FU plus irinotecan regimen (FOLFIRI) for mCRC after failure of an oxaliplatin based regimen (including bevacizumab pretreated patients). Patient for which the Physician has decided to prescribe ZALTRAP® independently from entry in study.

I 02. Age ≥18 years old.

I 03. Availability of a written informed consent.

10.2.2.2 Exclusion criteria

E 01. Patients concurrently participating in any clinical study.

E 02. Patients receiving concomitant anti-VEGF agents and/or receiving ZALTRAP® through an investigational clinical study or through any compassionate use program.

E 03. Patients receiving ZALTRAP® in combination with chemotherapy regimens other than FOLFIRI.

10.2.3 Analysis population(s)

All treated population: This population includes all patients who have given their informed consent and who received at least part of ZALTRAP® administration.

10.2.4 Modalities of recruitment

10.2.4.1 Physician selection

All oncologists and gastroenterologists with a recognized competency in oncology who treat mCRC and prescribe ZALTRAP® in combination with FOLFIRI after failure of an oxaliplatin-based regimen will be prospectively defined as sites for potential inclusion in the study in each participating countries.

Within each country, a target number of sites that can participate in the study will be determined accordingly to the protocol and to the possibilities of the country. This target number will be compatible with the total number of patients that should be recruited in each country.

Independently in each country, sites that will be offered participation in the study will be randomly selected in order to ensure representativeness of the sample.

The random-process will be stratified on country-specific criteria in order to accurately reflect routine clinical practices within each country.

The random selection process will provide each country with a list of potentially participating sites of at least 400% the final number required (when possible) in order to take into account physicians who decline to participate.

Each site who declines to participate will be replaced by the following one selected by the same random selection process in the same country.

The reason for non-participation will be collected during the selection and documented.

10.2.4.2 Patient selection

The prescription of therapies is under the only responsibility of the patient's physician.

The patients who will be enrolled in the study will be selected among the patients for whom the physician has decided to prescribe ZALTRAP® independently from study entry.

The physician should refer to the SmPC for any information on treatment prescribed.

Patients meeting the inclusion/exclusion criteria will be proposed to be included in this study.

Each participating physician will be asked to approach and include consecutive patients who meet eligibility criteria during the recruitment period starting from the initiation date at each site. Approaching patients consecutively will help to limit bias related to physician-led patient selection.

Each physician will include patients until the targeted number of patient in his/her country is reached.

A screening form will be implemented at each site to document this consecutive enrolment, and will capture why an eligible patient is not included.

10.3 VARIABLES

10.3.1 Evaluation criteria

10.3.1.1 Definition of the disease

Metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin containing regimen.

10.3.1.2 Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age, gender, race, height and weight), medical history, cancer diagnosis, prior anticancer therapy, prior medications (other than prior anticancer treatment for colorectal cancer) will be summarized at baseline.

10.3.1.3 Safety

Adverse events

The period of safety observation starts from the time when the patient gives informed consent and is divided into three periods:

- Pre-treatment period: The pre-treatment period is defined as the time between when the patient gives informed consent and the start of the first dose of ZALTRAP® or FOLFIRI (Irinotecan-5Fluorouracil), whichever is first.
- On-treatment period: The on-treatment period is the period from the first dose of ZALTRAP® or FOLFIRI, whichever is first, to 30 days after the last dose of ZALTRAP® or FOLFIRI, whichever is last.
- Post-treatment period: The post-treatment period is defined as the time starting 31 days after last dose of ZALTRAP® or FOLFIRI, whichever is last to the end of the follow-up period.

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

Three categories of Adverse Events are defined according to these three periods:

- Pre-treatment AEs: defined as any AE reported during the pre-treatment period.
- Treatment-emergent AEs (TEAEs): A TEAE is defined as an AE beginning, worsening or becoming serious during the on-treatment period.
- Post-treatment AEs: AE reported during the post-treatment period.

