AMENDED CLINICAL TRIAL PROTOCOL 2

COMPOUND: SAR245408 - SAR245409

International, multicenter, open-label, treatment-extension study for subjects who completed a Phase 1 or Phase 2 parental study to continue receiving treatment with SAR245408 or SAR245409 as a monotherapy or as a combination regimen

STUDY NUMBER: TED12414

CLINICAL STUDY DIRECTOR: [redacted], [redacted], [redacted]

NCT number: NCT01587040

Clinical Trial Protocol Amendment 2	Version no. 1	Date : 16-Jun-2014
Clinical Trial Protocol Amendment1	Version no. 1	Date : 21-Sep-2012
Clinical Trial Protocol	Version no. 1	Date : 16-Jan-2012
EudraCT number	2011-006140-78	
IND number (SAR245408)	77,339	
IND number (SAR245409)	77,636	

Total number of pages: 93

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Tel:
Mobile:

CLINICAL TRIAL SUMMARY

COMPOUNDS: SAR245408 and SAR245409	**STUDY No : TED12414**
TITLE	International, multicenter, open-label, treatment-extension study for subjects who completed a Phase 1 or Phase 2 parental study to continue receiving treatment with SAR245408 or SAR245409 as a monotherapy or as a combination regimen.
INVESTIGATOR/TRIAL LOCATION	International.
STUDY OBJECTIVE(S)	**Primary Objective** To determine the long term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen in subjects who are benefiting from treatment. **Secondary Objective(s)** Not applicable.
STUDY DESIGN	This treatment-extension, open-label, international, multicenter, nonrandomized study is designed to provide continued access to SAR245408 or SAR245409 as a monotherapy or as part of a combination regimen. All subjects in the study will receive SAR245408 or SAR245409; the respective dose will be either the recommended Phase 2 dose (400 mg SAR245408 [tablet formulation polymorph A] once daily or 50 mg SAR245409 [capsule formulation] twice daily) or the subject's established dose either as a monotherapy or in a combination regimen in the parental study. SAR245408 is administered orally and is supplied as a capsule or a tablet formulation polymorph A or E. SAR245409 is administered orally and is supplied as a capsule or a tablet formulation. For all subjects, the dose, regimen, formulation, and food condition for study drug intake of SAR245408 or SAR245409 (and the dose and regimen of combination medication(s) for subjects taking combination therapy) will be agreed on in writing between the site and the Sponsor prior to first dose. Subjects who will enter the treatment extension study on Day 1 of the Initiation Period are those who: • Received SAR245408 or SAR245409 for less than 2 cycles in the parental study • Had dose interruption in the parental study but fulfill parental protocol criteria to restart IMP • Fulfill the parental study criteria for IMP treatment continuation but have ongoing Grade 2 AE(s) • Will take a daily dose higher than their established dose in the parental study Subjects who received SAR245408 or SAR245409 for at least 2 cycles in the parental study will enter the treatment-extension study on Day 1 of the Extension Period.

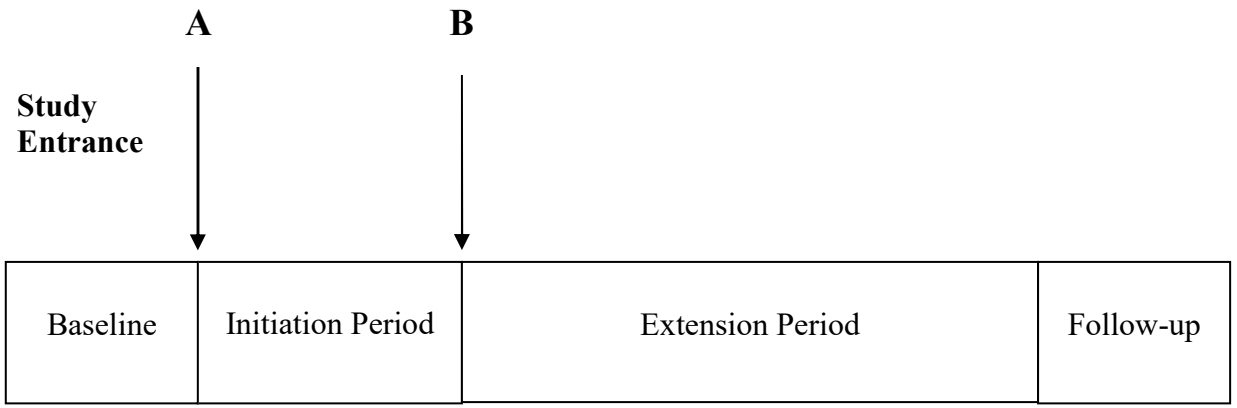
	Subjects may continue in the study until disease progression, unacceptable toxicity, withdrawal of consent, until commercial supplies of SAR245408 or SAR245409 are available to them outside of the clinical trial, or other reasons detailed in Section 22).
STUDY POPULATION **Main selection criteria:**	Males or females enrolled in Phase 1 or Phase 2 studies of SAR245408 or SAR245409 who have complete data collection for the primary endpoint(s) of the parental study or who are being treated beyond the parental study cut-off.
Total expected number of subjects:	Approximately 100-150.
Expected number of sites:	Approximately 28.
STUDY TREATMENT(s)	
Investigational Medicinal Product N° 1	**SAR245408**
Formulation:	(Form A) hard capsules: 25 and 100 mg. (Form A) tablets: 50, 100, 150, and 200 mg; and (form E) film-coated tablets 50, and 200 mg .
Route of administration:	Oral. Capsules or tablets should be taken with 8 ounces (240 mL) of water, with no food allowed for at least 2 hours before and 1 hour after dosing. The administration of polymorph E tablets with food is allowed, ie, with the morning meal with a full glass of non-carbonated water.
Dose regimen:	Recommended Phase 2 dose (400 mg [tablet formulation polymorph A] once daily) or established dose and regimen, either as a monotherapy or in a combination regimen in the parental study. Because of the expiration of (form A) tablet, patients need to be transitioned to (form E) film-coated tablet. Patients will continue taking the same dose that they were receiving of (form A) tablet. Subjects who are receiving in the parental study an established dose of SAR245408 different than the suggested dose above, may continue on the established dose. For subjects taking combination therapy, if in the Investigator's opinion the subject has maximally benefited from the combination therapy the subject may continue on SAR245408 only. For all subjects, the dose, regimen, and formulation of SAR245408 (and the dose and regimen of combination medication[s] for subjects taking combination therapy) should be agreed on in writing between the site and the Sponsor prior to first dose and should not exceed the maximum tolerated dose for the parental study.
Investigational Medicinal Product N° 2	**SAR245409**
Formulation:	SAR245409A hard capsules: 10, 30, 40, and 50 mg. When the sponsor has discontinued manufacture of the SAR245409A 10 mg hard capsule strength, ongoing patients who are receiving a dose lower than 30 mg will continue treatment at a comparable dose level in consultation with the sponsor (see Section 8.1.2). Film-coated tablets: 20 and 30 mg.

Route of administration:	Oral. Capsules or tablets should be taken with 8 ounces (240 mL) of water, with no food allowed for at least 2 hours before and 1 hour after dosing.
Dose regimen:	Recommended Phase 2 dose (50 mg [capsule formulation] twice daily) or established dose and regimen, either as a monotherapy or in a combination regimen. Subjects who are receiving in the parental study an established dose of SAR245409 different than the suggested dose above, including once daily dosing of SAR245409, may continue on the established dose. For subjects taking combination therapy, if in the Investigator's opinion the subject has maximally benefited from the combination therapy the subject may continue on SAR245409 only. For all subjects, the dose, regimen, and formulation of SAR245409 (and the dose and regimen of combination medication[s] for subjects taking combination therapy) should be agreed on in writing between the site and the Sponsor prior to first dose and should not exceed the maximum tolerated dose for the parental study.
Combination medications with SAR245408	Depending on the parental study, the following drugs may be used in combination with SAR245408: - paclitaxel and carboplatin - letrozole - trastuzumab - paclitaxel and trastuzumab Commercially available drugs will be used as combination medications with SAR245408.
Combination medications with SAR245409	Depending on the parental study, the following drugs may be used in combination with SAR245409: - letrozole - temozolomide - rituximab - bendamustine and rituximab Commercially available drugs will be used as combination medications with SAR245409.
PRIMARY AND SECONDARY ENDPOINT(S)	**Primary Endpoint** Incidence and frequency of adverse events (AEs) and laboratory abnormalities. **Secondary Endpoint(s)** Not applicable.
ASSESSMENT SCHEDULE	See flow chart in Section 1.2.
STATISTICAL CONSIDERATIONS	The sample size of this study will depend on the number of subjects transferred from the parental studies.

	Safety will be evaluated in safety population that consists of all subjects who take at least 1 dose of the study treatment. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Total incidence (ie, Grade 1 or higher) and incidence of Grade ≥3 of each AE will be summarized by system organ class and preferred term using frequencies and percentages. For subjects with several episodes of the same event during the on-treatment period, the worst grade will be used. Drug-related treatment-emergent AEs, deaths, serious AEs, and AEs leading to treatment discontinuation will be summarized similarly by treatment group. For each parameter that can be graded with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, number and percentage of subjects with laboratory abnormalities (all grades and Grade 3 to 4) using the worst grade during the on-treatment period will be provided. For other parameters, laboratory values outside of the normal ranges will be identified.
DURATION OF STUDY PERIOD (per subject)	Subjects may continue in the study until disease progression, unacceptable toxicity, withdrawal of consent, until commercial supplies of SAR245408 or SAR245409 are available to them outside of the clinical trial, or other reasons detailed in Section 22).

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



A – Subjects who received SAR245408 or SAR245409 for <2 cycles in the parental study, subjects who will take a daily dose of SAR245408 or SAR245409 higher than their established dose in the parental study, subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment, and subjects who fulfil the parental study criteria for IMP treatment continuation but have ongoing Grade 2 AE(s) will enter the treatment-extension study on Day 1 of the initiation period.

B – Subjects who received SAR245408 or SAR245409 for ≥ 2 cycles in the parental study will enter the treatment-extension study on Day 1 of the extension period.

1.2 STUDY FLOWCHART FOR SAR245408 OR SAR245409 TREATMENT

Assessments	Baseline[a]	Initiation[b]						Extension[b]	Follow-up 30±7 days
		Cycle 1 (Visits 1-4)				Cycle 2 (Visits 5-6)		Visits 7+	
		D1	D8	D15	D22	D1	D15	Every 4-6 wks	
Inclusion/exclusion criteria – Informed consent[c]	x								
Demography, cancer history	x								
Documentation of agreed dose and regimen[d]	x								
Pregnancy test (if applicable)	x								x
ECOG performance status	x					x			
Vital signs	x	x	x	x	x	x	x	x	x
Physical examination[e]	x					x			
Symptom-directed physical examination		x	x	x	x		x	x	x
Ophthalmologic exam[f]	x[g]							every 24 wks ± 4 wks	x[h]
12-lead electrocardiogram	x	x		x		x	x	x[k]	x
Urinalysis	x	x				x		x	x
Hematology	x	x		x		x	x	x	x
Serum chemistry	x	x		x		x	x	x	x
PT (INR)/aPTT	x	x				x		x	x
HbA1c	x							every 12 wks ± 4 wks[i]	x
Dispense study drug. Dispense, review, and/or collect patient diary		x				x		x	
Tumor assessment		per standard of care							
Combination medication(s)		per established schedule							
Adverse events	x	continuous throughout the study							x
Concomitant medications[j]	x	continuous throughout the study							x

D = day; wks = weeks; INR = international normalized ratio; PT = prothrombin time; PTT = activated partial thromboplastin time; HbA1c: hemoglobin A1c.

a Baseline assessments should be performed within 7 days prior to the first dose of IMP. End-of-treatment assessment from the parental study may be used as baseline assessments if obtained within 7 days prior to the first dose of IMP.

b All subjects complete baseline visit and then start at the beginning of the initiation or extension period based on the length of prior therapy with IMP. If <2 cycles, start with initiation; if ≥2 cycles, start with extension. Subjects who will take a SAR245408 or SAR245409 daily dose higher than their established dose in the parental study, subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment, and subjects who fulfill the parental study criteria for IMP treatment continuation but have ongoing Grade 2 AE(s) will enter the study on Day 1 of the initiation period. Subjects must complete all the visits in the initiation period before moving to the extension period. Subjects who are on 3-week therapy cycles will have assessments only on D1, D8, and D15 when in Cycle 1 and on D1 and D15 when in Cycle 2. Assessments for the initial visit do not need to be repeated if baseline assessment was obtained in the previous 72 hours. Baseline visit and initial visit may occur on the same day.

c A signed study informed consent is required prior to site personnel conducting any specific study procedures.

d Documentation of agreed dose, regimen, and formulation of SAR245408 or SAR245409 (and agreed dose and regimen of combination medication[s] for subjects taking combination therapy and study starting point [initiation or extension] must be signed by the Sponsor Medical Monitor and the site Principal Investigator prior to first dose on this protocol.

e Full physical examination including body weight.

f Ophthalmologic exam at baseline is for subjects on SAR245408 and for subjects on SAR245409; ophthalmologic exam during the extension period is only for subjects on SAR245409. Ophthalmologic exam must be conducted by a trained ophthalmologist or optometrist.

g Ophthalmologic exam from the parental study may be used as baseline assessment if conducted within 12 weeks prior to the first study treatment administration.

h Ophthalmologic exam at the follow-up visit is done only if any of the previous exams were abnormal.

i Every 24 wks ± 4 wks after 60 wks on treatment.

j Including all chemotherapeutic agents taken since initial diagnosis.

k During the Extension period, 12-lead electrocardiogram is performed approximately every 12 weeks and as clinically indicated.

