GEIS-32

CLINICAL TRIAL PROTOCOL

Title:

A Phase II Open-Label Trial of Pazopanib Administered as a Single Agent in Patients with Unresectable or Metastatic Solitary Fibrous Tumor (SFT) and Extraskeletal Myxoid Chondrosarcoma (EMC)

Sponsor Protocol Number: GEIS-32
EudraCT Number: 2013-005456-15

Protocol Version: 1.2 of November 4th 2014

International Sponsor: Grupo Español de Investigación en Sarcomas (GEIS)

Coordinating Investigators in Spain:

- Dr. Josefina Cruz – Hospital Universitario de Canarias
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PROTOCOL VERSION CHRONOLOGY

Version	Date	Summary of Changes
1.0	December 11th, 2013	• Original protocol
1.1	March 13th, 2014	• Addition of reference to the 64th World Medical Association General Assembly held in Fortaleza, Brazil, October 2013 (in section 13.3 and Appendix C). • Additional information included regarding the supply of the drug in section 6.1
1.2	November 4th, 2014	• Modification of schedule of "Procedures and assessments" due to changes on the Summary of Product Characteristics of pazopanib (section 1 – Trial summary – p. 14-15 and section 7.1 p. 36-37). • The differentiation of SFT cohort into 2 subgroups (Introduction - Background and scientific rationale – SFT – p. 17-18). • Additional information regarding statistical analysis (section 1.Trial Summary – Design & Statistics – p. 15-16 and section 11.3 Sample size and analytical methodology – p. 51-52). • Modification of section 4.3 (Permanent discontinuation criteria, p. 23). • Specification of methodology (section 7.1 - table 7- point 3: Hypoglycemia test – p. 37). • Additional information regarding efficacy assessments (section 7.7 - table 7: Choi/RECIST Criteria for Response Evaluation: included in Choi criteria the term SLD and how target lesions are selected – p. 42 (based on RECIST 1.1)). • Specification of efficacy assessments (section 7.7 – Thoracic-abdominal CT scan / MRI: Strongly recommended to use CT scan when feasible, instead of MRI – p. 42-43). • New indications added regarding biological sample collection (section 7.9 – p. 44). • Tumor samples will be analyzed for primary tumor and/or for subsequent biopsies (section 1. Trial Summary – p. 10, 3.3 Translational objectives – p. 20 and 12.2 Translational objectives – p. 53).

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PROTOCOL SIGNATURES PAGE

International Sponsor: Grupo Español de Investigación en Sarcomas (GEIS)

Study Title: A Phase II Open-Label Trial of Pazopanib Administered as a Single Agent in Patients with Unresectable or Metastatic Solitary Fibrous Tumor (SFT) and Extraskeletal Myxoid Chondrosarcoma (EMC)

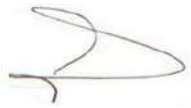
Sponsor Protocol Number: GEIS-32

EudraCT Number: 2013-005456-15

Protocol Version and Date: Version 1.2 of November 4th 2014

I read this protocol and I accept to conduct this trial in accordance with the protocol stipulations, GCP guidelines and the Declaration of Helsinki.

International Sponsor:



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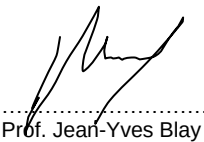

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BEV	Bevacizumab
BP	Blood Pressure
BSA	Body Surface Area
CBR	Clinical Benefit Rate
CR	Complete Response
e-CRF	Electronic Case Report Form
CLB	Centre Léon Bérard
CRO	Contract Research Organization
CT	Computed Tomography
DVT	Deep Venous Thrombosis
DP	Disease Progression
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMC	Extraskeletal Myxoid Chondrosarcoma
EORTC	European Organisation for Research and Treatment of Cancer
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GEIS	Grupo Español de Investigación en Sarcomas
GSK	GlaxoSmithKline
HPC	Hemangiopericytoma
HPF	High Power Field
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ISG	Italian Sarcoma Group
L	Liter
LPFV	Last Patient First Visit
LVEF	Left Ventricular Ejection Fraction
MDACC	MD Anderson Cancer Center
mg	Milligrams
mg/m^2	Milligrams per meter squared
mg/kg	Milligrams per kilogram
MRI	Magnetic Resonance Imaging
µg	Microgram
mL	Milliliter
mL/min	Milliliter per minute
mm	Millimeter
msec	Millisecond
MUGA	Multi-gated Radionuclide Angiography
MVD	Microvessel Density
NCI CTCAE 4.0	National Cancer Institute Common Terminology for Coding of Adverse Events version 4.0
NOS	Not Otherwise Specified
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PIS/IC	Patient Information Sheet / Informed Consent
PK	Pharmacokinetic
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SFT	Solitary Fibrous Tumor
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SBP	Systolic Blood Pressure
STS	Soft Tissue Sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TIA	Transient Ischemic Attack
TMG	Trial Management Group
TSC	Trial Steering Committee
TMZ	Temozolomide
ULN	Upper Limit of Normal

1. TRIAL SUMMARY

Study Type	A three-cohort phase II, open-label, non-randomized, international multicenter clinical trial of a licensed IMP.
International Sponsor	Grupo Español de Investigación en Sarcomas (GEIS) Velázquez, 7, 3rd Floor 28001, Madrid, Spain www.grupogeis.org
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Trial Title	A Phase II Open-Label Trial of Pazopanib Administered as a Single Agent in Patients with Unresectable or Metastatic Solitary Fibrous Tumor (SFT) and Extraskeletal Myxoid Chondrosarcoma (EMC)
Sponsor Protocol Number	GEIS-32
EudraCT Number	2013-005456-15
International Coordinating Investigators	Clinical trial: • SFT cohorts (typical/malignant and dedifferentiated): Dr. Josefina Cruz (Hospital Universitario de Canarias) & Dr. Javier Martín (Hospital Universitari Son Espases) • EMC cohort: Dr. Silvia Stacchiotti (Fondazione IRCCS Istituto Nazionale dei Tumori) Translational study: • Dr. Silvia Stacchiotti (Fondazione IRCCS Istituto Nazionale dei Tumori) • Dr. Enrique de Álava (Hospital Universitario Virgen del Rocío)
National Coordinating Investigators	• Spain: Dr. Josefina Cruz (Hospital Universitario de Canarias) & Dr. Javier Martín (Hospital Universitari Son Espases) • Italy: Dr. Silvia Stacchiotti (Fondazione IRCCS Istituto Nazionale dei Tumori) • France: Prof. Jean-Yves Blay (Centre Léon Bérard)
Planned Calendar	• Administrative start-up: 4 months • First subject first visit (FSFV): Second quarter 2014 • Total recruitment period duration: 36 months • Follow-up period: 18 months • Estimated end of study date: Second quarter 2018