10.3.1.4 Effectiveness

- Best Overall Response as defined by the physician: complete response, partial response, stable disease, progressive disease.
- PFS: will be evaluated from the date of 1st administration of ZALTRAP® or FOLFIRI to the date of disease progression or death due to any cause. Disease progression will be based on the treating physician judgment.
- OS: will be evaluated from the date of 1st administration of ZALTRAP® or FOLFIRI to the date of death due to any cause.

10.3.1.5 Study treatment exposure

- Date of administration of ZALTRAP® and FOLFIRI,
- Doses (intended and actual for ZALTRAP® and FOLFIRI),
- Doses reduction and doses delay for both ZALTRAP® and FOLFIRI,
- Reason for treatment discontinuation and the premedication administered,
- Cumulative dose, the duration of exposure and the total number of infusions for ZALTRAP®, 5FU and irinotecan.

10.3.1.6 Concomitant medications

- Diarrhoea prophylaxis and associated treatment including hydration,
- G-CSF use,
- Biphosphonates,
- and all other treatment administered, along with their intent (prophylaxis, treatment of a (S)AE, etc) will be collected from first administration of Zaltrap up to 30 days after last dose of the components of the Zaltrap/ FOLFIRI combination. Beyond 30 days, all treatments given to treat ongoing related non-serious AE and SAE(s) regardless of relationship will be collected until resolution or stabilization of the SAE (s).Health resource utilization
- Emergency room visits,
- Hospitalization (related to mCRC management and/or adverse events due to ZALTRAP® and/or FOLFIRI administration) including:
  - Number of days of hospitalization,
  - Type of hospitalization (intensive care unit versus standard ward versus palliative units).

10.4 DATA SOURCES

All the data will come from the e-CRF.

10.5 STUDY SIZE

10.5.1 Determination of sample size

The study plans to enroll approximately 750 patients; within this population, it is expected to have:

- About 40% of patients in the elderly (≥65 years old) group.
- Around 10% to 15% of patients in the non-Caucasian group
- Around 30% of patients in renal impairment group
- Around 18% of patients in hepatic impairment group

A subset of 40% (300), respectively 10%-15% (75-112), 30% (225) and 18% (135) of patients in each subgroup will allow having the below precision:

For safety/health resources event rates:

Sample Size	Expected 95%CI for various event rates					
	5%	10%	20%	30%	40%	50%
300	[2.5% - 7.5%]	[6.6% - 13.4%]	[15.5% - 24.5%]	[24.8% - 35.2%]	[34.5% - 45.5%]	[44.3% - 55.7%]
75	[1.0% - 9.9%]	[3.2% - 16.8%]	[10.9% - 29.1%]	[19.6% - 40.4%]	[28.9% - 51.1%]	[38.7% - 61.3%]
112	[1.0% - 9.0%]	[4.4% - 15.6%]	[12.6% - 27.4%]	[21.5% - 38.5%]	[30.9% - 49.1%]	[40.7% - 59.3%]
225	[2.2% - 7.8%]	[6.1% - 13.9%]	[14.8% - 25.2%]	[24.0% - 36.0%]	[33.6% - 46.4%]	[43.5% - 56.5%]
135	[1.3% - 8.7%]	[4.9% - 15.1%]	[13.3% - 26.7%]	[22.3% - 37.7%]	[31.7% - 48.3%]	[41.6% - 58.4%]

For overall survival:

Assuming an exponential distribution of the overall survival and a median survival of 12 months, the survival rate would be 50% at 12 months, 35% at 18 months and of 25% at 24 months. The precision (Greenwood's formula) around the overall survival rates (Kaplan-Meier estimates) at these timepoints is provided in the following table (SAS simulations performed on 5000 replicates - Lost to follow up are simulated using an exponential distribution, a 5% rate at 12 months is assumed).