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3 LIST OF ABBREVIATIONS

ADI:	actual dose intensity
AE:	adverse event
AESI:	adverse event of special interest
ALT:	Alanine aminotransferase
API:	active product ingredient
aPTT:	activated partial thromboplastin time
ASCO:	American Society of Clinical Oncology
AST:	aspartate aminotransferase
BSA:	body surface area
CLL:	chronic lymphocytic leukemia
CR:	complete response/remission
CRF:	case report form
CV:	curriculum vitae
DR:	duration of response
DRESS:	drug reaction with eosinophilia and systemic symptoms
DRF:	discrepancy resolution form
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
GCP:	Good Clinical Practice
HLGT:	high group level term
HLT:	high level term
IB:	investigator's brochure
ILD:	interstitial lung disease
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
IV:	intravenous
MedDRA:	Medical Dictionary for Regulatory Activities
MTD:	maximum tolerated dose
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR:	objective response rate
OS:	overall survival
PD:	progressive disease
PFS:	progression free survival
PR:	partial response/remission
PT:	preferred term
PT/INR:	prothrombin time/international normalized ratio
RDI:	relative dose intensity

SAE:	serious adverse event
SJS:	Stevens-Johnson syndrome
SLL:	small lymphocytic leukemia
SOC:	system organ class
TEAE:	treatment emergent adverse event
TEN:	toxic epidermal necrolysis

4 INTRODUCTION AND RATIONALE

This open-label, international, multicenter, treatment-extension study will enable cancer patients who are currently receiving benefit from either SAR245408, formerly known as XL147, or SAR245409, formerly known as XL765, as a monotherapy or as part of a combination regimen in a Phase 1 or Phase 2 study to continue receiving treatment and further assess safety and tolerability of SAR245408 and SAR245409.

4.1 INTRODUCTION

SAR245408 is an oral, potent and selective inhibitor of PI3K (phosphatidylinositol 3-kinase).

SAR245409 is an oral, potent ATP-competitive inhibitor of PI3K which also inhibits mTOR.

More detailed information is provided in the latest version of the Investigator Brochures (IBs) for SAR245408 and SAR245409.

4.2 RATIONALE

4.2.1 Study rationale

This study is designed to provide continued access to either SAR245408 or SAR245409, as a monotherapy, or as part of a combination regimen with a commercially available drug(s), to subjects enrolled in a sanofi-aventis sponsored Phase 1 or Phase 2 study of SAR245408 or SAR245409 who have complete data collection for the primary endpoint(s) of the parental study or who are being treated beyond the parental study cut-off date, and who are receiving benefit from the study treatment.

The primary objective of the study is to collect safety data on subjects who are benefiting from continued treatment. Safety assessments and the occurrence of adverse events (AEs) will be evaluated according to the study flow chart (see Section 1.2) and per standard of care if the subject is on a combination regimen.

4.2.2 Design rationale and risk assessment

This is a treatment-extension study which will be conducted as an open label, international, multi-institutional study. SAR245408 or SAR245409 will be given at a fixed dose as a monotherapy or in combination regimen. If in the Investigator's opinion a subject has maximally benefited from the combination regimen the subject may continue on SAR245408 or SAR245409 only.

The study is designed to collect long-term safety data on subjects who are benefiting from treatment with either SAR245408 or SAR245409.

4.2.3 Safety parameters rationale

4.2.3.1 SAR245408 treatment

As of June 2011, for 220 evaluable subjects who took SAR245408 as a single agent or in a combination regimen, regardless of relatedness to SAR245408, the most common side effects reported in ≥10% of subjects have been gastrointestinal related (such as nausea, diarrhea, vomiting, and constipation); constitutional (such as decreased appetite, fatigue, and asthenia); or an increase in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Transaminase elevations have been Grade 1 or Grade 2, with the exception of a Grade 3 transaminase increase, which was not accompanied by increase in bilirubin, observed in a subject treated with SAR245408 in combination with letrozole. The transaminase elevation resolved after SAR245408 was discontinued. Overall, approximately 36% of subjects developed rash (including erythematous, macular, pustular, and acneiform), approximately 25% developed dyspnea and cough, approximately 18% reported anemia. Neutropenia was noted in approximately 76% of subjects treated in combination with cytotoxic chemotherapy.

Grade 3 or 4 events assessed by Investigators as related to SAR245408 were diarrhea, peripheral oedema, rash and hyperglycemia. Three subjects have experienced a Grade 3 hypersensitivity reaction; each of which resolved with medical intervention and after holding study drug. In addition, 1 subject with adenoid cystic carcinoma of the lung who previously had a pneumonectomy enrolled on study TED11434 (XL147-002) (erlotinib-SAR245408 combination) and developed rash with eosinophilia; edema of the face, shoulders, and legs; and increasing dyspnea. The patient subsequently died. An autopsy showed widespread carcinomatosis in the remaining lung. The cause of death was considered to be malignant neoplasm progression and drug reaction with eosinophilia and systemic symptoms (DRESS). Two serious adverse events (SAEs) of pneumonitis possibly related to SAR245408 have been reported, one Grade 2 in combination with trastuzumab and paclitaxel and one Grade 4 in combination with letrozole; the second patient subsequently died of suspected drug-induced pulmonary toxicity.

Study subjects receiving SAR245408 should be closely monitored for:

- presence of skin rash and DRESS syndrome;
- liver function abnormalities: AST and ALT, bilirubin elevation;
- signs of pneumonitis, eg, dyspnea, cough.

4.2.3.2 SAR245409 treatment

As of June 2011, for 175 evaluable subjects who took SAR245409 as a single agent or in combination with other regimens the most common AEs, regardless of relatedness to SAR245409, reported in ≥10% of subjects across all SAR245409 studies have been gastrointestinal related (such as nausea, diarrhea, vomiting, and constipation); constitutional (such as decreased appetite, fatigue, and asthenia); transaminase elevations (elevations in both AST and ALT have been reported); as well as rash, headache, cough, and abdominal pain. The majority of transaminase elevations have been Grade 1 or Grade 2, asymptomatic, and not accompanied by a significant drug related increase in bilirubin of Grade ≥1. All elevations related to SAR245409 resolved with SAR245409 withdrawal or interruption. Various kinds of rash have been reported with SAR245409, including 1 subject receiving SAR245409 (70 mg once daily) and erlotinib who had a Grade 3 DRESS syndrome, which resolved with drug discontinuation and supportive care, including intravenous steroid treatments followed by oral and topical steroids.

Periodic ophthalmologic exams are currently being performed on SAR245409 studies due to the preclinical observation of focal cataracts in two rats dosed orally with SAR245409 for 180 consecutive days (1 male dosed at 3 mg/kg twice daily and 1 female dosed at 10 mg/kg twice daily).

Study subjects receiving SAR245409 should be closely monitored for:

- presence of skin rash and DRESS syndrome;
- liver function abnormalities: AST and ALT, bilirubin elevation.

5 STUDY OBJECTIVES

5.1 PRIMARY

To determine the long-term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen in subjects who are benefiting from treatment.

5.2 SECONDARY

Not applicable.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This open-label, international, multicenter, nonrandomized study is designed to provide continued access to SAR245408 or SAR245409, as a monotherapy or as part of a combination regimen, to subjects who are receiving benefit from the study treatment.

All subjects in the study will continue on the Investigational Medicinal Product (IMP) (SAR245408 or SAR245409) and combination medication(s) (for subjects taking combination therapy) they received during the parental study. The SAR245408 or SAR245409 dose will be either the recommended Phase 2 dose (400 mg SAR245408 [tablet formulation polymorph A] once a day every day or 50 mg SAR245409 [capsule formulation] twice a day every day) or the subject's established dose and formulation either as a monotherapy or in a combination regimen in the parental study.

When the supply of SAR245408 (form A) hard capsules and SAR245408 (form A) tablets is depleted, ongoing patients will be offered SAR245408 (form E) film-coated tablets in order to continue treatment (see Section 8.1.1).

When the sponsor has discontinued manufacture of the SAR245409A 10 mg hard capsule strength, ongoing patients who are receiving a dose lower than 30 mg may continue treatment at a comparable dose level in consultation with the sponsor. Patients receiving dose levels ≥30 to ≤ 100 mg (with 10 mg dose intervals) are not affected by discontinuation of the 10 mg capsule strength (see Section 8.1.2).

If in the Investigator's opinion, the subject has maximally benefited from the combination therapy in the parental study, the subject may continue on SAR245408 or SAR245409 as a monotherapy in this study. For all subjects, dose, regimen, formulation, and food condition for study drug intake of SAR245408 or SAR245409 (and dose and regimen of combination medication(s) for subjects taking combination therapy) will be agreed on in writing between the site and the Sponsor prior to first dose.

Subjects who received SAR245408 or SAR245409 for less than 2 cycles in the parental study will enter the treatment-extension study on Day 1 of the initiation period; subjects who received SAR245408 or SAR245409 for at least 2 cycles in the parental study will enter the treatment-extension study on Day 1 of the extension period. Subjects who will take a SAR245408 or SAR245409 daily dose higher than their established dose of SAR245408 or SAR245409, respectively, in the parental study will enter the treatment-extension study on Day 1 of the initiation period. Subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment and subjects who fulfill the parental study criteria for IMP treatment continuation but have ongoing Grade 2 AE(s) will start the treatment-extension study on Day 1 of the initiation period.

Subjects may continue in the study until disease progression, unacceptable toxicity, withdrawal of consent, until commercial supplies of SAR245408 or SAR245409 are available to them outside of the clinical trial, or other reasons detailed in Section 22).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each subject

The duration of the study for an individual subject will include:

- Baseline assessments: within 7 days prior to the first dose of IMP.
- Study treatment period(s):

  Subjects will start study treatment at the beginning of the initiation or extension periods based on the length of prior therapy with SAR245408 or SAR245409 (see Section 1.1):

  - if <2 cycles, start with initiation period; subjects must complete all the visits in the initiation period before moving to the extension period.
  - if ≥2 cycles, start with extension period; duration of extension period is unlimited.
  - subjects who will take a SAR245408 or SAR245409 daily dose higher than their established dose of SAR245408 or SAR245409, respectively, in the parental study will enter the study on Day 1 of the initiation period.
  - subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment will enter the treatment-extension study on Day 1 of the initiation period.
  - subjects who fulfill the parental study criteria for IMP treatment continuation but have ongoing Grade 2 AE(s) will enter the treatment-extension study on Day 1 of the initiation period.