Estimated Accrual Rate	3-4 cases per month (at international level)
Objectives	*Primary study objective* • To determine the objective response rate (ORR) (confirmed complete response [CR] and partial response [PR]) in patients with unresectable, locally advanced or metastatic solitary fibrous tumor and extraskeletal myxoid chondrosarcoma, using Choi and RECIST 1.1 criteria respectively. *Secondary study objectives* • To estimate the efficacy of pazopanib as measured by the progression-free survival (PFS) rate assessed by median time in patients with unresectable, locally advanced or metastatic solitary fibrous tumor and extraskeletal myxoid chondrosarcoma. • To evaluate overall survival (OS). • To evaluate clinical benefit rate (CBR). • To evaluate long term safety profile according to CTCAE 4.0. *Translational study objectives* SFT cohorts (typical/malignant and dedifferentiated): • To perform a central pathologic review (diagnosis confirmation) of paraffin-embedded tumor blocks for each recruited patient with SFT, including (exploratory) STAT6 immunohistochemistry. • To evaluate the serum profile of serum cytokine markers as indicator of response to pazopanib. The Luminex technology will be employed for the analysis of 12 cytokines [VEGF-A, PlGF-1, SDF-1 alpha (CXCL12), TNF alpha, IL-8, IL-6, PDGF–beta, HGF, E-Selectine, ICAM1, MMP-9 and FGFb]. • To evaluate the profile of angiogenic markers in the primary tumor and/or in the subsequent biopsies. Microvessel density (MVD) and VEGF/PDGF pathways will be evaluated by IHQ expression as well as their correlation with prognosis and their role as predictive factors to treatment with pazopanib (response, PFS and OS). • To evaluate pharmacodynamic markers (MVD, VEGF/PDGF) only in patients with paired samples (in the biopsies taken after treatment). EMC cohort: • To perform a central pathologic review (diagnosis confirmation) of paraffin-embedded tumor blocks for each recruited patient with EMC, including FISH analysis and/or RT-PCR NR4A3 and its partners (EWSR1, TAF15). • To evaluate the expression and activation profile of angiogenic targets (VEGFR, PDGFR, RET, MCSR1) in the primary tumor and/or in the subsequent biopsies by immunohistochemistry, pRTK array and IP/WB respectively.
Disease Under Study	• Stratum 1-a: Typical solitary fibrous tumor (SFT) • Stratum 1-b: Malignant and dedifferentiated solitary fibrous tumor (SFT) • Stratum 2: Extraskeletal myxoid chondrosarcoma (EMC)

Population	Patients with unresectable, locally advanced or metastatic solitary fibrous tumor (SFT) or extraskeletal myxoid chondrosarcoma (EMC)
Sample Size	82 patients: Maximum of 30 patients for stratum 1-a (typical SFT), 31 patients for stratum 1-b (malignant/dedifferentiated SFT) and 21 for stratum 2 (EMC).
Treatment	Single arm of pazopanib 800 mg (2x400 mg or 4x200 mg) given as a single agent once daily continuously. Treatment will continue until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient or investigator decision.
Drug Information	Presentation: The IMP pazopanib mono-hydrochloride salt (coded as GW786034B) is produced as tablets containing pazopanib mono-hydrochloride salt equivalent to 400 mg/200 mg of the free base. Refer to pazopanib SmPC for information regarding the physical and chemical properties of pazopanib and a list of excipients. Pharmaceutical form: Film-coated tablet. Route of administration: Oral.
Inclusion Criteria	1. Patients must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up. Informed consent must be obtained prior to start of the screening process. Procedures conducted as part of the patient's routine clinical management (e.g. blood count, imaging tests, etc.) and obtained prior to signature of informed consent may be used for screening or baseline purposes as long as these procedures are conducted as specified in the protocol. 2. Age ≥ 18 years or legal age of consent if greater than 18 years. 3. Histologic diagnosis of solitary fibrous tumor (stratum 1) or extraskeletal myxoid chondrosarcoma (stratum 2) (unresectable, locally advanced or metastatic disease) confirmed by central pathology review. Paraffin-embedded tumor tissue must be provided for all subjects for biomarker analysis before and (when feasible) after treatment with investigational product. 4. Patients with metastatic tumor suitable for complete resection can be recruited. In absence of progressive disease these patients should be treated with the study drug for at least 6 months. 5. For patients who have received previous anticancer treatments, progressive disease must be demonstrated within 6 months prior to enrollment. 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. 7. Measurable disease according to Choi (SFT) and RECIST 1.1 (EMC) criteria. Patients must have at least one measurable lesion (not in a previously irradiated area). If the only measurable disease is in a previously irradiated area, documented progression should exist after radiotherapy within the 6 months prior to enrollment. 8. Patients could have received a maximum of 4 lines of chemotherapy for metastatic disease prior to trial enrollment. 9. Patients must be able to swallow and retain the study drug.

10. Adequate organ system function as defined in the table below:

Table 1: Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (see Appendix A)	≥30 mL/min to ≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; see Appendix B)[d]	<1
Or, 24-hour urine protein	<1g

a. Patients may not have had a transfusion within 7 days of screening assessment.
b. Patients receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
d. If UPC ≥1, then a 24-hour urine protein must be assessed. Patients must have a 24-hour urine protein value <1 g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

11. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days of first dose of study treatment. All patients (both male and female) must agree to use effective contraception methods, as defined in the protocol.

12. Left ventricular ejection fraction (LVEF) must be above the lower limit of normal for the institution, either by echocardiogram or MUGA.

13. Patients in France will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion Criteria

1. Prior malignancy, except patients who have had another malignancy and have been disease-free for 10 years, or those with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma.

2. Central nervous system metastases at baseline, with the exception of patients who have previously-treated central nervous system metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and who meet both of the following criteria: a) are asymptomatic and b) have no requirement for steroids or enzyme-inducing anticonvulsants in prior 6-month time interval.

3. Patients who have received previous antiangiogenic agents.

4. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

    - Active peptic ulcer disease
    - Known intraluminal metastatic lesion(s) with risk of bleeding

- Inflammatory bowel disease (e.g. ulcerative colitis, Chrohn's disease), or other gastrointestinal conditions with increased risk of perforation
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment

5. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:

    - Malabsorption syndrome
    - Major resection of the stomach or small bowel

6. Corrected QT interval (QTc) > 480 msecs.

7. History of any one or more of the following cardiovascular conditions within the past 6 months:

    - Cardiac angioplasty or stenting
    - Myocardial infarction
    - Unstable angina
    - Coronary artery bypass graft surgery
    - Symptomatic peripheral vascular disease
    - Class II, III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)

8. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP/DBP ratio must be <140/90 mmHg (or 150/90 mm Hg) in order for a patient to be eligible for the study.

9. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Patients with recent DVT who have been treated with anti-coagulating agents for at least 6 weeks are eligible.

10. Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (catheter placement and similar procedures are not considered to be major surgery).

11. Evidence of active bleeding or bleeding diathesis.

12. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. Lesions infiltrating major pulmonary vessels (contiguous tumor and vessels) are excluded; however, the presence of a tumor that is touching, but not infiltrating (abutting) the vessels is acceptable (CT with contrast is strongly recommended to evaluate such lesions).

13. Recent hemoptysis (≥½ teaspoon of red blood within 8 weeks before first dose of study drug).

14. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures.

15. Unable or unwilling to discontinue use of prohibited medications listed in the protocol for at least 14 days or 5 half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.

16. Treatment with any of the following anti-cancer therapies:

    - Radiation therapy, surgery or tumor embolization within 28 days prior to the first dose of pazopanib or
    - Chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib

17. Administration of any non-oncologic investigational drug within 30 days or 5 half-lives (whichever is longer) prior to receiving the first dose of study treatment.

18. Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 (except anemia, see Table 1 above) and/or that is progressing in severity, except alopecia.

19. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib.