Sample size	Expected 95%CI for various survival time points		
	OS rate at 12 months 50%	OS rate at 18 months 35%	OS rate at 24 months 25%
300	[44.1% ; 55.6%]	[29.5% ; 40.5%]	[20.1% ; 30.2%]
75	[38.1% ; 60.7%]	[24.3% ; 46.0%]	[15.7% ; 35.6%]
112	[40.3% ; 58.9%]	[26.1% ; 44.0%]	[17.2% ; 33.6%]
225	[43.2% ; 56.4%]	[28.6% ; 41.4%]	[19.4% ; 31.0%]
135	[41.1% ; 58.1%]	[26.9% ; 43.2%]	[17.8% ; 32.8%]

10.5.2 Sample size

It is planned to recruit approximately 750 patients, in 170 centers in 14 countries, mainly in Europe.

10.6 DATA MANAGEMENT

10.6.1 Data collection schedule

Due to the observational nature of this study there will be no fixed study visit schedule and the study will not impose any additional procedures, assessments or changes to routine management of patients. The visits will take place done according to the clinical practice.

Physicians will be asked to record data for study endpoint assessments at inclusion, every 3 (± 15 days) months through the observation period from ZALTRAP® treatment start (interim data collection) and at the end of study. For Safety reporting see obligations in Section 12.

Inclusion

It should be performed when the patient satisfies the inclusion/exclusion criteria, when disease progression during or after the oxaliplatin treatment is observed and a decision of ZALTRAP® FOLFIRI treatment has been made. The physician will review the inclusion/exclusion criteria and will ask the patient to confirm his willingness to participate by signing the informed consent form.

Inclusion should be as close as possible and prior to the first administration of ZALTRAP® (ideally within one week).

Interim period:

Clinical visits should be performed according to the clinical practice.

End of Study:

It should be completed at the end of the observational period (defined as completion of 2 years follow-up post initiation of ZALTRAP® and/or FOLFIRI treatment or death, whichever occurs first).

In case the patient does not return to the site, every effort should be made to re-contact him and to enquire about his health status.

As this is an observational research, data routinely collected in clinical practice will be recorded. This observational study will not impose any additional procedures, assessments or changes to routine management of patients.

10.6.2 Data collected

10.6.2.1 Site / Physician questionnaire

Before starting the recruitment a site questionnaire will be filled in by each participating physician. This questionnaire will collect the following information:

- Address,
- Type of center (academic/non-academic, public or private practices),
- Physician specialty (medical oncologist, gastroenterologist),
- Number of patients with mCRC treated per year.

This information will be entered in the clinical database.

10.6.2.2 Screening form

Screening forms will be completed by each site from site initiation until the end of the inclusion period. The enrolment period is planned to around 24 months.

The participating physicians should complete an anonymous screening form as soon as they have identified a patient who could satisfy the study criteria.

For the patients who are not enrolled, the reason for non-participation will be reported (eg, informed consent refusal, follow-up not possible in this ward, physician's refusal or other).

The following data will be reported:

- Date of patient's visit,
- Patient number (if relevant),
- The reason for non-enrollment.

10.6.2.3 Patient data

For information recorded per routine clinical practice, data will be requested for transcription to an electronic case report form (e-CRF). This data will include the following:

10.6.2.3.1 Inclusion Information-pretreatment period

- Date of written informed consent
- Inclusion and exclusion criteria
- Patient characteristics:
  - Demographics (age at inclusion, sex, race)
  - Physical examination (ECOG PS, height and body weight)
  - Prior medical/surgical history (including prior history of high blood pressure, venous and arterial thromboembolic events (eg, DVT/PE/MI/CVA), and gastrointestinal perforation or fistula)
  - Concomitant medication still ongoing at the time of ZALTRAP® first administration
- Disease history:
  - Primary site
  - Date of initial diagnosis
  - Stage of the disease at time of initial diagnosis
  - Date of mCRC diagnosis
  - Details on prior anticancer therapy: surgery, radiotherapy, chemotherapy and other anticancer therapies (including biological treatment)
  - KRAS and BRAF status, if available
- Disease characteristics at inclusion:
  - Date of last disease progression
  - Extent of disease (sites of metastasis and primary tumor)
  - Measurable or not measurable disease
- Laboratory data at inclusion: Blood count, Biochemistry (including hepatic and renal function assessment), urinary.
- From the time period spanning from the informed consent signature and the 1st administration of ZALTRAP® (pre-treatment period) all AEs (including SAE), graded as per NCI-CTCAE version 4.03, will be collected.