  Subjects may continue to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until commercial supplies of SAR245408 or SAR245409 are available to them outside of the clinical trial (see Section 8.1.2.3).

- Follow-up assessments: 23 to 37 days after the last dose of IMP.

6.2.2 Determination of end of clinical trial (all subjects)

The end of clinical trial will occur when all subjects have completed their last follow up visit as defined in Section 12.1.3.

6.3 INTERIM ANALYSIS

Not applicable.

6.4 STUDY COMMITTEES

Safety reviews of the IMPs will be conducted at least quarterly by the designated sanofi-aventis team members under the lead of the Global Safety Officer. It is the responsibility of the Sponsor Safety Committee to review all available safety data (AEs and SAEs) from ongoing clinical trials in order to assess and monitor evolving safety trends, evaluate potential changes to clinical trial protocols based on safety analysis, and, ultimately, to safeguard subject safety. Additional ad hoc meetings will convene as required to address specific safety concerns.

7 SELECTION OF SUBJECTS

7.1 NUMBER OF SUBJECTS PLANNED

The number of subjects in this study will depend on the number of subjects who will continue receiving treatment from the parental studies. It is expected that approximately 100 to 150 subjects will be treated in this study.

7.2 INCLUSION CRITERIA

I 01. Males or females enrolled in Phase 1 or Phase 2 studies of SAR245408 or SAR245409 as monotherapy or in combination with other regimens who have complete data collection for the primary endpoint(s) of the parental study or who are being treated beyond the parental study cut-off and meet all the criteria to continue to be treated per the parental protocol.

I 02. All sexually active subjects (male and female) must agree to continue to use accepted methods of barrier contraception (ie, condoms) during the course of the study and for 3 months after discontinuation of study treatment. For women of childbearing potential and for men who can father a child, a second method of contraception in addition to a barrier method is recommended. Hormonal contraception should be avoided in subjects taking SAR245408 due to possible drug-drug interaction.

I 03. Female subjects of childbearing potential must have a negative pregnancy test at baseline. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens, or ovarian suppression.

I 04. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document.

7.3 EXCLUSION CRITERIA

E 01. The subject discontinued the parental study due to toxicity.

E 02. Ongoing Grade 3 or higher AE.

E 03. Ongoing SAE.

E 04. Subject with ongoing dose interruption for any reason unless the subject fulfills the criteria in the parental protocol for restarting IMP. In such case subject will start the treatment-extension study on Day 1 of the initiation period.

E 05. The subject has a ≥ Grade 3 of any of the laboratory values:

- Absolute neutrophil count (ANC),
- Platelet count,
- Hemoglobin, Bilirubin,
- Serum creatinine, or calculated creatinine clearance, Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST),
- Fasting plasma glucose,
- Prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT).

E 06. The subject has a baseline corrected QT interval (QTc) >481 msec or if a subject has had a QTc interval increase of ≥60 msec from parental protocol baseline to an absolute value of >470 msec.

E 07. The subject has a known allergy or hypersensitivity to components of the study treatment formulation(s).

E 08. The subject is pregnant or breastfeeding.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

8.1.1 SAR245408

8.1.1.1 Pharmaceutical form

SAR245408 capsules and tablets are used in parental studies and may be used in this study:

- SAR245408 (form A) hard capsules: powder-in-capsule formulation supplied at strengths of 25 and 100 mg of drug substance free base form A in size 0 hard gelatin capsules. The formulation contains no excipients other than the hard gelatin capsule. Each strength is presented in a different capsule color.
- SAR245408 (form A) tablets: immediate-release tablet formulation with 50 % w/w API load, supplied at strengths of 50, 100, 150, and 200 mg of drug substance SAR245408 (form A) free base . Each strength will be presented in a different tablet shape and/or size.
- SAR245408 (form E) film-coated tablets: Immediate-release film-coated tablet with 50% w/w drug substance load, supplied at strength of 50 mg or 200 mg (based on the amount of drug substance SAR245408 (form E) free base).

Rationale to transition from SAR245408 (form A) hard capsules and (form A) tablets to SAR245408 (form E) film-coated tablets

When the supply of SAR245408 (form A) hard capsules and SAR245408 (form A) tablets is depleted, ongoing subjects will be offered SAR245408 (form E) film-coated tablets in order to continue treatment.

The SAR245408 drug substance used for initial phase 1 and 2 clinical studies, was a single anhydrous polymorph (form A). A new anhydrous polymorph (form E) of SAR245408 drug substance was later evidenced in development. The form E is thermodynamically more stable than form A. It was therefore decided to pursue the SAR245408 development with the drug substance (form E). The drug substance (form E) is additionally micronized in order to reach a similar particle size distribution as drug substance (form A) previously used in the first clinical studies.

In order for subjects to continue treatment, it is necessary to transition from drug substance (form A) to drug substance (form E). Subjects must be informed of this new information, have the opportunity to discuss the transition and alternative treatment options with the Investigator, and document their consent to transition to a new formulation via an updated IRB/IEC approved informed consent.

Transition from SAR245408 (form A) hard capsule to SAR245408 (form A tablet)

Two completed SAR245408 studies provide data to support the transition from SAR245408 (form A) hard capsule to (form A) tablet

1. Study TED11433 (NCT00486135): SAR245408 (form A) hard capsule vs. (form A) tablet

Study TED11433 (NCT00486135) evaluated the SAR245408 (form A) hard capsule using either an intermittent (21 days on, 7 days off) or continuous daily dosing (CDD) treatment schedule. In patients with solid tumors (n=69), dose-limiting toxicities were maculopapular rash and hypersensitivity reaction. Of note, skin reactions are an expected toxicity for SAR245408 and for PI3K inhibitors as a class. The maximum tolerated dose for the SAR245408 (form A) hard capsule was 600 mg QD for both schedules. The recommended phase 2 dose for the SAR245408 (form A) hard capsule was 600 mg administered on a CDD schedule(1).

Study TED11433 also included a cohort of patients with B-cell malignancies (n=25) treated with 600 mg QD SAR245408 (form A) hard capsules. One DLT (grade 3 rash) was reported. The PK profile of SAR245408 in this cohort was consistent with the solid tumor cohort who received 600 mg (form A) hard capsules once daily.

An additional 22 patients with advanced solid tumors received SAR245408 (form A) tablets at doses ranging from 100 to 600 mg QD. No dose-limiting toxicities were reported. The recommended phase 2 dose for SAR245408 (form A) tablet administered on the CDD schedule was determined to be 400 mg based on the PK exposure at this dose, which was similar to the exposure achieved with 600 mg (form A) hard capsule.

1. Study ARD11437 (NCT01082068): SAR245408 (form A) tablet

Study ARD11437 (NCT01082068), a phase 1/2 trial of patients with hormone receptor positive breast cancer, further evaluated the 400 mg (form A) tablet in combination with letrozole with a CDD schedule. Thirty-one (31) of 37 patients enrolled to receive SAR245408 were treated with the 400 mg (form A) tablet with 2.5 mg letrozole. In the Phase 1 portion of the study, one DLT, serious grade 3 drug reaction with eosinophilia and systemic symptoms, was reported among the 6 patients enrolled at 400 mg QD. In the Phase 2 portion (n=25), 1 patient had pneumonitis approximately 1 month after the last dose of study drug. The event was considered possibly related to study drug and resulted in the patient's death approximately 4 months after discontinuing study treatment

Transition from SAR245408 (form A) tablet to (form E) film-coated tablet

Two studies (1 completed [BDR12246] and 1 ongoing [TED12863 (NCT01943838)] provide data to support the formulation transition from SAR245408 (form A) tablet to (form E) film-coated tablet.

1. Study BDR12246: Bioavailability of SAR245408 (form A) tablet vs. SAR245408 (form E) film-coated tablet

Results of a single (reduced) dose (50 mg) relative bioavailability study in healthy male patients indicate the bioavailability of SAR245408 (form E) film-coated tablets relative to SAR245408 (form A) tablets administered as a 50-mg tablet in the fasted state was generally lower based on the point estimates for C_{max}, AUC_{last}, AUC_{0-120}, and AUC geometric mean ratios, with a decrease in the point estimates in the range of 15% to 22%. A moderate fat meal did not appear to have an appreciable impact on the exposure of SAR245408 (form E).

2. Study TED12863 (NCT01943838): SAR245408 (form E) film-coated tablet

Sanofi is currently testing the safety, tolerability and pharmacokinetics of SAR245408 (form E) film-coated tablets in a phase 1 dose escalation study in patients with solid tumors or lymphomas. Among the first 6 patients enrolled to receive 400 mg QD SAR245408 (form E) film-coated tablets, no dose limiting toxicities were observed. Two patients experienced grade 2 rash assessed as related to study treatment. In both cases, rash was managed with topical steroid treatment. The exposure of 400 mg (form E) film-coated tablets was similar when compared with 400 mg (form A) tablets, as well as with 600 mg (form A) hard capsules on C1D1 and C1D28 or C2D1. High inter-patient variability was observed and consistent with data from (form A) hard capsules and (form A) tablets in the above mentioned Study TED11433. Based on the absence of DLTs in the 400 mg cohort, patients are now being enrolled to receive (form E) film coated tablets at 600 mg QD. Based on these clinical data, the SAR245408 400 mg (form E) film-coated tablet is considered as a safe dose with comparable exposure to the 400 mg (form A) tablet.

8.1.1.2 Dose preparation and administration

Subjects will take 400 mg SAR245408 (tablet formulation polymorph A) once a day every day (ie, the recommended SAR245408 Phase 2 dose and regimen). Subjects who are receiving in the parental study an established dose of SAR245408 (tablet polymorph A or E) different from 400 mg (tablet polymorph A) may continue on the established dose. Subjects who will take a SAR245408 daily dose higher than their established dose of SAR245408 in the parental study and subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment will enter the study on Day 1 of the initiation period.

The recommendations for transition of SAR245408 formulation are (see Table 1):

- Patients taking SAR245408 (form A) hard capsules at a dose level of 400 mg QD transition to 200 mg (form A) tablets (as supply permits) or 200 mg (form E) film-coated tablets
- Patients taking SAR245408 (form A) hard capsules at a dose level of 600 mg QD transition to a dose level of 400 mg using 200 mg (form A) tablets (as supply permits) or 200 mg (form E) film-coated tablets
- Patients taking SAR245408 (form A) tablets transition to the same dose with SAR245408 (form E) film-coated tablets

Table 1 - Recommendations for Transition of SAR245408 Formulation

Current Formulation	Current Daily Dose	New Formulation	New Daily Dose
Form A hard capsule	400mg*	Form E tablet	200mg
Form A hard capsule	600mg*	Form E tablet	400mg
Form A tablet	Any	Form E tablet	Same dose as Form A tablet

*For patients taking any other dose of the Form A hard capsule, consult sponsor for recommended daily dose for the Form E tablet.

For all subjects, the dose, regimen, and formulation of SAR245408 should be agreed on in writing between the site and the Sponsor prior to first dose and should not exceed the maximum tolerated dose (MTD) for the parental study. The number of capsules or tablets and strength will vary depending on the dose level assignment. SAR245408 dose may be modified for toxicity as described in Section 8.3.

The guidelines for treatment delay or dose modification provided in Section 8.3 are applicable regardless of formulation. SAR245408 doses should be taken at approximately the same time each day with a full glass (8 fluid ounces or 240 mL) of water. If a dose is missed, the missed dose can be taken up to 12 hours after the normal dosing time, but subjects must be instructed not to make up missed doses of SAR245408 outside of the 12 hour allowable time window. Subjects treated with SAR245408 (form A) tablets must fast for 2 hours before and for 1 hour after each dose. Extra doses should not be taken if the subject vomits after taking SAR245408. For subjects treated with SAR245408 (form E) film-coated tablets, the administration of the IMP with food is allowed as per their parental protocol, ie, with the morning meal with a full glass of noncarbonated water.