Procedures and Assessments

Protocol section reference	Study stages >>	BEFORE TREATMENT	TREATMENT										END OF TREATMENT
		Screening (≤ 28 days of start of treatment)	Week 0 Day 1	Week 1 Day 8	Week 3 Day 22	Every 4 Weeks	Week 5	Week 7	Every 8 Weeks	Week 9	Week 12	Week 16	
7.2	**Patient information and consent**												
	Patient information	X (prior to screening)											
	Informed consent	X (prior to screening)											
7.3	**Eligibility and enrollment procedures**												
	Screening number assignment	X											
	Central pathology review	X											
	Eligibility confirmation	X											
	Patient enrollment	X											
7.4	**Clinical assessments**												
	Demographic data and medical history	X											
	ECOG[1]	X	X			X							X
7.5	**Laboratory assessments (+/- 3 days)**												
	Clinical chemistry[2]	X	X	X[3]	X	X	X[2]	X[2]		X[2]	X[2]	X[2]	X
	Hematology	X	X	X	X	X							X
	Coagulation tests	X	X			X							
	Urinalysis for proteinuria (UPC)	X	X			X							
	Thyroid function test	X							X[4]				
	Pregnancy test[5]	X											X
7.6	**Safety assessments**												
	Physical examination	X				X[6]							X
	Vital signs	X	X	X[7]	X	X							X
	Adverse events		X	X	X	X							X
	Concomitant medication	X	X	X	X	X							X
	ECG	X				X[8]							
	LVEF	X											X

7.7	**Efficacy assessments**												
	Thoracic-abdominal CT scan / MRI	X							X				X
	Bone scintigraphy (if clinically indicated)	X	Every 6 months up to progression										
	Central radiology review												X
7.8	**Treatment control**												
	Medication dispensation		X			X							
	Treatment fulfilment					X							X
7.9	**Biological sample collection**												
	Tumor block collection	X(9)											X(10)
	Blood sample collection(11)	X											X

(1) ECOG performance status will be assessed at screening: 14 days and 7 days prior to the start of study drug administration.
(2) Monitoring of LFTs pre and post enrollment. Monitor serum liver tests: Before initiation of treatment with pazopanib. Weeks 3, 5, 7, 9, 12 (month 3) and 16 (month 4). Subsequently, as clinically indicated. Periodic monitoring should continue after month 4.
(3) Hypoglycemia test (Glucose in serum).
(4) Thyroid function test (T4 and TSH) monitored every 8 weeks after 6 months of treatment.
(5) Pregnancy test must be done within 7 days prior to the first treatment administration.
(6) Physical examination every 4 weeks until 6 months of treatment and every 8 weeks after 6 months of treatment.
(7) Monitoring of BP only: A measurement of BP should be taken at day 8+/-3 days. BP can be assessed by any method (i.e. at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.
(8) ECG: Every 4 weeks until 6 months of treatment. Every 8 weeks after 6 months, until end of treatment.
(9) Tumor sample will be collected before treatment.
(10) Selected patients for whom post-treatment biopsy could be performed.
(11) Serum will be collected as described:
- Within 72 hours prior to starting treatment (baseline).
- Within 72 hours after radiological response is documented.
- Within 72 hours after progressive disease is documented.

Design & Statistics

Phase II, open-label, non-randomized, international multicenter clinical trial with three strata (1-a: typical SFT, 1-b: malignant/dedifferentiated SFT, and 2: EMC). 8 sites in Spain, 5 sites in Italy and 5 sites in France. Patients will receive oral pazopanib at 800 mg once daily continuously**.** Patients will continue to receive treatment until there is evidence of progressive disease, unacceptable toxicity, non-compliance, withdrawn consent or investigator decision.

To estimate the sample size for stratum 1 (typical SFT), a 1-stage phase II design has been used, having considered the published response rate based on Choi criteria in SFT patients which correspond to 40% in monotherapy. For a design with P0=0.40, P1=0.60; α=0.1 and β=0.2. Thus, 30 patients should be enrolled into the study, and to reject the null hypothesis for the typical SFT stratum 16 responses or more (Choi criteria), out of the 30 patients, are needed.

To estimate the sample size for stratum 2 (malignant-dediferentiated SFT), a Simon 2-stage phase II design has been used, having considered the published response rate based on Choi criteria in SFT patients which correspond to 40% in monotherapy. For a design with P0=0.40, P1=0.60; α=0.1 and β=0.2. At the first stage, 23 patients should be enrolled into the study, if there are fewer than 12 responses (11 or less) the trial will be terminated and it will be concluded that pazopanib is not sufficiently active. At the second stage, another 8 patients (total 31 patients) would be enrolled into the study. To reject the null hypothesis for the SFT stratum 16 responses or more (Choi criteria), out of the 31 patients, are needed.

To estimate the sample size for stratum 3 (EMC), a 1-stage phase II design has been used, having considered the published response rate based on RECIST criteria. For a design with P0= 0.05, P1= 0.20, α=0.1 and β=0.2. Thus, 21 patients should be enrolled into the study, and to reject the null hypothesis for the EMC stratum 3 responses or more (RECIST criteria), out of the 21 patients, are needed.

	For variables that follow binomial distributions (e.g. response rate) frequency and percentages will be calculated, together with their corresponding exact 95% confidence intervals. For time-to-event variables (e.g. PFS or OS) Kaplan-Meier estimations will be used. To analyze the reduction of risk and the influence of other variables on time-to-event variables Cox Regression will be applied. To correlate pharmacodynamics markers and biomarkers with clinical response standard methods for bivariate and multivariate regression and correlation will be used. Multivariate methods will be used only if the required assumptions are verified.
Analytical Endpoints	*Primary endpoint* • Objective response rate (ORR) (confirmed complete response [CR] and partial response [PR]), measured using Choi and RECIST 1.1 criteria. Response criteria will be based on the baseline identification of target lesions and follow-up until tumor progression. *Secondary endpoints* • Efficacy measured by the progression-free survival (PFS) rate assessed by median time. • Overall survival (OS) measured since treatment start date until date of death, whichever the cause. • Clinical benefit rate (CBR). Patients who have reached CR, PR or SD during 6 months or more, presenting clinical improvement of symptoms, will be considered as having experienced clinical benefit. • Long term safety profile of pazopanib, through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using NCI-CTCAE 4.0.

2. INTRODUCTION

2.1 Background and scientific rationale

Soft tissue and bone sarcomas are rare malignant tumors, which encompass a large family of more than 50 histologically distinct tumor subtypes, all of which share a putative mesenchymal origin. In the case of soft tissue sarcomas (STS), surgical excision is the mainstay of treatment, but despite curative surgery attempt, around 40% of patients will develop distant metastases and die from disease. Few therapeutic approaches are currently available to patients with unresectable, locally advanced, or metastatic STS and only anthracyclines, ifosfamide and trabectedin have shown activity, with response rates of 20–40% in previously untreated patients. Recent and ongoing trials have investigated a variety of combination of chemotherapeutic regimens (mainly based on ifosfamide, doxorubicin and dacarbazine, among others), which have yielded at the most improvements in response rate but which have had little impact on survival. In recent years, some specific treatments have emerged in distinct sarcoma entities deemed more beneficial, in terms of progression free survival and overall survival, than chemotherapy. Examples are PEComa, myofibroblastic inflammatory tumor, alveolar soft part sarcoma, giant cell tumor of bone and other. Thus, there is a critical need of exploring new specific treatments in distinct entities in prospective clinical trials with a robust rationale.

Pazopanib is an oral angiogenesis inhibitor that targets mainly VEGFRs, PDGFRs and c-kit. The results of PALETTE study[1], a phase III trial of pazopanib in STS, showed an active drug in anthracycline pretreated metastatic non-adypocitic STS patients. This is reflected by a 3-fold increase in PFS as compared to placebo although overall survival is not statistically significant. FDA and EMEA approved this drug after failure of prior chemotherapy.

Solitary Fibrous Tumor (SFT)

Hemangiopericytoma (HPC) and solitary fibrous tumors (SFT) are rare soft tissue tumors whose origin and classification have been debated over time. They have been initially separate entities often misdiagnosed for each other, but the latest WHO classification has considered them to be representing two ends of an overlapping spectrum of mesenchymal neoplasm, probably fibroblastic in nature.