10.6.2.3.2 Follow-up Data Post Initiation of ZALTRAP® treatment: Interim period

Data will be collected at approximately 3-monthly [± 15 days] intervals throughout the observation period for a total period of 24 months or death whichever comes first:

- Patient status:
  - Alive (date of last contact),
  - Dead: date and cause (whether due to colon cancer, adverse event or other),
  - Lost to follow-up (date of last contact).
- Treatment period:
  - ZALTRAP® treatment pattern including
    - date of dosing , dose (intended and actual),
    - dose modification: dose reduction, dose delay,
    - reason for treatment discontinuation.
  - Associated chemotherapy (FOLFIRI) including
    - date of dosing, dose (intended and actual),
    - dose modification: dose reduction, dose delay,
    - reason for treatment discontinuation.
  - Concomitant medication: including irinotecan premedication, diarrhoea prophylaxis including hydration, G-CSF support, biphosphonates and other corrective treatment to treat AE/ SAE.
  - Adverse events graded as per NCI-CTCAE version 4.03:
    - AEs (including SAEs): from first administration of ZALTRAP® and/or FOLFIRI through 30 days after last ZALTRAP® and/or FOLFIRI administration, and corrective medication will be recorded. After the 30 days follow-up period, only AEs (including SAEs) related to ZALTRAP® and/or FOLFIRI will be recorded.
    - Laboratory, vital signs or ECG abnormalities will be recorded in the AE pages only if they are medically relevant: symptomatic, leading to treatment modification (delay, reduction or discontinuation) and/or fulfilling a seriousness criterion.
  - Health resources utilization: to be collected during treatment with ZALTRAP® and/or FOLFIRI and up to 30 days after its complete discontinuation :
    - Number of hospitalization days linked to management of mCRC and Serious Adverse Events related to ZALTRAP® and/or FOLFIRI
    - Type of hospitalizations (ICU, standard wards, ER admissions if >1 night).
- Physician assessed Best Overall Response (BOR) during treatment with ZALTRAP® and/or FOLFIRI:
  - Type of best overall response (BOR): complete response, partial response, stable disease, progressive disease, with the method used for assessment.
  - If progressive disease
    - Physician assessed date of progression (for PFS)

- First subsequent lines of treatment actually received:
  - Start date of first subsequent therapy following discontinuation of ZALTRAP® and/or FOLFIRI.
  - Type of subsequent therapy:
    - Systemic agents (chemotherapy, targeted therapy),
    - Surgery (palliative or curative),
    - Radiotherapy (palliative or curative).

10.6.2.3.3 End of Study:

The end of study period is defined as death or completion of 24 months observation period, whichever occurs first. The following is to be documented:

- Reason for completing study,
- Related AE to be followed and/or reported.

10.6.3 Procedure for withdrawal of patients from study follow-up schedule

The participating Physician should make every effort to re-contact the patient, to identify the reason why he failed to attend the visit, and to document his health status in the End of Study e-CRF section, including at least his vital status.

All the information available in the patient's file until the date of last contact or visit should be entered in the e-CRF.

Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up. The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

10.6.4 Logistic aspects

Site and patient number:

The patient number is the association of the country number (3-digit ISO code), site number (assigned by the Company), and patient number (automatically allocated by the e-CRF).