Doses will be administered at the study site at specific protocol-defined visits. Subjects will be provided with a sufficient supply of SAR245408 and instructions for self-administration at home on all other study days. For SAR245408 doses taken at home, the subject will record precisely the date and time of self-administration on the provided diary.

8.1.1.3 Duration of treatment

Subjects may continue to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until commercial supplies of SAR245408 are available to them outside of the clinical trial or other reasons detailed in Section 22).

Note: subjects who are experiencing tumor shrinkage in response to study treatment but who have disease progression limited to the CNS may receive local radiation therapy (if needed) and remain on study treatment with the permission of the Sponsor.

8.1.2 SAR245409

8.1.2.1 Pharmaceutical form

SAR245409 capsules and tablets are used in parental studies and may be used in this study:

- SAR245409A hard capsules: powder-in-capsule formulation supplied at strengths of 10, 30, 40, and 50 mg of drug substance HCl salt in size 0 hard gelatin capsules. The formulation contains no excipients other than the hard gelatin capsule. Each strength will be presented in a different capsule color.
- SAR245409 film-coated tablets: immediate-release film-coated tablet formulation with 20% w/w drug substance load, supplied at strengths of 20 and 30 mg of API free base form 1. Each strength will be presented in a different size and embossing.

When the supply of SAR245409A 10 mg hard capsules is depleted, ongoing patients whose dose has included the 10 mg capsule strength will be offered continuation of treatment at a comparable dose level with a revised schedule in consultation with the sponsor. For example, patients unable to tolerate 30 mg capsules BID may be permitted to take 30 mg capsules QD. Treatment will be discontinued for patients who cannot tolerate 30 mg capsules QD.

The current supply of strengths covers treatment from 30 mg to 100 mg in 10 mg increments. Only patients receiving a capsule dose below 30 mg will be affected.

8.1.2.2 Dose preparation and administration

Subjects will take 50 mg SAR245409 (capsule formulation) twice a day every day (ie, the recommended SAR245409 Phase 2 dose and regimen). Subjects who are receiving in the parental study an established dose of SAR245409 different from 50 mg (capsule formulation), including once daily dosing of SAR245409, may continue on the established dose and regimen. Subjects who will take a SAR245409 daily dose higher than their established dose of SAR245409 in the parental study and subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment or who have ongoing Grade 2 AE (s) will enter the treatment-extension study on Day 1 of the initiation period.

For all subjects, the dose, regimen, and formulation of SAR245409 should be agreed on in writing between the site and the Sponsor prior to first dose and should not exceed the MTD for the parental study. The number of capsules or tablets and strength will vary depending on the dose level assignment. As indicated above, when the supply of SAR245409A 10mg hard capsules is depleted, ongoing patients impacted will be offered continuation of treatment at a comparable dose regimen in consultation with the sponsor. SAR245409 dose may be modified for toxicity as described in Section 8.3.

SAR245409 doses should be taken at approximately the same times each day with a full glass (8 fluid ounces or 240 mL) of water, allowing a 12-hour (± 2 hours) interval between morning and evening doses. If a dose is missed, the missed dose can be taken up to 4 hours after the normal dosing time, but subjects must be instructed not to make up missed doses of SAR245409 outside of the 4 hour allowable time window. Subjects must fast for 2 hours before and for 1 hour after each dose. Extra doses should not be taken if the subject vomits after taking SAR245409.

Doses will be administered at the study site at specific protocol-defined visits. Subjects will be provided with a sufficient supply of SAR245409 and instructions for self-administration at home on all other study days. For SAR245409 doses taken at home, the subject will record precisely the date and time of self-administration on the provided diary.

8.1.2.3 Duration of treatment

Subjects may continue to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until commercial supplies of SAR245409 are available to them outside of the clinical trial or other reasons detailed in Section 22).

Note: Subjects who are experiencing tumor shrinkage in response to study treatment but who have disease progression limited to the CNS may receive local radiation therapy (if needed) and remain on study treatment with the permission of the Sponsor.

8.2 COMBINATION MEDICATIONS

This study is designed to provide continued access to either SAR245408 or SAR245409 as a monotherapy, or SAR245408 or SAR245409 as part of a combination regimen with a commercially available drug(s). Only the combination regimen from the parental study is allowed in this study. The dose and regimen of the combination medication(s) should be agreed on in writing between the site and the Sponsor prior to first dose.

Depending on the parental study, the following drugs may be used in combination with SAR245408:

- paclitaxel and carboplatin
- letrozole
- trastuzumab ± paclitaxel

Depending on the parental study, the following drugs may be used in combination with SAR245409:

- letrozole
- temozolomide
- rituximab

- bendamustine and rituximab

Commercially available drugs will be used as combination medications with SAR245408 or SAR245409. For details on description, preparation, administration, and precautions for use for combination medications, please refer to package insert or summary of product characteristics.

8.3 TREATMENT DELAY OR DOSE MODIFICATIONS

Subjects will be monitored for AEs while on-study and will be instructed to notify their physician as soon as possible at the sign of any new or worsening AEs. As a general approach, it is suggested that all AEs be treated with supportive care when possible at the earliest signs of toxicity.

Subjects experiencing one or more AEs due to the study treatment may require dosing interruptions or reductions in their IMP doses in order to continue with study treatment.

Guidelines for the management of AEs and SAR245408 and SAR245409 dose modifications (ie, dose interruptions and dose reductions) are presented in details in Section 8.3.1 and Section 8.3.2. Commercially available drug(s) given in combination with SAR245408 or SAR245409 should be managed according to the product label and standard of care.

For SAR245408, each dose reduction should be at least ≥25% of the current dose. For a subject dosed at 400 mg, first dose reduction will be 300 mg and second 200 mg. A subject requiring more than 2 dose reductions of SAR245408 - considering **both** the parental study and the treatment-extension study - (or less than 100 mg SAR245408), or if SAR245408 is held for more than 6 weeks due to an AE, should be permanently discontinued from study treatment.

For SAR245409, each dose reduction should be at least 10 mg below the current dose. For a subject dosed at 50 mg twice a day, first dose reduction will be 30 mg twice a day and second 20 mg twice a day. When the supply of SAR245409A 10mg hard capsules is depleted, patients requiring dose reduction below 30 mg will be offered continuation of treatment at a reduced dose and/or schedule in consultation with the sponsor. A subject requiring more than 2 dose reductions of SAR245409 - considering **both** the parental study and the treatment-extension study - (or less than 20 mg SAR245409), or if SAR245409 is held for more than 21 days due to an AE, should be permanently discontinued from study treatment.

All dose reductions should be discussed with the Sponsor.

Once a subject's dose has been reduced, the dose may be re-escalated 1 dose level if the toxicity that led to the dose reduction was Grade ≤3 and does not reoccur after the subject has been treated at the reduced dose level for at least 4 weeks. Additional safety monitoring should be implemented upon dose re-escalation.

However, dose re-escalation is not allowed for subjects remaining on study treatment after experiencing a Grade 4 AE, regardless of causality, and is only allowed one time for any specific AE (Grade ≤3) that led to a dose reduction.

No dose re-escalation will be permitted for SAR245409 if the dose was reduced for transaminase elevations.

8.3.1 General guidelines for the management of non-hematologic and hematologic adverse events

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 2 and Table 3, respectively.

For more specific guidelines on AEs including skin, pulmonary, hepatobiliary, and gastrointestinal disorders, hyperglycemia, and QT interval prolongation, refer to Section 8.3.2 .

Table 2 - Management guidelines for non-hematologic adverse events

CTCAE v4.03 Grade	Guidelines / Intervention
Grade 1:	No dose adjustments.
Grade 2:	
Grade 2 AEs that are subjectively tolerable	Continue SAR245408/SAR245409 at the current dose levels.
Grade 2 AEs subjectively intolerable, or an AE deemed unacceptable in the Investigator's judgment	Interrupt SAR245408/SAR245409 until the AE resolves to Grade ≤1 or baseline. Upon recovery, resume SAR245408/SAR245409 at the same dose or at a reduced dose as clinically indicated. If the dose is not reduced after the first occurrence, a dose reduction must be implemented after a second recurrence. All SAR245408/SAR245409-related transaminase elevations require dose reduction.
Grade 3:	
Grade 3 AEs without optimal prophylaxis or are easily managed with or without medical intervention	Interrupt SAR245408/SAR245409 until the AE resolves to Grade ≤1 or baseline. Upon recovery, resume SAR245408/SAR245409 at the same dose or at a reduced dose as clinically indicated. If the dose is not reduced after the first occurrence, a dose reduction must be implemented after a second recurrence.
Grade 3 AEs despite optimal prophylaxis or are not easily managed	Interrupt SAR245408/SAR245409 until recovery to Grade ≤1 or baseline, and resume SAR245408/SAR245409 with 1 dose reduction
Grade 4:	Discontinue SAR245408/SAR245409 permanently unless determined by the Investigator and agreed to by the Sponsor that the subject is deriving clinical benefit. In this case, the subject may be re-treated at a reduced dose that is agreed upon by the Investigator and the Sponsor once the AE resolves to Grade ≤1.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

The following guidelines for hematologic AEs apply for subjects with solid tumors and subjects with lymphoma (except chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL)) without bone marrow involvement who are not receiving concurrent cytotoxic chemotherapy in combination and who had baseline blood count values for neutrophils and platelets of Grade ≤1 (Table 3).

Table 3 - Management guidelines for hematologic adverse events

Adverse event (CTCAE v4.03 grading)	Guidance
Grade ≥3 neutropenia *or*	
Grade 3 thrombocytopenia associated with clinically significant bleeding *or*	Interrupt SAR245408/SAR245409 until resolution to Grade ≤2, and resume SAR245408/SAR245409 at 1 dose level lower.
Grade 4 thrombocytopenia	
Grade 3 febrile neutropenia	Interrupt SAR245408/SAR245409 until recovery of ANC to Grade ≤1 and temperature to ≤38°C, and resume SAR245408/SAR245409 at 1 dose level lower.
Grade 4 febrile neutropenia	Discontinue SAR245408/SAR245409.
All other clinically significant Grade 4 hematologic AEs	Interrupt SAR245408/SAR245409 until resolution to Grade ≤2, and resume SAR245408/SAR245409 at 1 dose level lower, as agreed to by the Investigator and the Sponsor.

AE(s) = adverse event(s); ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.

The following guidelines for hematologic AEs apply for subjects who are receiving concurrent cytotoxic chemotherapy in combination:

- Treatment with SAR245408/SAR245409 may continue.
- Chemotherapy agents should be delayed, interrupted or reduced and supportive care should be provided according to product label and standard of care.

The following guidelines for hematologic AEs apply for subjects with CLL/SLL, and subjects with compromised bone marrow function (baseline blood count values for neutrophils and platelets of Grade ≥2):

- Interrupt SAR245408/SAR245409 as clinically indicated. The Sponsor must be notified of the dose interruption.
  - If the subject does not recover from the hematologic AEs to baseline values within 6 weeks for SAR245408 treatment and within 21 days for SAR245409 treatment, the subject should be discontinued from SAR245408/SAR245409.
  - If the subject recovers from the hematologic AEs to baseline values, SAR245408/SAR245409 can be resumed with or without a dose reduction, as agreed to by the Investigator and the Sponsor.

8.3.2 Specific guidelines for the management of adverse events

8.3.2.1 Skin disorders

Prophylactic skin care recommendations for all subjects include sunscreen with SPF ≥30, hypoallergenic moisturizing products for dry skin, and gentle skin care with fragrance-free soaps and detergents.

Subjects must contact the Investigator immediately if they develop a new rash or have worsening of an existing rash while on study. A complete blood count with differential and serum chemistry that includes liver function tests should be obtained, and subjects should be evaluated for any associated systemic involvement (cardiac, hepatic, pulmonary, or renal) at least weekly with either new onset or worsening of existing rash.