Overall, data regarding the long-term outcome of patients with SFT is limited. The estimated incidence is <0.1/100.000/year and SFT is a ubiquitous sarcoma being able to arise from almost all anatomic sites. The natural history of SFT is characterized by a high cure rate after complete surgery, but with a 10-15% risk of metastasis. Metastatic disease is associated with a shortened survival, with lung, bones, and liver being common sites. On the other hand, the percentage of locally advanced disease could be as high as 40% of cases.

Adjuvant radiotherapy has been used to prevent recurrences, but its efficacy still remains to be better studied. Finally, the efficacy of chemotherapy in unresectable and/or metastatic setting is not well established in the current literature. In a retrospective analysis of 36 HPC patients treated at MD Anderson Cancer Center (MDACC), 10 were treated with either neoadjuvant or adjuvant anthracycline therapy. 1/10 experienced major radiographic response (reduction in tumor size > 50%), but chemotherapy did not seem to prolong survival in that group[2]. The Istituto Nazionale dei Tumori reviewed retrospectively the long term outcome of 65 patients operated between 1990-2008.The overall incidence of metastases was 17% (lung was the commonest site). The 5-year post-metastasis overall survival was 45%[3]. Conventional chemotherapy with doxorubicin or ifosfamide achieved just some stable disease with modest duration.

The rich vascular characteristics of SFT have been long recognized. IHC expression of VEGF has been noted both in SFT tumor cells as well as in endothelium, with VEGFR1 and VEGFR2 overexpressed in endothelium only, suggesting that both autocrine and paracrine activation of the VEGF–VEGFR pathway may exist in SFT biology. Data regarding the molecular pathogenesis of SFT overall, however, are quite limited.

Three pathologic variants haven been proposed for SFT: (1) Typical SFT (usually with favorable outcome), (2) Malignant SFT (characterized by higher mitotic index of more than 4 mitosis x 10 HPF; necrosis and pleomorphism) and (3) Dedifferentiated SFT (component of high grade NOS sarcoma).

Due to suspected differences in the outcome between these pathologic variants of SFT, and in order to study these variants deeper, the cohort has been divided into two subgroups: Typical SFT (1-a) (which usually has a more favorable outcome) and malignant/dedifferentiated SFT (1-b) (more aggressive and less responsive).

From a clinical point of view, studying the behavior of the tumor variants that are initially classified in the same groups, separately, will contribute to understanding the future treatments for the different variants.

Novel therapies are currently under development in soft tissue sarcomas, and in SFT. Sunitinib, sorafenib and the combination of temozolomide (TMZ) and bevacizumab (BEV) have demonstrated activity in the literature[4]. Fourteen patients with HPC/SFT who began treatment with TMZ/BEV at MDACC between the time period of May 2005 and June 2007 were analyzed[5]. The main reasons for starting treatment were: Symptomatic disease in 7 neoadjuvant treatments; disease recurrence/progression in 8 and 5 with new development of metastatic disease. Seven patients had metastatic disease at the time of initiation of treatment. The most common site of primary disease was the meninges. No patients had extremities as their primary disease. Eleven out of 14 patients achieved partial response (PR) by Choi criteria after starting TMZ/BEV therapy. PR was seen both as decrease in size, or in density. Best response assessment using conventional RECIST criteria, one patient had a RECIST PR. Median progression-free survival period for the entire group was 8.87 months. Median follow-up period for the group was 20 months. Sunitinib in a retrospective revision of Istituto Nazionale dei Tumori showed in 31 patients clinical benefit (PR+SD) > 60%[6]. Other similar experiences have been seen with sunitinib and sorafenib[6-9], and some isolated with pazopanib[10].

SFT has been related to hypoglycemic caused by paraneoplastic overexpression and secretion of high-molecular-weight insulin-like growth factor II[11]. Additionally, the treatment with figitumumab, an anti-IGFR, has been successful, in combination with sunitinib, in one SFT progressive with sunitinib. On the other hand, it has been shown that most SFT have strongly activated PDGFR B, EGFR and IGFR (interdependency across receptors). The same authors found overexpression of AKTp and mTOR in more aggressive SFT subsets[12].

Interestingly, pazopanib has been related to growth suppression of synovial sarcoma through the inhibition of PI3K pathway[13].

Extraskeletal Myxoid Chondrosarcoma (EMC)

Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant neoplasm characterized by multinodular growth of primitive chondroid cells in an abundant myxoid matrix. It is considered highly resistant to conventional radiation and chemotherapy and surgical removal is the only option for curative treatment. EMC is distinguished from other sarcomas by its unique histology and a characteristic chromosomal translocation, typically t(9;22)(q22;q12.2), fusing EWSR1 to NR4A3 (genes formerly termed EWS and CHN, TEC, or NOR1, respectively). A small proportion of EMC have a different translocation, t(9;17)(q22;q11.2), which results in a RBP56-NR4A3 fusion gene and neuroendocrine differentiation in some cases. The chromosomal translocations result in fusion gene products responsible for alterations in cellular growth and differentiation[14]. Less frequently two different translocations t(9;17)(q22;q11,2) and t (9;15)(q22;q21) have been described also in EMC. Most EMC arise from extremities and limb girdles and typically exhibit a very slow growth. Metastases are reported in at least 50% of cases being soft part and lungs the commonest sites. Patients with metastases can live during long-term, thus almost 60% of metastatic patients live more than 15 years.

Interestingly, a dimensional response has been described in a case report of metastatic EMC treated with sunitinib. The authors postulate an inhibition of autocrine/paracrine VEGFR mechanism instead a direct interaction with the fusion protein derived from specific translocation of EMC[15].

Following the previous knowledge, the GEIS-32 trial plans to explore pazopanib[16] prospectively in locally advanced or metastatic SFT and in a second cohort of EMC patients. This compound could also be more suitable than sunitinib or sorafenib in SFT since pazopanib is a less potent Flt-3 inhibitor being thus less myelosupressive. Moreover, pazopanib has a more favorable safety profile in comparison with sunitinib or sorafenib, a relevant fact considering the potential long-term use in this indication.

2.2 Rationale for pazopanib dose

The pazopanib dose to be used in this study is 800 mg daily. Pazopanib 800 mg once daily is the recommended monotherapy dose based on clinical and preclinical results. Once daily doses of 50 mg to 2000 mg pazopanib were investigated in the “First Time in Human”, Phase I Study VEG10003. Increases in the pazopanib dose above 800 mg once daily when administered in the fasted state did not result in a consistent increase in systemic exposure at steady state. Therefore, no further benefit is expected at pazopanib doses above 800 mg once daily.

Pharmacodynamic data indicate that pazopanib, at a monotherapy dose of 800 mg once daily, results in effects consistent with inhibition of the VEGF receptors it was designed to target. Concentration-effect relationships were observed between trough plasma pazopanib concentrations and the development of hypertension in Study VEG10003 and the percent change from baseline in sVEGFR2 nadir in Study VEG102616. The trough plasma pazopanib concentrations associated with one-half the maximal effect (EC50) in both concentration-effect relationships were similar (21.3 µg/mL and 15.3 µg/mL) and demonstrate that there is a consistent inhibition of VEGF receptor(s) in subjects with cancer when plasma pazopanib concentrations are maintained above 15 µg/mL. The plasma pazopanib EC50 values for biologic effects observed in the clinical studies are similar to the plasma concentration of 40 µM (17.5µg/mL) required for optimal inhibition of VEGFR-2 phosphorylation in mice [GSK Report RH2003/00005/00].

Progression Free Survival (PFS) in subjects with renal cell cancer in Study VEG102616 was compared between subjects whose trough plasma pazopanib concentrations (Cmin) at Week 4 were above or below selected threshold values. The deciles of the observed Cmin values were selected as threshold values so that approximately equal numbers of subjects were included in each Cmin interval. Subjects with a Cmin at Week 4 above the threshold values had significantly better PFS, compared to the remaining subjects, when the threshold concentrations steady were 12.6µg/mL, 17.4µg/mL, and 20.6µg/mL. Use of thresholds higher than 21µg/mL did not result in a significant improvement in PFS between patients with Cmin values above and below the threshold. Patients with Cmin concentrations above 20.6µg/mL also had significantly better response rate and tumor shrinkage than the remaining patients.