10.7 DATA ANALYSIS

All statistical analyses will be descriptive using 2-sided 95% confidence intervals.

10.7.1 Primary analysis

Safety endpoints will be summarized as count and frequencies with 95% confidence interval.

The primary focus of AEs reporting will be on TEAEs. Pre-and post-treatment AEs will be described separately.

In addition, specific adverse events terms will be summarized by grouping pre-specified MedDRA preferred terms recorded in the AE page, for at least the following categories:

- Acute drug reaction
- Cardiac dysfunction
- Haemorrhage
- Hypertension
- Gastrointestinal perforation
- Fistula (from gastrointestinal or other origin)
- Osteonecrosis
- Wound healing
- Renal failure
- Proteinuria including nephrotic syndrome

Adverse events incidence tables will be presented by using MedDRA classification up to the preferred term (PT).

The grade will be taken into account in the summary. For patients with multiple occurrence of the same event, the worst grade (NCI CTCAE, version 4.03) will be used.

Summaries will be provided for all grades and grades (≥3) combined, unless otherwise specified.

TEAEs, possibly related TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to permanent study treatment discontinuation as well as all deaths will be summarized.

The following safety subgroup analyses will be performed at least in the following subgroups:

- Elderly (≥65 years),
- Hepatic impairment patients (defined as: patients with at baseline either total bilirubin >UNL or transaminases >1.5 UNL) or
- Renal impairment patients **(**defined as: patients with at baseline creatinine clearance ≤80 mL/Min),
- Non Caucasian,
- Number and type of prior anti-cancer therapy (eg, prior bevacizumab)

Those analyses will consist of each of the subgroup summary vs. the rest of the population.

Best Overall Response will be summarized as count of patients and frequencies with 95% confidence interval.

For the PFS and OS outcomes, the Kaplan-Meier estimates (including curves) will be computed and the 95% confidence interval for the median survival times / survival rates at given time points will be provided.

10.7.2 Secondary analysis

The following effectiveness subgroup analyses will be performed at least in the following subgroups:

- Elderly (≥65 years),
- Hepatic impairment patients (defined as: patients with at baseline either total bilirubin >UNL or transaminases >1.5 UNL) or
- Renal impairment patients **(**defined as: patients with at baseline creatinine clearance ≤80 mL/Min),
- Non Caucasian.
- Number and type of prior anti-cancer therapy (eg, prior bevacizumab)

Those analyses will consist of each of the subgroup summary vs. the rest of the population.

These analyses will also include multivariate analyses adjusting for any potential confounding prognostics variables. For PFS and OS, Cox models will be used. Logistic regressions will be done for best overall response.

Health resources endpoints will be summarized as count and frequencies with 95% confidence interval. The number of hospitalization and the cumulated length of stay of hospitalization will be summarized on the whole population and per patient concerned. Hospitalizations will be described by reason of hospitalization and by unit.

Site questionnaires, population characteristics, study treatment exposure, and concomitant medications will be summarized into:

- count of non-missing data, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean for quantitative variables,
- and count and frequencies with 95% confidence interval for categorical data.

10.7.3 Interim analysis

No interim analysis is planned for this study.

10.8 QUALITY CONTROL

10.8.1 Data collection, validation and data quality control at company level

Data will be collected using an e-CRF.

The computerized handling of the data by the Company after receipt of the CRFs may generate additional requests to which the participating Physician is obliged to respond by confirming or modifying the data questioned.

Data collection and validation procedures will be detailed in appropriate operational documents.

10.8.2 Data quality control at site level

Data quality control will be performed on active sites (which have enrolled at least one patient).

Quality Control will be performed by qualified designated personnel in each country.

The methodology of data Quality Control and appropriate consecutive corrective actions will be detailed in the study guidebook.

10.9 LIMITATIONS OF THE RESEARCH METHODS

This is a prospective, international, multicenter observational (non-interventional on the therapeutic strategy) cohort study.