It is recommended that a dermatologist be involved in subject management, especially for severe or life-threatening rash. A skin biopsy for histopathological diagnosis is strongly encouraged, and serial digital photographs are recommended (photography guidelines in the study manual). Photographs and biopsy results should be sent to the Sponsor and/or designee. Biopsy samples should be made available to the Sponsor and/or designee for additional evaluation upon request.

Permanent discontinuation of study treatment (SAR245408 or SAR245409) will be required for subjects who develop a Grade 4 skin AE, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN). Additionally, permanent discontinuation of study treatment is required for subjects with study treatment-related skin rash associated with:

- Grade 3 systemic organ (cardiac, hepatic, pulmonary, or renal) dysfunction (with or without eosinophilia)
- Any of the following symptoms of an allergic/hypersensitivity reaction:
  - Any grade anaphylaxis, angioedema, or bronchospasm;
  - Grade 2 or greater urticaria (urticarial lesions covering ≥10% of the body surface area (BSA), or oral or intravenous (IV) intervention indicated);
  - Grade 3 or greater hypotension (hypotension for which urgent medical intervention or hospitalization is indicated, or is life threatening).

Note: rash with associated eosinophilia but without associated systemic symptoms is not an absolute indication to permanently discontinue study treatment. Discussion with the Sponsor is recommended in these cases.

For study treatment-related skin AEs **not** meeting the above criteria for permanent discontinuation of study treatment, the following guidelines must be followed regarding dosing of SAR245408/SAR245409):

- Please refer to Table 4 for management guidelines for macular or papular rash, pruritus, dry skin, and palmar-plantar erythrodysesthesia syndrome;
- The general guidelines for other skin AEs are the following:
  - Grade 1 or tolerable Grade 2 events: SAR245408/SAR245409 may be continued at the current dose with symptomatic treatment based on the specific type of AE. Reassess at least weekly; if skin reactions worsen at any time or do not improve with 2 weeks of symptomatic treatment, proceed to the guidelines for the next grade events.
  - Intolerable Grade 2 or Grade 3 events: SAR245408/SAR245409 must be held, with treatment of symptoms based on the specific type of AE. Reassess at least weekly; if skin reactions do not improve with 2 weeks of symptomatic treatment, permanently discontinue the subject from study treatment. Resume SAR245408/SAR245409 at a reduced dose if the reaction recovers to Grade ≤1. Permanently discontinue the subject from study treatment if intolerable Grade 2 or Grade 3 reaction recurs at a reduced dose.

For any subject with a rash, obtain bacterial and/or viral cultures if infection is suspected.

Table 4 - Treatment guidelines for specific skin adverse events

CTCAE (v4.03) AEs Type of rash	Intervention
Rash maculopapular	
Grade 1 (<10% of BSA)	Study drug[a] may be continued at the current dose. Monitor for changes in severity. Start application of topical treatments to affected areas: alclometasone 0.05% cream to the face and neck and mometasone 0.05% cream to the body. Reassess at least weekly. If skin rash worsens at any time or does not improve with 2 weeks of treatment, proceed to the management guidelines for Grade 2 maculopapular rash (or Grade 3 if rash covers ≥30% of BSA).
Grade 2 (≥10% but ≤30% of BSA)	Study drug may be continued at the current dose*. Monitor for changes in severity. Start (or continue) application of topical treatments to affected areas: alclometasone 0.05% cream to the face and neck and mometasone 0.05% cream to the body. Start oral treatment with prednisone 0.5 mg/kg PO or the equivalent amount of dexamethasone. Reassess at least weekly. If skin rash worsens at any time or does not improve after 1 week of treatment, proceed to the management guidelines for Grade 3 maculopapular rash. * Study drug may be held for patients who cannot tolerate Grade 2 rash (see the management guidelines for Grade 3 rash for restarting study drug and reducing oral steroids).
Grade 3 (>30% of BSA)	Study drug must be held. Monitor for changes in severity. Start (or continue) application of topical treatments to affected areas: alclometasone 0.05% cream to the face and neck and mometasone 0.05% cream to the body. Start (or continue) oral treatment with prednisone 0.5 mg/kg PO or the equivalent amount of dexamethasone for at least 7 days. Reassess at least weekly. If skin rash worsens or does not improve with 2 weeks of topical and oral treatment, discontinue patient from study drug. Otherwise, resume study drug at a reduced dose if reaction recovers to Grade ≤1. Oral corticosteroids should continue for at least 1 week after resumption of reduced dose of study drug prior to starting corticosteroid taper. Discontinue patient from study drug if intolerable Grade 2 or Grade 3 reaction recurs at a reduced dose.
Pruritus	
Grade 1	Study drug may be continued at the current dose. Start application of topical agents such as hypoallergenic moisturizing cream, over the counter antipruritic creams or topical triamcinolone 0.1% cream. Reassess at least weekly; if skin pruritus worsens at any time or does not improve with 2 weeks of treatment, proceed to the management guidelines for Grade 2 pruritus (or Grade 3 pruritus if these criteria are now met).
Grade 2	Study drug may be continued at the current dose*. Start (or continue) application of topical agents such as hypoallergenic moisturizing cream, over the counter antipruritic creams or topical triamcinolone 0.1% cream. Start oral antihistamines (hydroxyzine 25 mg TID or diphenhydramine 25 mg TID) or GABA agonists (eg, gabapentin 300 mg TID or pregabalin 75 mg TID). Reassess at least weekly; if pruritus worsens at any time or does not improve with 2 weeks of treatment, proceed to the management guidelines for Grade 3 pruritus. * Study drug may be held for intolerable Grade 2 pruritus.

CTCAE (v4.03) AEs Type of rash	Intervention
Grade 3	Interrupt study treatment. Start (or continue) application of topical agents such as hypoallergenic moisturizing cream, over the counter antipruritic creams or topical triamcinolone 0.1% cream. Start (or continue) oral antihistamines (hydroxyzine 25 mg TID or diphenhydramine 25 mg TID) or GABA agonists (eg, gabapentin 300 mg TID or pregabalin 75 mg TID). Start doxepin 25 mg BID. Reassess at least weekly; if skin reactions do not improve with 2 weeks of symptomatic treatment, discontinue patient from study drug. Resume study drug at a reduced dose if reaction recovers to Grade ≤1. Discontinue patient from study drug if intolerable Grade 2 or Grade 3 reaction recurs at a reduced dose.
Dry skin	
Grade 1	Study drug may be continued at the current dose. Start application of over the counter hypoallergenic moisturizing cream or ointment to the face BID and ammonium lactate 12% cream to the body BID. Reassess at least weekly; if dry skin worsens at any time or does not improve with 2 weeks of treatment, proceed to the management guidelines for Grade 2 dry skin (or Grade 3 dry skin if these criteria are now met).
Grade 2	Study drug may be continued at the current dose*. Start (or continue) over the counter hypoallergenic moisturizing cream or ointment to the face BID and ammonium lactate 12% cream or salicylic acid 6% cream (if lesions are hyperkeratotic) to the body BID or equivalent. Reassess at least weekly; if dry skin worsens at any time or does not improve with 2 weeks of treatment, proceed to the management guidelines for Grade 3 dry skin * Study drug may be held for intolerable Grade 2 dry skin.
Grade 3	Interrupt study treatment. Start (or continue) over the counter hypoallergenic moisturizing cream or ointment to the face BID and ammonium lactate 12% cream or salicylic acid 6% cream (if lesions are hyperkeratotic) to the body BID or equivalent. Start triamcinolone 0.25% cream to eczematous areas BID. Reassess at least weekly; if dry skin does not improve with 2 weeks of symptomatic treatment, discontinue patient from study drug. Resume study drug at a reduced dose if dry skin recovers to Grade ≤1. Discontinue patient from study drug if intolerable Grade 2 or Grade 3 dry skin recurs at a reduced dose.
Palmar-plantar erythrodysesthesia syndrome (PPE)	
Grade 1 or tolerable Grade 2	Study drug may be continued at the current dose. Start urea 20% cream BID and clobetasol 0.05% cream QD. Reassess at least weekly; if PPE worsens at any time or does not improve with 2 weeks of treatment, proceed to the management guidelines for the next grade event.
Intolerable Grade 2 or Grade 3	Interrupt study treatment. Start (or continue) clobetasol 0.05% cream BID and add analgesics (eg, NSAIDs, GABA agonists, and/or narcotics). Reassess at least weekly; if PPE does not improve with 2 weeks of symptomatic treatment, discontinue patient from study drug. Resume study drug at a reduced dose if reaction recovers to Grade ≤1. Discontinue patient from study drug if intolerable Grade 2 or Grade 3 reaction recurs at a reduced dose.

a "Study drug" refers to SAR245408 or SAR245409.

BID: twice daily; BSA: body surface area; GABA: gamma-aminobutyric acid; NSAID: nonsteroidal antiinflammation drug; PO: oral; QD: once a day; TID: 3 times a day.

Notes: Please refer to Appendix C for a chart to estimate BSA. For all recommended therapeutic interventions, an equivalent class/ strength of medication may be substituted.

8.3.2.2 Pulmonary symptoms

In this study, subjects should be instructed to contact the Investigator promptly for new or worsening unexplained pulmonary symptoms such as dyspnea or cough. A chest x-ray and/or a high-resolution chest CT scan (for higher sensitivity when clinically indicated) should be obtained at the onset of clinically significant pulmonary symptoms such as dyspnea and cough to assess for interstitial lung disease (ILD). Study treatment (SAR245408 or SAR245409) interruption will be required for subjects who develop clinically significant pulmonary symptoms. Subjects with pulmonary AEs should be monitored closely as clinically indicated (eg, by chest x-ray, high-resolution CT scan, and/or pulmonary function tests (eg, measuring the diffusing capacity of carbon monoxide [DLCO]). Permanent discontinuation of the study drug will be required for subjects who have symptomatic and radiographic evidence of ILD.

8.3.2.3 Hepatobiliary disorders

Study treatment (SAR245408 or SAR245409) must be interrupted for subjects who develop Grade ≥2 transaminase or bilirubin elevations deemed possibly related to the study drug. Subjects must have at least weekly monitoring of liver function tests until the AE has returned to Grade ≤1 or baseline. All subjects with Grade ≥2 toxicity must have their dose reduced by 1 dose level, if study treatment is resumed; for SAR245409, no dose re-escalation will be permitted after dose reduction. Any subject experiencing Grade 4 toxicity should be evaluated by a hepatologist and must be permanently discontinued from study treatment. Subjects who develop elevation of ALT ≥3 x ULN in conjunction with bilirubin ≥2 x ULN should be evaluated by a hepatologist and must be permanently discontinued from study treatment, unless a correctable non-drug related cause of hepatic injury is identified.

8.3.2.4 Gastrointestinal disorders

Diarrhea should be treated promptly with supportive care and loperamide at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Nausea and vomiting should be treated as indicated with supportive care and anti-emetics. For dose reductions for diarrhea, nausea and vomiting, refer to Table 2.

8.3.2.5 Hyperglycemia

SAR245408 and SAR245409 may augment food-induced changes in plasma insulin resulting in hyperglycemia. Subjects who develop hyperglycemia should have a confirmatory fasting blood sugar drawn and should be managed according to standards of care for hyperglycemia. If, in the opinion of the Investigator, the hyperglycemia is possibly related to study treatment, and requires treatment with oral hypoglycemic agents, metformin is recommended as first-line therapy. Dose modifications are as outlined in Table 2.

8.3.2.6 Corrected QT interval prolongation

If a subject taking SAR245408 or SAR245409 has a QTc interval increase of ≥60 msec from baseline to an absolute value of >470 msec OR increase to an absolute value of >500 msec at any evaluation, and if the subject is asymptomatic (ie, does not have palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on electrocardiogram (ECG), or a change in vital signs), the following actions should be taken:

- The study treatment should be halted.
- Electrolytes, especially magnesium and potassium, should be checked and abnormalities should be corrected as clinically indicated.
- A blood sample for pharmacokinetics should be obtained.
- ECGs should be repeated hourly until the QTc is <60 msec increased over the baseline value and ≤470 msec.
- The Sponsor should be contacted prior to restarting study treatment. Subjects with a second prolongation of the QTc to >500 msec will be permanently discontinued from study treatment.