Pazopanib C24 at steady state was greater than 15µg/mL in 93% of subjects who received 800 mg once daily in Study VEG10003. Individual subjects receiving pazopanib doses below 800 mg once daily can achieve plasma concentrations over 15µg/mL, albeit at a lower frequency compared with what is observed at 800 mg once daily. Therefore, the pharmacokinetic and pharmacodynamic results across clinical studies demonstrate that pazopanib 800 mg once daily results in plasma concentrations that provide optimal biologic effects associated with VEGFR inhibition in the greatest proportion of subjects.

3. OBJECTIVES

3.1 Primary study objective

- To determine the objective response rate (ORR) (confirmed complete response [CR] and partial response [PR]) in patients with unresectable, locally advanced or metastatic solitary fibrous tumor and extraskeletal myxoid chondrosarcoma, using Choi and RECIST 1.1 criteria respectively.

3.2 Secondary study objectives

- To estimate the efficacy of pazopanib as measured by the progression-free survival (PFS) rate assessed by median time in patients with unresectable, locally advanced or metastatic solitary fibrous tumor and extraskeletal myxoid chondrosarcoma.
- To evaluate overall survival (OS).
- To evaluate clinical benefit rate (CBR).
- To evaluate long term safety profile according to CTCAE 4.0.

3.3 Translational objectives

SFT cohorts:

- To perform a central pathologic review (diagnosis confirmation) of paraffin-embedded tumor blocks for each recruited patient with SFT, including (exploratory) STAT6 immunohistochemistry.
- To evaluate the serum profile of serum cytokine markers as indicator of response to pazopanib. The Luminex technology will be employed for the analysis of 12 cytokines [VEGF-A, PlGF-1, SDF-1 alpha (CXCL12), TNF alpha, IL-8, IL-6, PDGF –beta, HGF, E-Selectine, ICAM1, MMP-9 and FGFb].
- To evaluate the profile of angiogenic markers in the primary tumor and/or in the subsequent biopsies. Microvessel density (MVD) and VEGF/PDGF pathways will be evaluated by IHQ expression as well as their correlation with prognosis and their role as predictive factors to treatment with pazopanib (response, PFS and OS).
- To evaluate pharmacodynamic markers (MVD, VEGF/PDGF) only in patients with paired samples (in the biopsies taken after treatment).

EMC cohort:

- To perform a central pathologic review (diagnosis confirmation) of paraffin-embedded tumor blocks for each recruited patient with EMC, including FISH analysis and/or RT-PCR NR4A3 and its partners (EWSR1, TAF15).
- To evaluate the expression and activation profile of angiogenic targets (VEGFR, PDGFR, RET, MCSR1) in the primary tumor and/or in the subsequent biopsies by immunohistochemistry, pRTK array and IP/WB respectively.

4. SELECTION OF PATIENTS

4.1 Inclusion criteria

1. Patients must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up. Informed consent must be obtained prior to start of the screening process. Procedures conducted as part of the patient's routine clinical management (e.g. blood count, imaging tests, etc.) and obtained prior to signature of informed consent may be used for screening or baseline purposes as long as these procedures are conducted as specified in the protocol.

2. Age ≥ 18 years or legal age of consent if greater than 18 years.

3. Histologic diagnosis of solitary fibrous tumor (stratum 1) or extraskeletal myxoid chondrosarcoma (stratum 2) (unresectable, locally advanced or metastatic disease) confirmed by central pathology review. Paraffin-embedded tumor tissue must be provided for all subjects for biomarker analysis before and (when feasible) after treatment with investigational product.

4. Patients with metastatic tumor suitable for complete resection can be recruited. In absence of progressive disease these patients should be treated with the study drug for at least 6 months.

5. For patients who have received previous anticancer treatments, progressive disease must be demonstrated within 6 months prior to enrollment.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

7. Measurable disease according to Choi (SFT) and RECIST 1.1 (EMC) criteria. Patients must have at least one measurable lesion (not in a previously irradiated area). If the only measurable disease is in a previously irradiated area, documented progression should exist after radiotherapy within the 6 months prior to enrollment.

8. Patients could have received a maximum of 4 lines of chemotherapy for metastatic disease prior to trial enrollment.

9. Patients must be able to swallow and retain the study drug.

10. Adequate organ system function as defined in the table below:

Table 1: Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (see Appendix A)	≥30 mL/min to ≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; see Appendix B)[d]	<1
Or, 24-hour urine protein	<1g

a. Patients may not have had a transfusion within 7 days of screening assessment.
b. Patients receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
d. If UPC ≥1, then a 24-hour urine protein must be assessed. Patients must have a 24-hour urine protein value <1 g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

11. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days of first dose of study treatment. All patients (both male and female) must agree to use effective contraception methods, as defined in the protocol.

12. Left ventricular ejection fraction (LVEF) must be above the lower limit of normal for the institution, either by echocardiogram or MUGA.

13. Patients in France will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.2 Exclusion criteria

1. Prior malignancy, except patients who have had another malignancy and have been disease-free for 10 years, or those with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma.

2. Central nervous system metastases at baseline, with the exception of patients who have previously-treated central nervous system metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and who meet both of the following criteria: a) are asymptomatic and b) have no requirement for steroids or enzyme-inducing anticonvulsants in prior 6-month time interval.

3. Patients who have received previous antiangiogenic agents.

4. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

    - Active peptic ulcer disease
    - Known intraluminal metastatic lesion(s) with risk of bleeding
    - Inflammatory bowel disease (e.g. ulcerative colitis, Chrohn's disease), or other gastrointestinal conditions with increased risk of perforation
    - History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment

5. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:

    - Malabsorption syndrome
    - Major resection of the stomach or small bowel

6. Corrected QT interval (QTc) > 480 msecs.

7. History of any one or more of the following cardiovascular conditions within the past 6 months:

    - Cardiac angioplasty or stenting
    - Myocardial infarction
    - Unstable angina
    - Coronary artery bypass graft surgery
    - Symptomatic peripheral vascular disease
    - Class II, III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)

8. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood

pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP/DBP ratio must be <140/90 mmHg (or 150/90 mm Hg) in order for a patient to be eligible for the study.

9. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Patients with recent DVT who have been treated with anti-coagulating agents for at least 6 weeks are eligible.

10. Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (catheter placement and similar procedures are not considered to be major surgery).

11. Evidence of active bleeding or bleeding diathesis.

12. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. Lesions infiltrating major pulmonary vessels (contiguous tumor and vessels) are excluded; however, the presence of a tumor that is touching, but not infiltrating (abutting) the vessels is acceptable (CT with contrast is strongly recommended to evaluate such lesions).

13. Recent hemoptysis (≥½ teaspoon of red blood within 8 weeks before first dose of study drug).

14. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures.

15. Unable or unwilling to discontinue use of prohibited medications listed in the protocol for at least 14 days or 5 half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.

16. Treatment with any of the following anti-cancer therapies:

    - Radiation therapy, surgery or tumor embolization within 28 days prior to the first dose of pazopanib or
    - Chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib

17. Administration of any non-oncologic investigational drug within 30 days or 5 half-lives (whichever is longer) prior to receiving the first dose of study treatment.

18. Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 (except anemia, see Table 1 above) and/or that is progressing in severity, except alopecia.

19. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib.