In order to limit potential bias in patient's selection, participating physicians will be randomly selected, and will be asked to propose inclusion to all consecutive patients meeting the study criteria.

The data collected are expected to represent a realistic characterization of the patient population treated with ZALTRAP® and a rational evaluation of clinical outcome measures related to effectiveness and safety as assessed by the physicians in routine clinical practice.

Although the visits will be done according to the clinical practice (no fixed study visit are scheduled), the physicians will be asked to record data for study endpoint assessments every 3 months.

10.10 OTHER ASPECTS

Not Applicable.

11 PROTECTION OF HUMAN SUBJECTS

11.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

The Physician/Health Care Provider will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Physician/Health Care Provider's responsibility to obtain written informed consent from patients prior to inclusion in the study, to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

Physician/Health Care Provider, and under the Health Care Provider's responsibility, should fully inform the Patient of all pertinent aspects of the study including the written information. All patients 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 study, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form and the Information Sheet used by the Physician/Health Care Provider for obtaining the Patient's Informed Consent must be reviewed and approved by the Company prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval / favorable opinion.

11.2 RESPONSIBILITIES OF SANOFI

The Sanofi is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The Sanofi is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

11.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

11.3.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

11.3.2 Laws and regulations

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (USA (5) and European (6)).

Each participating country should locally ensure all necessary regulatory submissions (eg, IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

11.3.3 Data protection

The patient's personal data and Physician's personal data which may be included in the Sanofi database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Physician and/or to the patients, Sanofi shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.3.4 Insurance

Participating countries may contract insurance according to local specific requirements.

11.3.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the Physician (or any action carried out by the company on their behalf), including the present protocol and the CRF, are exclusive property of the Company.

These materials or information (both global and partial) cannot be given or disclosed by the Physicians or by any person of her/his group to unauthorized persons without the prior formal written consent of the Company.

The Physician shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

11.3.6 Record retention

The physician shall arrange for the retention of study documentation until the end of the study. In addition the physician will comply with specific local regulations/ recommendations with regards to patient record retention.

It is recommended that the Physician retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the Physician Agreement in line with additional standards and/or local laws.

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

11.3.7 Discontinuation of the study

The Company can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Physician.

Similarly, should the Physician decide to withdraw from the study, she/he will have to inform the Company in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

11.3.8 Company audits and inspections by competent authorities

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

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

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 competent authorities will be communicated by the Physician to the Company.

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

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

All AEs, regardless of seriousness or relationship to ZALTRAP® and/or FOLFIRI, spanning from the signature of the informed consent form through 30 days after the last administration of ZALTRAP® and/or FOLFIRI, are to be recorded on the corresponding page(s) of the e-CRF.

After this 30 day period only AEs (including SAEs) considered by the physician to be caused by ZALTRAP® and/or FOLFIRI with a reasonable possibility will be collected.

12.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

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. Overdose and pregnancy will be considered as medically important event,
- Suspected transmission of infectious agent ; is any suspected transmission of an infectious agent via a medicinal product (eg, product contamination),

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.

12.1.1 Obligations of the Physician regarding safety reporting

Adverse Events collection

All Adverse Events regardless of relationship to ZALTRAP® and/or FOLFIRI, spanning from the signature of the informed consent form until the end of the collection period as defined by the protocol for each patient, are to be recorded **immediately** (within 24 hours of awareness) for serious AE and within 30 days of awareness for non-serious AE on the corresponding page(s) included in the Case Report Form or e-CRF, as explained below.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The physician should specify the date of onset, intensity, action taken with respect to ZALTRAP® and/or FOLFIRI, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by ZALTRAP® and/or FOLFIRI.

Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if they are medically relevant: symptomatic, leading to treatment modification (delay, reduction or discontinuation) and/or fulfilling a seriousness criterion.