8.4 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUP

The IMP will be administered only to subjects included in this study following the procedures set out in this clinical trial protocol. Subjects withdrawn from the study retain their subject number, and new subjects must always be allotted a new subject number. Subjects will be assigned a 9 digit subject identification number according to the site number and IMP (SAR245408 or SAR245409) and corresponding to his/her order of enrollment in the study. This number will differ from the subject number on the parental study, but the subject number from the parental study and the parental study number will be collected for each subject.

8.5 PACKAGING AND LABELING

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

8.6 STORAGE CONDITIONS

Storage of IMP should be in a secure area with restricted access in accordance with labeling specifications.

8.7 RESPONSIBILITIES

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

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

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

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

8.8 CONCOMITANT MEDICATION

All treatments being taken by the subject 30 days prior to the first study drug administration and at any time during the study in addition to the IMP are regarded as concomitant treatments and the type, dose, and route of administration must be documented on the appropriate pages of the Case Report Form (e-CRF).

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the subject's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the e-CRF. Concomitant treatments will be collected through 30 days after the last dose of IMP.

- Concurrent systemic anticancer therapy, including investigational or noninvestigational cytotoxic agents, small molecules, biologics, immunotherapies, hormones, leukapheresis, and therapeutic radiation therapies, is prohibited unless it is part of the combination regimen from the parental study and agreed on in writing at the time of study entry.
- Radiotherapy may be administered for palliation of symptoms (eg, pain, obstruction) only if in the opinion of the Investigator, the symptoms do not represent progressive disease. The sanofi-aventis representative should be notified prior to treatment if palliative radiotherapy is being considered.
- The concomitant use with SAR245408 of drugs which are CYP1A2 or CYP3A substrates, or CYP2C9 substrates with narrow therapeutic index, or strong inducers of CYP3A, is discouraged and should be avoided if possible. For a list of relevant compounds, see Appendix D and Appendix E.

- The concomitant use with SAR245409 of drugs which are CYP1A2 substrates, or strong inducers or strong inhibitors of CYP1A2, is discouraged and should be avoided if possible. For a list of relevant compounds see Appendix F.
- Systemic corticosteroids are prohibited unless required for management of hypersensitivity reactions or skin disorders. If required for management of drug-related rash, recommendation in Table 4 should be followed. Oral prednisone ≤10 mg daily topical or inhalation maintenance steroids for comorbidities are permitted but may not be dose escalated.
- Long-acting antacids, histamine H2-receptor antagonists, and proton pump inhibitors should be avoided. Short-acting antacids as well as supplemental calcium carbonate are permitted but must not be given either 2 hours before or 2 hours after SAR245408 or SAR245409 dose. In the event that antacids are not adequate to control symptoms, the use of short-acting histamine H2-receptor antagonists is permitted but must be taken 2 hours after SAR245408 or SAR245409 dose.
- Antiemetics (other than corticosteroids) and antidiarrheals are permitted, if clinically indicated (see also Section 8.3.2.4).
- Use of myeloid hematopoietic growth factors and erythropoetin should be in accordance with the American Society of Clinical Oncology (ASCO) treatment guidelines.
- Transfusions of red blood cells and platelets may be performed according to standard of care.
- For lymphoma subjects:
  - Infectious disease prophylaxis is permitted and recommended for subjects with CD4 counts <200 cell/mm^3.
  - Prophylaxis with uricosurics for tumor lysis syndrome is permitted at the discretion of the Investigator.
  - Subjects with hypogammaglobulinemia may receive intravenous immunoglobulin as indicated.
  - All live vaccines are prohibited.

Permitted concomitant medications can be administered with water at the same time as taking SAR245408 or SAR245409, except for gastrointestinal pH-altering medications, including histamine H2-receptor antagonists, proton pump inhibitors, antacids, and calcium supplements (see above).

8.9 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Administration of IMP will be supervised by the Investigator or subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the IMP is received from sanofi-aventis,

dispensed for subject and destroyed or returned to sanofi-aventis. The packaging batch number must be recorded on the drug accountability form.

The person responsible for study treatment administration to the subject at the study site will record precisely the date and the time of the study treatment administration. Subjects will be provided a study treatment diary with dosing instructions to record study treatment taken on an outpatient basis during the study treatment period. For subjects starting study treatment at the beginning of the initiation period (see Section 1.1), the diary will be initially distributed on Cycle 1 Day 1. On Cycle 2 Day 1 and at each subsequent site visit during the extension period, the diary will be collected from the subject and a new diary will be provided. For subjects starting study treatment at the beginning of the extension period (see Section 1.1), the diary will be initially distributed on the first site visit of the period. At each subsequent site visit, the diary will be collected from the subject and a new diary will be provided. The diary will serve as source documentation and be maintained with other subject clinical source documents. Study site staff should carefully review the diary with the subject and/or caregiver to ensure it is complete and accurate before transcription to the CRFs.

8.10 RETURN AND/OR DESTRUCTION OF TREATMENTS

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 SAFETY

The primary objective of this study is to determine the long-term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen in subjects who are benefiting from treatment. Safety is thus the primary study endpoint and will be assessed continuously.

The safety profile will be assessed from the findings of physical examination, vital signs measurement, laboratory data, ECGs, ophthalmologic assessments, concomitant medications and treatments, and date of study treatment withdrawal and cause.

The safety profile will be based on incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 [NCI CTCAE v4.03]) (see Appendix B), and cumulative nature of AEs. Adverse event seriousness, severity grade, and relationship to IMP will be assessed by the Investigator.

Serious adverse events, pregnancy and symptomatic overdose must be reported to the Sponsor within 24 hours (see Section 10.5.2).

The general and study-specific safety assessments/evaluations are described in details in Section 10.1. Additional safety assessments/evaluations for the subjects on a combination regimen will be done per standard of care.

9.2 PHARMACOKINETICS

No pharmacokinetic assessment is planned.

9.3 PHARMACODYNAMICS

No pharmacodynamic assessment is planned.

9.4 EFFICACY

Tumor assessment will be performed per standard of care, and tumor response as per Investigator will be collected for each tumor assessment. No tumor measurement data will be collected in this study.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

The safety profile will be assessed from the findings of physical examination, vital signs measurement, laboratory data, ECGs, ophthalmologic assessments, concomitant medications and treatments, and date of study treatment withdrawal and cause.

The safety profile will be based on incidence, severity (as graded by the NCI CTCAE v4.03; see Appendix B), and cumulative nature of AEs. Adverse event seriousness, severity grade, and relationship to IMP will be assessed by the Investigator.

10.1.1 Performance status

The Eastern Cooperative Oncology Group (ECOG) performance status scale (see Appendix A) will be used to assess performance status.

Please refer to the study flow chart in Section 1.2 for performance status assessment schedule.

10.1.2 Physical examination

Full physical examination consists of examination of major body systems (including neurologic, gastrointestinal, cardiovascular, respiratory, skin, and lymphatics), body weight, and height (at baseline visit only).

Symptom-directed physical examination is a physical examination relevant to the subject's symptoms.

If abnormal findings emerge or worsen from baseline assessment, then the AE page of the e-CRF should be completed for these findings. If a finding meets the criteria for an SAE, then the appropriate procedures for reporting such events should be followed as described in Section 10.5.

Please refer to the study flow chart in Section 1.2 for physical examination schedule.

10.1.3 Vital signs measurement

Vital signs consist of body temperature, blood pressure, and heart rate. Vital signs should be taken within 1 hour before dosing.

Please refer to the study flow chart in Section 1.2 for vital signs measurement schedule.

10.1.4 Laboratory tests

Local laboratories will perform all laboratory tests, and results will be provided to the Investigator. Blood and urine samples for hematology, serum chemistry, coagulation, and urinalysis will be prepared using standard procedures. If the serum chemistry panel is not performed in the fasted state and an abnormal glucose result is observed, it should be followed with a fasting plasma glucose assessment after an overnight fast.

Laboratory tests are detailed in Table 5. Please refer to the study flow chart in Section 1.2 for laboratory tests schedule.

All laboratory tests performed as part of standard of care for a combination regimen or for assessment of a possible AE outside of the scheduled visits will also be collected as unscheduled assessments.

Table 5 - Laboratory tests

Hematology	Serum chemistry	Coagulation	Urinalysis	Others
• White blood cell (WBC) count with differential[a] • Hemoglobin • Platelet count	• Albumin • Alkaline phosphatase (ALP) • Amylase • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Calcium • Carbon dioxide • Chloride • Creatinine • γ-glutamyltransferase (GGT) • Glucose • Lipase • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin	• Prothrombin time / International normalized ratio (PT/INR) • Activated partial thromboplastin time (aPTT)	• Protein • Glucose • Bilirubin • Occult blood[b]	• Hemoglobin A1c (HbA1c) • Serum pregnancy test (β-HCG)

a Including at minimum: neutrophils, basophils, eosinophils, lymphocytes, and monocytes.

b Microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive.

10.1.5 Ophthalmologic examination

Ophthalmologic examination at baseline is for subjects taking SAR245408 and for subjects taking SAR245409; ophthalmologic examination during the extension period is only for subjects taking SAR245409. Ophthalmologic examination will be conducted by an ophthalmologist or an optometrist and will include a slit lamp examination. New adverse findings should be evaluated more frequently as medically indicated and reported in the e-CRF. Investigators have the discretion to request an ophthalmology consultation for any emerging ophthalmologic conditions at any time during the study.

10.1.6 Electrocardiogram

Twelve (12)-lead ECGs will be performed at baseline, during the treatment period and at the follow-up visit.

10.1.7 Pregnancy test

A serum pregnancy test will be performed on women of child bearing potential within 7 days prior to first study treatment administration and at the follow-up visit.

10.1.8 Adverse event reporting

Adverse events observed by the Investigator or reported by the subject will be graded and documented as described in Section 10.4.

10.2 SAFETY INSTRUCTIONS

Please refer to Section 8.3 for dosing interruptions and reductions in the IMP dose due to IMP-related toxicity.

Subjects requiring more than 2 dose reductions of IMP (SAR245408 or SAR245409) - considering **both** the parental study and the treatment-extension study - will be permanently discontinued from study treatment. If IMP is held for more than 6 weeks (SAR245408) or more than 21 days (SAR245409) due to an AE, subject should be permanently discontinued from study treatment.

10.3 ADVERSE EVENTS MONITORING

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

10.4 DEFINITIONS OF ADVERSE EVENTS

10.4.1 Adverse Event

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.

10.4.2 Serious Adverse Event

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 (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following medically 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 (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia…),
  - convulsions (seizures, epilepsy, epileptic fit, absence…)
- Development of drug dependency or drug abuse;
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x 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 Investigators in oncology studies);
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged as unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.3 Adverse Event of Special Interest

An Adverse Event of Special Interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them and may require follow-up beyond the planned time of study completion.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 General guidelines for reporting Adverse Events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the first dose of IMP in the study until the end of the study as defined by the protocol for that subject, are to be recorded on the corresponding screen(s) of e-CRF.
- For continuity of evaluation of safety through the parental and treatment-extension studies, for each subject that may have an AE or SAE in the treatment-extension study, the parental study number, subject ID in the parental study and a specific designation for the parental study will be collected as mandatory fields on the corresponding screen(s) of e-CRF of the treatment-extension study.
- 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 IMP, 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 the IMP.
- The Investigator should take appropriate measures to follow all treatment related AEs and SAEs until clinical recovery is complete, laboratory results have returned to patient's baseline level or until stabilization or death, in order to ensure the safety of the subjects. This may imply that observations will continue beyond the last planned visit per protocol, and that

additional investigations may be requested by the Monitoring Team up to as noticed by the Sponsor.

- When treatment is prematurely discontinued, the subject's observations will continue until the end of the study as defined by the protocol for that subject.
- Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- See Table 6 for a summary of AE reporting guidelines.