4.3 Patient withdrawal criteria

Permanent discontinuation

Patients will receive investigational product until any of the following events occur:

- Disease progression according to RECIST 1.1 for EMC. SFT will be evaluated by Choi criteria and the first evaluation will be at week 8. If the patient has a Choi progression, this will be a reason for discontinuation.
- Unacceptable toxicities or an adverse event that would, in the judgment of the investigator, make continued administration of the study regimen an unacceptable risk
- The patient is considered by the investigator or the Sponsor to be significantly non-compliant with the requirements of the protocol
- A delay in treatment administration longer than 3 weeks

- Study is closed or terminated
- Subject withdraws consent for study participation

The reason for discontinuing treatment must be clearly recorded on the electronic case report form (e-CRF).

A temporary interruption in study medication due to an AE is not considered to be permanent discontinuation from investigational product.

Study withdrawal

Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time. Investigators may also, at their discretion, withdraw the patient from participating in this study at any time, or the Sponsor may discontinue the study.

Reasons for early withdrawal from the study should be documented in the e-CRF, such as:

- Study closed/terminated
- Subject lost to follow-up
- Investigator's decision
- Subject withdrew consent
- Major protocol violations
- Death

Date of withdrawal from the study, with reason for withdrawal, will be recorded on the e-CRF. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.

Patients withdrawn from the trial for any reason cannot enter again.

4.4 Screening failures

A patient is considered to be a screening failure if the he or she signs the informed consent, but withdraws before study enrollment. All potential subjects who are screened in this study (including screening failures) will be listed on the patient screening log but will not be entered in the study database. Reasons for exclusion will be recorded for potential subjects who do not enter the study.

5. TREATMENT

5.1 Pazopanib

Pazopanib is an oral tyrosine kinase inhibitor of the VEGFR, PDGFR and KIT with a dual activity both as an antiagiogenic and also and anti-tumoral agent. It is produced as tablets containing pazopanib monohydrochloride salt equivalent to 200 mg or 400 mg of the free base. Please refer to the pazopanib SmPC for information regarding the physical and chemical properties of the drug and a list of excipients. Pazopanib is provided by GSK.

5.2 Treatment administration

Study treatment can only be started if the patient has signed the informed consent and the site has properly completed the enrollment process.

The treatment consists of pazopanib 800 mg (2x400mg or 4x200 mg) per day (once a day) taken orally without food at least 1 hour before or at least 2 hours after a meal. The time of day for administration of pazopanib should be relatively constant, but it does not need to be recorded on the e-CRF. If a subject misses a dose, the subject should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

Pazopanib should begin within 7 days after enrollment date (longer delays must be discussed with the study CRO).

5.3 Dose interruptions and modifications

As a general rule, if dose reduction of IMP is necessary, the dose should be reduced stepwise by 200 mg at each step, and the subject should be monitored for approximately 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the IMP may need to be interrupted and/or the dose further decreased with continued monitoring for an additional 10-14 days at each dose level, and so on.

If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the IP dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).

If a subject's treatment has been interrupted for more than 21 days, the Investigator must use his/her clinical judgment to assess benefit/risk and contact the GSK Medical Monitor to review the subject's condition in order to resume the treatment.

Table 2: Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Step 1. Continue investigational product (IMP) at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Consider reducing or interrupting IMP, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart IMP dose-reduced by 200 mg if IMP was interrupted.

AE Terms & Descriptions	Dose Modification Algorithms
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt IMP Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4. Once BP is well-controlled, restart IMP dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue IMP and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs. Please refer to ECG section.	
QTc ≥480 < 500 msec	Continue IMP; monitor as clinically indicated.
QTc ≥500 msec	Discontinue IMP and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt IMP. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC ≥3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2. Step 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow-up per protocol.
Hemorrhage/Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	For hemoptysis, interrupt pazopanib and contact the GSK Study Physician to discuss whether further treatment with pazopanib is appropriate. For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue IMP and continue follow-up per protocol. Otherwise, interrupt IMP until the AE resolved to ≤ Grade 1. Step 2. Restart IMP; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue IMP and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue IMP at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt IMP. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume IMP at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on

AE Terms & Descriptions	Dose Modification Algorithms
	anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in IMP dosing (e.g. re-initiating, escalating/de-escalating, or discontinuing IMP), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue IMP and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue IMP and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue IMP with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt IMP until toxicity resolves to ≤ Grade 2. Step 2. Restart IMP dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue IMP and follow-up per protocol.
Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue IMP at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold IMP 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart IMP with a dose reduction to 400 mg 4. If recurrent consider a further dose reduction to 200mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self-care ADLs	1. Discontinue IMP
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue IMP; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt IMP until toxicity resolves to ≤ Grade 1. Step 2. Restart IMP dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue IMP and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4.0)

Abbreviations: BP, blood pressure; IMP, investigational medicinal product.

Dose Modifications and Management of Liver toxicity

Recommendations for IMP dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in the table below. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications (and ensure all are recorded in the e-CRF), and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Record alcohol use on appropriate

forms. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy.

Table 3: Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria:** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Report the event to GSK as an SAE **within 24 hours** of learning of its occurrence and complete the e-CRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then consult a GSK medical monitor before reintroducing pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks. Re-challenge[d] may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. If approval for re-treatment is granted, the subject must be re-consented (with a separate informed consent specific to hepatotoxicity). **Recurrence – Liver Event Stopping Criteria[c]:** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. At the time of the recurrence, complete the e-CRF liver event forms.

Event	Dose Modification Algorithms
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria:** (1) Discontinue pazopanib immediately, report the event to GSK as an SAE **within 24 hours** of learning of its occurrence, and complete the e-CRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 hours to repeat liver chemistries and liver event follow up assessments. (2) Consult a gastroenterologist / hepatologist, and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging - Consider toxicological blood screen for possible contributing chemical/medical entities (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs[a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin elevation without concurrent ALT increases (defined as ALT <3 X ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. (2) If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available.
If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.
c. Please refer to Investigator's Brochure, Summary of Data and Guidance for Investigator, Warning and Precautions, Hepatic Effects for information about rechallenge dose.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; e-CRF, electronic case report form; IMP, investigational medicinal product; LFT, liver function tests; SAE, serious adverse event; ULN, upper limit of normal.

Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly to GSK once the investigator determines that the event meets the protocol definition for that event.

5.4 Treatment overdose

No maximum tolerated dose was reached in dose escalation studies of pazopanib administered as a single agent at doses of up to 2000 mg/day. Pazopanib exposure at higher doses appeared to reach a plateau level at a dose of 800 mg daily. In the event of overdose (defined as administration of more than the protocol-specified dose), investigators should contact the Sponsor's appointed CRO and additional monitoring of the subject for AEs/SAEs and laboratory abnormalities should be considered. Decisions regarding dose interruptions or modifications will be discussed by the investigator in consultation with the Sponsor's coordinating investigators based on the clinical evaluation of the patient. Information regarding the quantity of the excess dose should be documented in the e-CRF.

5.5 Concomitant medications

All patients will be requested to provide a complete list of prescription and medications that have been taken within 4 weeks prior to screening. Investigators must be informed as soon as possible about any new medication(s) taken from the time of screening until the completion of the post-treatment follow-up visit. All concomitant medications taken during the study will be recorded in the electronic case report form (e-CRF) including indication, dose information, and dates of administration. If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

No initial dose reduction permitted

Concomitant medications and non-drug therapies

Please refer to current Investigator's Brochure for list of concomitant and permitted medications.

Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

All concomitant medications taken during the study will be recorded in the electronic case report form (e-CRF) with indication, dose information, and dates of administration.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of $\leq$2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Permitted Medications – Use with Caution

Specific Recommendations Regarding Anticoagulants

Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

Specific Recommendations Regarding Hypoglycemic Therapy Including Insulin

Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib (Billemont, 2008). Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

Specific Recommendations Regarding the Use of Simvastatin and Other Statins

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib dose modification and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

The Effects of Pazopanib on Other Drugs

In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

The Effects of Other Drugs on Pazopanib

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with **CAUTION**.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section on Prohibited Medications); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.
CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. **Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to)**:

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamezepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

Prohibited Medications

Subjects should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] while on treatment in this study.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study. **Strong CYP3A4 inhibitors include (but are not limited to)**:

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole
- Antidepressants: nefazodone

The time period that subjects should not receive any other investigational drugs prior to the first dose of study drug should be specified in the eligibility criteria.

The time period that subjects should not receive any other investigation drugs after receiving the last dose of study drug will depend on the objectives and endpoints of each particular study as well as whether pazopanib is being administered in combination with drugs with longer half-lives. In general, as far as pazopanib is concerned, subjects should not receive any other investigational drug within 15 days of the last dose of pazopanib and until post-treatment blood draws are completed.

Billemont B, Medioni J, Tailade L, Helley D, Meric JB, Rixe O, Oudard S, Blood glucose levels in patients with metastatic renal cell carcinoma treated with sunitinib. British Journal of Cancer. 2008: 99, 1380-1382.

5.6 Supportive care guidelines for diarrhea, nausea and vomiting

These general guidelines are provided to facilitate subject care in the event of diarrhea, thereby avoiding serious complications. Guidelines such as these should never replace sound clinical judgment. Experience thus far suggests that use of monotherapy pazopanib is associated with an increased incidence of diarrhea, primarily of Grade 1 or 2. In rare cases, diarrhea can be debilitating and potentially life threatening, with dehydration, renal insufficiency, and electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology panel for treating chemotherapy-induced diarrhea [Benson, 2004].

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns while on treatment can be identified. An assessment of frequency, consistency, and duration of diarrhea, as well as knowledge of other symptoms such as fever, cramping, abdominal pain, nausea, vomiting, dizziness and thirst should be taken at baseline, permitting identification of patients at high risk of diarrhea. Patients should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the study site physician.

The NCI CTCAE Version 4.0 criteria for defining diarrhea are provided below.

Table 4: NCI CTCAE Version 4.0 Criteria for Defining Diarrhea

Toxicity Grade	**Diarrhea (includes diarrhea of small bowel or colonic origin and/or ostomy diarrhea)**
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living
4	Life threatening consequences, urgent intervention indicated
5	Death

Uncomplicated diarrhea is considered mild to moderate and is defined as CTCAE Grade 1 to 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with one or more of the following signs or symptoms: severe cramping, ≥Grade 2 nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, obvious bleeding, dehydration.

Management Guidelines

Uncomplicated diarrhea of CTCAE Grade 1 or 2

- Hydration: have subject drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
- If Grade 2 diarrhea, consider dose reduction of investigational products.
- Dietary modifications: have subject stop all lactose-containing products and eat frequent, small meals
- Pharmacologic intervention using loperamide:
  - Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
  - Continuation of loperamide is suggested until diarrhea-free for 12 hours.
  - If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes.
  - If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

Complicated diarrhea of CTCAE Grade 3 or 4 diarrhea or Grade 1 or 2 with complicating features requires aggressive management

- Subject must call study site physician immediately in response to any event of severe diarrhea with or without complications as listed above.
- Hospitalization may be required for subjects most at risk for life-threatening complications.
- Interrupt investigational products until symptoms resolve; consider reintroducing at a reduced dose (discuss with GSK Medical Monitor or designee).
- If loperamide has not been initiated, begin loperamide usage immediately at an initial dose of 4 mg followed by 2 mg every 2 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
- If no improvement in severity after 24-hours of maximal loperamide dosing, subject must visit study site and be evaluated.
- For dehydration, use intravenous fluids as appropriate.
- Antibiotic therapy should be considered in patients, who present with signs and symptoms of bacterial diarrhea such as fever, bloody diarrhea, and presence of fecal leukocytes. Investigators should have a low threshold to start such treatment in patients with Grade 3 or Grade 4 neutropenia.
- Before initiation of antimicrobial therapy, stool cultures should be obtained. When bacterial etiology for diarrhea is suspected, study-treatment and anti-motility agents (loperamide or others) should be held.
- Intervention should be continued until diarrhea free for 24 hours.

Alternative pharmacologic intervention for uncomplicated and complicated diarrhea

- Lomotil (dephenoxylate 2.5 mg + atropine 0.025 mg) can be used. The recommended dose is 2 tablets 4 times daily. When diarrhea is under control, a dose reduction should be attempted.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by flouropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 μg twice daily to 500 μg 3 times daily, with a maximum-tolerated dose of 2000 μg 3 times daily in a 5-day regimen.

Nausea and vomiting

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are unable to retain pazopanib.

Routine pre-medication for nausea is not necessary, but symptomatic subjects should be treated with standard anti-nausea/anti-emetic therapy as necessary.

If a subject vomits after taking study medication, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists, then the subject should contact their physician.

To prevent or treat nausea and vomiting standard medications are recommended. Depending upon approved medications in your region, these may include: 5-HT_3 receptor antagonist (granisetron, ondansetron, dolasetron mesylate); NK-1 receptor antagonists such as aprepitant, metoclopramide, phenothiazines (prochlorperazine); corticosteroids, (dexamethasones, prednisone); and cannibinoids (dronabinol).

Reference:
Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA, et al., Recommended Guidelines for the Treatment of Cancer-Inducted Diarrhea. J Clin Oncol. 2004, 22; 2918-26.

6. DRUG MANAGEMENT

6.1 Supply of study drug

Pazopanib (Votrient) is a drug developed and marketed by GSK. In the GEIS-32 trial, pazopanib will be supplied by GSK through the drug distribution company Alcura Health España, S.A.

6.2 Packaging, labelling and distribution

The contents of the investigational product label will be in accordance with all applicable regulatory requirements of each country. The study drug will be labelled and distributed directly to each center pharmacy service by the drug distribution company Alcura Health España, S.A., in coordination with the study CRO.

6.3 Conservation at local pharmacies

Pazopanib must be stored in a secure area under the appropriate physical conditions for the product (pazopanib does not require any special storage conditions). Access to and administration of the investigational product will be limited to the investigators and authorized site staff.

6.4 Dispensation to patients

The investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

6.5 Product accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to the Sponsor, when applicable. Product accountability records must be maintained throughout the course of the study.

6.6 Treatment fulfillment

A record of the number of pazopanib tablets dispensed to and returned by each patient must be maintained and reconciled with the e-CRF. After completion of the study, all unused study drug will be inventoried and either packaged for return shipment to Sponsor or destroyed at the site. Copies of all forms documenting receipt of study drug by the study site and return of study drug (if applicable), together with drug accountability records, will be retained according to the local regulations governing record retention.

6.7 Local pharmacy responsibilities

The responsibilities of the designated responsible pharmacist(s) at each participating center include, but are not limited to, ensuring that:

- Study drug is handled and stored safely and according to product specific requirements;
- The study drug is dispensed only to trial patients and in accordance with the protocol;
- There is a sufficient supply of study drug for patients' continued treatment, and in a timely manner arrange for re-supply of stock;
- Study drug expiry dates are monitored and drug is used in order of expiry date (i.e. earliest expiry first);
- Unused study drug is destroyed locally in accordance with local protocol;
- Study drug receipt, accountability and destruction records are maintained.