Adverse event reporting to MAH/MAH representative

In case of Serious Adverse Events

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send the notification to the representative of MAH after approval of the Physician within the e-CRF or automatically after a pre-set delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the MAH whose name, fax number and email address appear on the first page of this Protocol;. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Study are properly mentioned on any copy of source document provided to MAH/MAH REPRESENTATIVE. 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 MAH/MAH REPRESENTATIVE within 24 hours of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (7 days) following initial notification.

A back-up plan is used (using paper flow) in case the e-CRF system does not work.

Overdose

Any case of accidental or intentional symptomatic overdose (defined as administration of any components of the combination at least 33% above the intended dose), even not fulfilling a seriousness criterion, is to be reported to the representative of sanofi immediately (within 24 hours) using the AE form to be entered in the e-CRF. Overdoses with no AE, but which require hospitalization, however, are considered as SAEs (medically important event) and handled as such. In case of overdose the patient should remain under observation for as long as it is considered as appropriate by the physician and closely monitored. Appropriate symptomatic measures should be taken.

Pregnancy

Pregnancy occurring in the patient or the partner of a patient included in the study will be recorded as an AE in all cases. It will be qualified as SAE (medically important event). In the event of pregnancy, the representative of sanofi should be informed immediately (within 24 hours), using the AE form (e-CRF) together with the SAE complementary form to be sent to the representative of sanofi name, telephone number, fax number and email address appear on the first page of this Protocol. Follow-up of the pregnancy is mandatory until the outcome has been determined.

In case of non-Serious Adverse Events

All non-serious AE are to be entered into the appropriate screens in the e-CRF within 30 days of awareness of the event (ref. Adverse Events collection). Further update(s) will be entered as necessary. A back-up plan using paper CRF will be used in case the e-CRF is not working.

12.2 SAFETY OBSERVATIONS

- The Physician should take all appropriate measures to ensure the safety of the patients as per normal practice.
- In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study.

12.2.1 Obligations of MAH/MAH REPRESENTATIVE

During the course of the study, the MAH/MAH REPRESENTATIVE will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations.

The MAH will report all safety observations made during the conduct of the study in the final study report.

13 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

13.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the Company conducting the study Sanofi.

The Steering/Publication Committee will have full access to the final data allowing for appropriate academic analysis and reporting of the study results.

13.2 PUBLICATIONS

A Publication Committee is responsible for the overall publication plan. Its main mission could be:

- To define the overall publication plan including the primary publications reporting new scientific findings/data from the study,
- To review and approve (or abstain) all other publications proposals and draft manuscripts regarding subsequent publications including local publications.

The Steering/Publication committee is responsible for presentations and/or publications. The study results must be submitted to the review of the Steering/Publication Committee before publication.

All study physicians give full authority to the Steering/Publication Committee for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for sub-studies) must be approved by the Steering/Publication Committee and make reference to the study and the primary publication. The final decision to publish any manuscript/ abstract/ presentation will be made by the Steering/Publication Committee after prior notice to the Company allowing for its internal review and comments. All manuscript/ abstract/ presentation must be submitted to the internal review of the Company at least forty-five (45) calendar days in advance of submission. The Company may request that the Company's name and/or names of one or several of its employees appear or do not appear in such publication.

The Company can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

14 REFERENCES

1. Cancer facts and figures. American Cancer Society, 2005.

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.

3. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin. 1999;49(1):8-31.

4. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, et al. Addition of ZALTRAP® to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30:3499–506.

5. International Society for Pharmocoepidemiology, April 2007. 'Guidelines for Good Pharmacoepidemiology Practices'.

6. Good Epidemiological Practice (GEP) proper conduct in epidemiology research – IEA European Federation (April 2007).

ANNEXES

Not applicable.

OBS13597 Amended Protocol 02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
Magherini, Emmanuelle	Clinical Approval	02-Feb-2016 10:56 GMT+01
Assadourian, Sylvie	Clinical Approval	02-Feb-2016 11:53 GMT+01