10.5.2 Instructions for reporting Serious Adverse Events

In the case of occurrence of a SAE, the Investigator must immediately:

- 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 Monitoring Team after approval of the Investigator within the e-CRF or after a standard 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 Monitoring Team whose name, fax number and email address appear on the clinical trial protocol. Care should be taken to ensure that the subject's identity is protected and the subject'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, subject status ...) should be sent (by fax or e-mail) to the Monitoring Team 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 available and should be used (using paper CRF process) when the e-CRF system does not work.
- In case of any SAE brought to the attention of the Investigator at any time after the end of the study for the subject and considered by him/her to be caused by the IMP with a reasonable possibility, this should be reported to the Monitoring team.
- Any SAE occurring within 30 days after last study treatment administration, regardless of relationship to the study treatment must be reported within 24 hours.

- All SAEs related to the study drug occurring beyond 30 days must also be reported within 24 hours.
- All deaths regardless of cause, including progression of disease that occur within 30 days of study drug need to be reported as SAE, regardless of relationship to the study drug.
- All SAEs related to study treatment must be followed until resolution, stabilization or death.

10.5.3 Guidelines for reporting Adverse Events of Special Interest

Skin toxicities (SAR245408 and SAR245409) and transaminases elevation (for SAR245409) are AESIs. Please refer to the specific guidance for management of skin disorders and hepatobiliary disorders in Section 8.3.2.1 and Section 8.3.2.3, respectively, for monitoring and management of these events and to the latest IB for additional information.

10.5.3.1 Reporting of AESI with immediate notification

For AESIs with immediate notification, the Sponsor will be informed immediately (ie, within 24hours), as per SAEs notification instructions described in Section 10.5.2, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

- Grade ≥2 increase in ALT (for SAR245409 only)
- Pregnancy
  - Pregnancy occurring in a female subject included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
  - In the event of pregnancy, IMP should be discontinued.
  - The follow-up of the pregnancy will be mandatory until the outcome has been determined.
- Symptomatic overdose with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is defined as any dose exceeding the intended dose in a single day which is suspected by the Investigator or reported by the subject (not based on systematic pills count)

10.5.3.2 Reporting of AESI without immediate notification

- Asymptomatic overdose with IMP/NIMP
- Skin toxicities ≥ Grade 2 (SAR245408 and SAR245409)
  - The Investigator is required to provide additional information for skin toxicities as per the specific supplemental AE form.

Table 6 - Summary of Adverse Event reporting instructions

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Comple-mentary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.2	Yes	Yes	No
Adverse Event of Special Interest WITHOUT immediate notification (non-SAE)	Routine	Asymptomatic overdose with IMP/NIMP	Yes	No	No
		≥ grade 2 Skin toxicities (SAR245408 and SAR245409)	Yes	No	Yes
Adverse Event of Special Interest WITH immediate notification (non-SAE)	Expedited (within 24 hours)	Pregnancy of female subject	Yes	Yes	No
		Symptomatic overdose with IMP/NIMP	Yes	Yes	No
		Grade ≥2 increase in ALT (SAR245409)	Yes	Yes	Yes
Laboratory, vital sign, or ECG abnormality (non-SAE, non-AESI) that is: - symptomatic - requiring corrective treatment or consultation - leading to IMP discontinuation or dose modification	Routine	NA	Yes	No	No

10.6 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 Health Authorities, IECs/IRBs as appropriate and to the Investigators.

- all SAEs that are expected and at least reasonably related to the IMP to the Health Authorities, according to local regulations.

Any other AE not listed as an expected event in the IB or in this protocol will be considered as unexpected.

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

11 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined if the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, the subject should remain in the study as long as possible.

Pregnancy will lead to definitive study treatment discontinuation in all cases.

11.1 TEMPORARY TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

Please refer to Section 8.3.

All temporary treatment discontinuation, whatever the duration, should be recorded by the Investigator on the appropriate screen(s) of the e-CRF.

11.2 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

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

11.2.1 List of criteria for definitive treatment discontinuation

The subjects may withdraw from treatment with IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Treatment with IMP should be definitively discontinued in any of the following cases:

- Unacceptable AE (including AE requiring more than 2 dose reductions of SAR245408 or SAR245409 - considering **both** the parental study and the treatment-extension study - or interruption of SAR245408 for more than 6 weeks, or interruption of SAR245409 for more than 21 days);
- Disease progression;
- Poor compliance to the study protocol;
- Loss of follow-up;

11.2.2 Handling of patients after permanent treatment discontinuation

Subjects will be followed up according to the study procedures as specified in this protocol up to the Day 23-37 follow-up visit (see Section 1.2), or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All permanent treatment discontinuation should be recorded by the Investigator on the appropriate screens of the e-CRF when considered as confirmed.

11.3 PROCEDURE AND CONSEQUENCE FOR PATIENT WITHDRAWAL FROM STUDY

The subjects may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason:

- All study withdrawals should be recorded by the Investigator on the appropriate screens of the e-CRF and in the subject's medical records when considered as confirmed (at least date of withdrawal and reason for).
- If possible, the subjects are assessed using the procedures normally planned for the Day 23-37 follow-up visit (see Section 1.2).

For subjects who fail to return to the site, the Investigator should make the best effort to re-contact the subject (eg, contacting subject's family or private physician, review available registries or health care database), and to determine his/her health status, including at least his/her vital status. Attempts to contact such subjects must be documented in the subject's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). The statistical analysis plan will specify how these subjects lost to follow-up for their primary endpoints will be considered.

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

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

During the course of the study, all subjects entering the study must be evaluated according to the schedule outlined in the flow chart in Section 1.2 and described below. The results of the evaluation will be recorded on the e-CRF screens until the subjects are not followed anymore. Safety assessments will be evaluated according to the schedule outlined in the flow chart in Section 1.2 and per standard of care if the subject is on a combination regimen.

This study consists of a 7-day baseline period and treatment cycles. A cycle is 28-days for SAR245408 and SAR245409 given as monotherapy; cycle duration may be different for SAR245408 and SAR245409 given as a combination regimen. After the baseline visit, all the subjects eligible and included in the study will continue on the IMP (SAR245408 or SAR245409) and combination medication(s) (for subjects taking combination therapy) they received during the parental study and will start the study treatment period at the beginning of the initiation or extension period based on the length of prior treatment with SAR245408 or SAR245409 in the parental study:

- if <2 cycles, start with initiation period;
- if ≥2 cycles, start with extension period;
- subjects who will take a SAR245408 or SAR245409 daily dose higher than their established dose of SAR245408 or SAR245409, respectively, in the parental study will start with initiation period;
- subjects who had dose interrupted in the parental study but fulfill parental protocol criteria to restart IMP treatment will start the treatment-extension study on Day 1 of the initiation period;
- subjects who fulfil the parental study criteria for IMP treatment continuation but have ongoing Grade 2 AE(s) should start the treatment-extension study on Day 1 of the initiation period.

Subjects will have a visit on site every week (Cycle 1) or every 2 weeks (Cycle 2) during the initiation period (if applicable), and every 4 to 6 weeks during the extension period. Subjects must complete all the visits in the initiation period before moving to the extension period.

Subjects may continue to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until commercial supplies of SAR245408 or SAR245409 are available to them outside of the clinical trial. A complete visit will be performed about 30 days after last IMP administration, corresponding to the follow-up visit. The subjects will be followed until recovery or consolidation of any IMP-related AE or until deemed irreversible by the Investigator.

12.1.1 Pretreatment period

Please also refer to flow chart in Section 1.2 and to Section 10.1.

The baseline evaluations are to be performed within 7 days prior to the first study treatment administration. The end-of-treatment assessments from the parental study may be used as baseline assessments for this study if obtained within 7 days prior to the first study treatment administration.

The informed consent will have to be signed by the subject before any procedure specific to the study is performed.

The following evaluations will be performed:

- Demography and disease history
- ECOG performance status.
- Vital signs.
- Full physical examination and height.
- Ophthalmologic exam (ophthalmologic exam from the parental study may be used as baseline assessment if conducted within 12 weeks prior to the first study treatment administration).
- 12-lead ECG.
- Laboratory tests (see Table 5):
  - hematology;
  - serum chemistry;
  - PT/INR, aPTT;
  - HbA1c;
  - urinalysis.
- Serum pregnancy test: female subjects of childbearing potential must have a negative serum pregnancy test (β-hCG) within 7 days prior to the first study treatment administration.

Subjects who meet all the inclusion criteria, and none of the exclusion criteria, will be eligible for inclusion in the study. Each subject will receive an incremental identification number corresponding to his/her order of enrollment in the study.

Documentation of agreed dose, regimen, and formulation of SAR245408 or SAR245409 (and of agreed dose and regimen of combination medication(s) for subjects taking combination therapy) and starting point of the study treatment period (initiation or extension) must be signed by the Sponsor Medical Monitor and the site Principal Investigator prior to first dose.

12.1.2 Treatment period

12.1.2.1 Initiation period (if applicable)

Please also refer to flow chart in Section 1.2 and to Section 10.1.

The baseline assessments may be used as Cycle 1 Day 1 assessments if obtained within 72 hours of Cycle 1 Day 1. The baseline visit and the initial visit may occur on the same day. All subjects receiving monotherapy with SAR245408 or SAR245409 should be followed using 28-day treatment cycles during the initiation period. A 21-day treatment cycle should only be used for subjects who are receiving a combination regimen based on a 21-day treatment cycle.

The following evaluations will be performed (subjects on 28-day treatment cycles):

- ECOG performance status: on Cycle 2 Day 1.
- Vital signs: on Cycle 1 Day 1, Day 8, Day 15, and Day 22, and on Cycle 2 Day 1 and Day 15.
- Full physical examination: on Cycle 2 Day 1.
- Symptom-directed physical examination: on Cycle 1 Day 1, Day 8, Day 15, and Day 22, and on Cycle 2 Day 15.
- 12-lead ECG: on Cycle 1 Day 1 and Day 15, and on Cycle 2 Day 1 and Day 15.
- Laboratory tests (see Table 5):
  - hematology: on Cycle 1 Day 1 and Day 15, and on Cycle 2 Day 1 and Day 15;
  - serum chemistry: on Cycle 1 Day 1 and Day 15, and on Cycle 2 Day 1 and Day 15.
  - PT/INR, aPTT: on Cycle 1 Day 1 and Cycle 2 Day 1.
  - urinalysis: on Cycle 1 Day 1 and Cycle 2 Day 1.

Subjects on 21-day treatment cycles will have assessments only on Day 1, Day 8, and Day 15 when in Cycle 1 and on Day 1 and Day 15 when in Cycle 2.

Tumor assessment will be performed per standard of care.

12.1.2.2 Extension period

Please also refer to flow chart in Section 1.2 and to Section 10.1.

The following evaluations will be performed every 4 to 6 weeks:

- Vital signs.
- Symptom-directed physical examination.

- 12-lead ECG (approximately every 12 weeks and as clinically indicated)
- Laboratory tests (see Table 5):
  - hematology;
  - serum chemistry;
  - PT/INR, aPTT;
  - HbA1c (every 12 weeks (± 4 weeks) until 60 weeks on treatment and every 24 weeks (± 4 weeks) after 60 weeks on treatment);
  - urinalysis.

Ophthalmologic examination will be performed (only for subjects taking SAR245409) every 24 weeks (± 4 weeks)).

Tumor assessment will be performed per standard of care.

12.1.3 Post-treatment period

Please also refer to flow chart in Section 1.2 and to Section 10.1.

Subjects will return to the study site 23-37 days after the last dose of IMP for a follow-up visit. Additional follow up may be required in case of unresolved toxicities.

The following evaluations will be performed:

- Vital signs.
- Symptom-directed physical examination.
- 12-lead ECG.
- Laboratory tests (see Table 5):
  - hematology;
  - serum chemistry;
  - PT/INR, aPTT;
  - HbA1c;
  - urinalysis.
- Serum pregnancy test (female subjects of childbearing potential).

Ophthalmologic examination will be performed if any of the previous examinations were abnormal.

12.2 DEFINITION OF SOURCE DATA

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

Source documents are original documents, data, and records (eg, 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, magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at the medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within a CRF.

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

The sample size of this study will depend on the number of subjects who will continue receiving treatment from the parental studies. It is expected that approximately 100 to 150 subjects will be treated in this study. There is no statistical power consideration for this treatment-extension study, as the study is for investigating the long term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen.

13.2 ANALYSIS ENDPOINTS

13.2.1 Demographic and baseline characteristics

13.2.1.1 Demographic and baseline characteristics

Demographic and baseline characteristics are sex (male, female), race (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other), age in years (quantitative and qualitative variable: <65, 65 – 75, and ≥75 years), weight, ethnicity (Hispanic, Non Hispanic). Medical history, cancer diagnosis and prior anti-cancer therapy will be collected at baseline. Baseline safety variables include signs and symptoms at baseline, laboratory tests and vital signs, and baseline value is defined as the last value or measurement taken before and up to the first study dose in this study.

13.2.1.2 Prior or concomitant medications (other than anti-cancer therapies)

All medications will be coded by the Medical Dictionary for Regulatory Activities (MedDRA). Prior medications will record any medications (except the study medications in the parental study) taken within 30 days prior to the first study drug administration. Concomitant medications are any treatments received by the subjects concomitantly with the study drugs from the start of the first study drug dose to the last study drug dose + 30 days.

13.2.2 Safety endpoints

Safety endpoints include AEs (including deaths), vital signs, physical examination, ophthalmologic examination, ECG, and laboratory data.

Observation period

The observation of safety data will be as follows:

- Treatment period: the treatment period is defined from the date of the first dose of any study drug up to 30 days after the last dose of any study drug.
- On-study observation period: the on-study period is defined as the time from the first dose of any study drug until the end the study (see Section 6.2.1).
- Post-treatment period: post-treatment period is defined as the time from the day after the end of treatment period to the end of the study (see Section 6.2.1).

13.2.2.1 Adverse events

AE observation period:

The AE observations are per the on-study observation periods defined above, and will include all treatment-emergent AE (TEAE), serious AE, AESI (AE of special interest), AE leading to death, AE that causes dose reduction and/or delay, AE that causes treatment interruption, AE that causes treatment discontinuation, and AE related to treatment. AEs which occur after the first dose of any study drug in this study will be reported to this study regardless of the timing of the last dose of study drug in the parental study.

TEAE is defined as any AE that is new, worsened in severity or becomes serious from the first dose of any study drug up to 30 days after the last dose of any study drug.

13.2.2.2 Deaths

Death observation period:

The death observations are per the observation periods defined above. In addition, post-study death includes all deaths reported after the end of study.

13.2.2.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry, PT/INR and aPTT, and HbA1c) and urinalysis. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

13.2.2.4 Vital signs

Vital signs include body temperature, blood pressure, and heart rate.

13.2.2.5 12-lead ECG

ECG values and abnormalities will be used for the safety analyses.

13.2.2.6 Other safety endpoints

Results from physical examination and ophthalmologic examination will be used for the safety analyses.

13.2.3 Pharmacokinetic variables

Not applicable.

13.2.4 Pharmacodynamic variables

Not applicable.

13.3 DISPOSITION OF PATIENTS

All treated subjects (safety population) are those who took at least one dose of the study drug.

13.4 ANALYSIS POPULATIONS

13.4.1 Safety population

This population includes all subjects who took at least 1 dose of study drug during the study.

13.4.2 Efficacy population

Evaluable population: this population includes all subjects who have at least 1 valid post-baseline tumor response assessment per Investigator.

13.5 STATISTICAL METHODS

13.5.1 Demographic and baseline characteristics

Standard demographic and baseline characteristics, medical history, cancer diagnosis and prior anti-cancer therapy will be collected at baseline. Baseline value is defined as the last value or measurement taken up to the first dose in the study. Baseline safety variables include sign and

symptoms at baseline, laboratory tests and vital signs. Parameters will be summarized on safety population by treatment group (SAR245408 and SAR245409).

13.5.2 Prior or concomitant medications (other than anti-cancer therapies)

The prior and concomitant medications will be presented on the safety population by treatment group (SAR245408 and SAR245409). Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized; subjects will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication, therefore subjects may be counted multiple time for the same medication.

13.5.3 Extent of study treatment exposure

Extent of study treatment exposure will be assessed on the safety population by treatment group (SAR245408 and SAR245409).

Duration of study drug exposure is defined as: last dose date – first dose date + 1 day regardless of unplanned intermittent discontinuations. The first and the last study dose administration is any dose of first and last administration of study drug.

Dose information will be assessed by the following variables:

- Total number of cycles administered (by formulation)
- Cumulative dose: sum of all doses administered for all cycles while the subject is on treatment
- Actual dose intensity (ADI): defined as the cumulative dose divided by duration of study drug exposure in terms of the number of weeks on study (by formulation)
- Relative dose intensity (RDI): defined as the ratio of the actual dose intensity to the planned dose intensity. The RDI is an indicator of the feasibility of the chosen schedule of administration.
- Dose reduction and reason for dose reduction.
- Dose interruption and reason for dose interruption.

13.5.4 Analyses of safety data

The summary of safety results will be presented by treatment group (SAR245408 and SAR245409) on the safety population. Analyses of AEs and laboratory data will be descriptive and performed on the safety population. For each of the safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study. Descriptive analyses will be presented for TEAEs, AESIs, SAEs and AEs that cause dose reduction, dose delay and treatment discontinuation.

Treatment-emergent adverse event (TEAE) incidence tables will present by system-organ-class (SOC) and preferred term (PT) by treatment group (SAR245408 and SAR245409), using number and percentage of subjects experiencing an AE. Multiple occurrences of the same event in the same subject will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

The grade will be taken into account in the summary. For subjects with multiple occurrences of the same event, the maximum grade is used.

The following deaths summaries will be generated:

- Number (%) of subjects who died during on-treatment period and reasons for deaths summarized on the safety population by treatment received.
- TEAEs leading to deaths (death as an outcome on the AE e-CRF page as reported by the Investigator) and related TEAEs leading to death by primary SOC, high group level term (HLGT), high level term (HLT), and PT, showing number (%) of subjects sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adverse events of special interest (AESIs), AEs related to study treatment, AEs leading to study treatment discontinuation, AEs leading to dose delay/reduction will be summarized in a similar way.

Ophthalmologic examination results will be summarized by number and percentage of subjects with abnormality by treatment group at respective visits.

ECG results will be summarized by treatment group at respective visits. Vital signs and change from baseline will be summarized by treatment group at respective visits.

Hematological toxicities will be assessed from laboratory parameters. Worst NCI CTCAE v4.03 grades will be calculated. Qualitative and quantitative results will be summarized for hematological toxicities.

Serum chemistry will be analyzed in a similar way using the worst NCI CTCAE v 4.03 grade, whenever applicable (laboratory normal ranges, otherwise), calculated from laboratory values.

Prothrombin time/international normalized ratio, HbA1c and their changes from baseline will be summarized by treatment group at respective visits.

Subgroup safety analyses will be performed by parental study, monotherapy and combination therapy, when appropriate. In addition, cumulative incidence combining parental and extension studies may be provided for TEAEs, SAEs, AESIs, etc., as appropriate.

13.5.5 Analyses of efficacy endpoints

13.5.5.1 Analyses of primary and secondary efficacy endpoints

This treatment-extension study is for investigating the long term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen, and thus there is no primary or secondary efficacy endpoint. All the efficacy variables and analyses are exploratory.

13.5.5.2 Analyses of exploratory efficacy endpoints

Tumor response as per Investigator will be summarized by treatment group (SAR245408 and SAR245409) in the evaluable population. Overall Survival (OS), Progression Free Survival (PFS), Objective Response Rate (ORR), and Duration of Response (DR) will be summarized and the survival curves will be estimated using Kaplan-Meier estimates by treatment group. Tumor response will be summarized by number and percentage of subjects in each response category by treatment group.

Overall survival is defined as the time (days) from the study Day 1 of the parental study to the date of death (whatever the cause) in the study (treatment-extension study). If death is not observed during the study, data on OS will be censored at the last date subject is known to be alive or the cut-off date (if defined during the study), whichever occurs first.

Progression free survival is defined as the time (days) from the study Day 1 of the parental study to the date of progressive disease (PD) or death (regardless of cause) in the study (treatment-extension study). The actual dates of tumor assessments will be used for this calculation. If death or disease progression is not observed, data on PFS will be censored at the earlier of the date of last tumor assessment without evidence of progression.

Objective response rate is defined as the proportion of subjects who experience complete response/remission (CR) or partial response/remission (PR) in the study (treatment-extension study).

Duration of response is defined as the time (days) from the date of first tumor response (CR or PR) in the parental study or in the study (treatment-extension study), whichever occurs first, to the time of the first tumor assessment of PD or death due to any cause. This endpoint is defined only for those subjects with a tumor response.

Subgroup efficacy analyses will be performed by parental study, monotherapy and combination therapy, when appropriate.

13.5.5.3 Multiplicity Considerations

Due to the nature of the exploratory analyses, no adjustment for multiple efficacy analyses will be made.

13.5.6 Analyses of pharmacokinetic variables

Not applicable.

13.5.7 Analyses of pharmacodynamic variables

Not applicable.

13.6 DATA HANDLING CONVENTIONS

Missing dates will be handled using conservative approaches, and no imputation will be applied at the data level:

- If the date of the last dose of IMP is missing, the exposition duration should be kept as missing.
- If a medication date is missing or partially missing, it will be considered as a prior, concomitant, and a follow-up medication, when no reasonable conclusion can be reached in this situation.
- If onset dates are missing or partially missing, the AE will be classified as treatment-emergent.
- If the date of the first study drug dose in the study is missing, all AEs that occurred on or after the day the subject entered into the study will be considered as treatment-emergent AEs.

Handling of missing relationship to IMPs of AEs: if the assessment of the relationship to IMPs is missing, then the relationship to IMPs has to be assumed and the AE considered as such in the frequency tables of possibly-related AEs.

Handling of missing severity/grades of AEs: if the severity/grade is missing for 1 of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences a “missing” category will be added in the summary table.

13.7 INTERIM ANALYSIS

No interim analysis is planned for this study.

13.8 DATABASE LOCK

The database is planned to be locked within 4 to 8 weeks from the last subject last visit.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

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

In compliance with sanofi-aventis public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov 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.

14.2 LAWS AND REGULATIONS

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

14.3 INFORMED CONSENT

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

Prior to a patient’s participation in the clinical trial, the written ICF 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 ICF will be provided to the patient.

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

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

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

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, IB, Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

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

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

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for GCP 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 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 will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. 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. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for GCP, the Monitoring Team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the e-CRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities: Oracle Clinical;
- For statistical activities: SAS;
- For pharmacovigilance activities: AWARE;
- For monitoring activities: IMPACT and POLARIS;
- For medical writing activities: DOMASYS.

No external data loading is planned for this clinical trial.

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-Investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITES(S)

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

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

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

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

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

17 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the CRFs, the IB and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. 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 (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

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

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

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

18 PROPERTY RIGHTS

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

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

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

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

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

19 DATA PROTECTION

The patient's personal data, which are 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.

The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

20 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 of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics committees/IRB or Health Authorities in countries requiring this document.

21 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

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

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

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

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

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

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

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

22.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio.
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for GCP.
- If the total number of patients are included earlier than expected.
- Drug supply or manufacturing issues.
- The Sponsor’s decision to discontinue the development of the IMP.

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

22.2 DECIDED BY THE INVESTIGATOR

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

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

23 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

24 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. However, if no multicenter publication has occurred within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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 study.

25 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

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

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

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change and patient signature should be re-collected if necessary.

26 BIBLIOGRAPHIC REFERENCES

1. Shapiro GI, Rodon J, Bedell C, Kwak EL, Baselga J, Brana I, et al. Phase I safety, pharmacokinetic, and pharmacodynamic study of SAR245408 (XL147), an oral pan-class I PI3K inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2014;20:233-245.Not applicable.