7. STUDY PROCEDURES AND ASSESSMENTS

7.1 Calendar of activities

Table 5: Calendar of Activities

Protocol section reference	Study stages >>	BEFORE TREATMENT	TREATMENT										END OF TREATMENT
		Screening (≤ 28 days of start of treatment)	Week 0 Day 1	Week 1 Day 8	Week 3 Day 22	Every 4 Weeks	Week 5	Week 7	Every 8 Weeks	Week 9	Week 12	Week 16	
7.2	**Patient information and consent**												
	Patient information	X (prior to screening)											
	Informed consent	X (prior to screening)											
7.3	**Eligibility and enrollment procedures**												
	Screening number assignment	X											
	Central pathology review	X											
	Eligibility confirmation	X											
	Patient enrollment	X											
7.4	**Clinical assessments**												
	Demographic data and medical history	X											
	ECOG[1]	X	X			X							X
7.5	**Laboratory assessments (+/- 3 days)**												
	Clinical chemistry[2]	X	X	X[3]	X	X	X[2]	X[2]		X[2]	X[2]	X[2]	X
	Hematology	X	X	X	X	X							X
	Coagulation tests	X	X			X							
	Urinalysis for proteinuria (UPC)	X	X			X							
	Thyroid function test	X							X[4]				
	Pregnancy test[5]	X											X
7.6	**Safety assessments**												
	Physical examination	X				X[6]							X
	Vital signs	X	X	X[7]	X	X							X
	Adverse events		X	X	X	X							X
	Concomitant medication	X	X	X	X	X							X
	ECG	X				X[8]							
	LVEF	X											X
7.7	**Efficacy assessments**												
	Thoracic-abdominal CT scan / MRI	X							X				X
	Bone scintigraphy (if clinically indicated)	X	Every 6 months up to progression										
	Central radiology review												X

7.8	**Treatment control**												
	Medication dispensation		X			X							
	Treatment fulfilment					X							X
7.9	**Biological sample collection**												
	Tumor block collection	X(9)											X(10)
	Blood sample collection(11)	X											X

(1) ECOG performance status will be assessed at screening: 14 days and 7 days prior to the start of study drug administration.
(2) Monitoring of LFTs pre and post enrollment. Monitor serum liver tests: Before initiation of treatment with pazopanib. Weeks 3, 5, 7, 9, 12 (month 3) and 16 (month 4). Subsequently, as clinically indicated. Periodic monitoring should continue after month 4.
(3) Hypoglycemia test (Glucose in serum).
(4) Thyroid function test (T4 and TSH) monitored every 8 weeks after 6 months of treatment.
(5) Pregnancy test must be done within 7 days prior to the first treatment administration.
(6) Physical examination every 4 weeks until 6 months of treatment and every 8 weeks after 6 months of treatment.
(7) Monitoring of BP only: A measurement of BP should be taken at day 8+/-3 days. BP can be assessed by any method (i.e. at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.
(8) ECG: Every 4 weeks until 6 months of treatment. Every 8 weeks after 6 months, until end of treatment.
(9) Tumor sample will be collected before treatment.
(10) Selected patients for whom post-treatment biopsy could be performed.
(11) Serum will be collected as described:
- Within 72 hours prior to starting treatment (baseline).
- Within 72 hours after radiological response is documented.
- Within 72 hours after progressive disease is documented.

7.2 Patient information and consent

All candidate patients will receive a patient information sheet (PIS) describing, in simple language, the goals, scope, procedures and relevant implications of the clinical trial. The PIS will integrate an informed consent (IC) form to be signed by the patient, which is indispensable for study participation. Written informed consent must be given by each patient before screening process initiation (prior to undergoing protocol-specific evaluations and prior to receiving treatment). The patient should sign two separate informed consent forms: one for the main study and another one for the biological samples. Subjects must be willing to comply with treatment and follow-up. Procedures conducted as part of the patient's routine clinical management (e.g. blood count, imaging studies such as CT/MRI scans) and obtained prior to signing of informed consent may be utilized for screening/baseline purposes provided these procedures are conducted as specified in the protocol.

7.3 Eligibility and enrollment procedures

Screening number assignment

Once the required informed consent forms have been signed, a unique screening number will be assigned to each patient. Each site will receive inside the Site Investigator File a screening log form with a list of predetermined screening numbers to be assigned. This document should be always at site under the research team custody. This screening number will identify patients throughout the procedures needed to confirm their suitability for the trial protocol (clinical laboratory tests, imaging tests, central pathology review, etc.).

Central pathology review

After screening number assignment, at least one pre-treatment representative formaline-fixed paraffin-embedded tumor block will be collected for central pathology review. First diagnosis sample or another more recent available sample obtained during the routine care previous to study entry will be acceptable. Patients cannot be included in the study unless a tumor block is available. Tumor biopsy at the start of the study is not compulsory but recommended if clinically acceptable. The tumor sample is to be shipped by courier to the central pathology review laboratory (country-based reviewers) along with (1) the trial-specific pathology review form and (2) the center's anonymized pathology report. Diagnosis confirmation from the central pathology reviewer will be available in approximately one week. The central pathology review is a compulsory requirement for trial entry in all cases without exception. The study treatment should not be initiated unless the diagnosis has been confirmed by this means.

An additional document will be provided in the Investigator Site File with detailed tumor collection and shipment procedures.

The main contact point to coordinate tumor block shipments will be:

Sofpromed Investigación Clínica, SLU
Ctra. Valldemossa, Km. 7,4, ParcBit - Edifici Disset
2nd Floor – Office C-7, 07121 Palma de Mallorca, Spain
Telephone: +34 971439900
Mobile: +34 648414261
Fax: +34 971570222
E-mail: ensayos@sofpromed.com

The central pathology reviewers in each country will be:

Spain:

Dr. Enrique de Álava
Hospital Universitario Virgen del Rocío
Department of Pathology
Avda. Manuel Siurot s/n
41013 Sevilla, Spain
Italy:

Dr. Silvana Pilotti
Fondazione IRCCS Istituto Nazionale dei Tumori
Department of Pathology
Via Venezian 1
20133 Milan, Italy

France:

Dr. Dominique Ranchere / Dr. Caroline Renard
Centre Léon Bérard
Department of Pathology
28 Promenade Léa et Napoléon Bullukian
69008 Lyon, France

Eligibility confirmation

The Principal Investigator (PI) of each site will be responsible for confirming that the patient to be recruited meets all inclusion criteria and does not meet the exclusion criteria. Patient enrollment will be carried out after eligibility confirmation.

Patient enrollment

Following completion of all screening procedures and eligibility confirmation, patients will then be enrolled to begin study treatment.

The procedure to enroll a patient is described as follows:

- Complete and sign the patient enrollment form (the form must be signed by an authorized investigator).

- Send (via email or fax) the enrollment form directly to the study CRO in Spain:

Sofpromed Investigación Clínica, SLU
Fax: +34 971570222
E-mail: ensayos@sofpromed.com

- The study CRO will carry out the patient enrollment process and will then send back (via email and fax) to the center the patient enrollment confirmation notification. This notification will contain a unique patient number that will identify the patient at all times during the trial.

Additional documentation will be provided in the Investigator Site File with detailed patient enrollment guidelines.

7.4 Clinical assessments

Demographic data and medical history

Demographic information, past or current medical conditions and treatments, current medications, medications taken within 30 days of inclusion, date of diagnosis, prior cancer therapy and surgery, pathological confirmation of malignancy, and staging of SFT/EMC should be recorded. Any pre-existing toxicity (e.g. Grade 1 fatigue) should be documented and at this time.

ECOG

ECOG performance status will be assessed at screening: 14 days and 7 days prior to the start of study drug administration. Thereafter, every 4 weeks at every treatment visit before the study drug is administered. If subjects discontinue study treatment without disease progression (e.g. withdrawal of study treatment due to unacceptable toxicity), continue the assessments of ECOG performance status in accordance with the disease assessments until subjects experience disease progression.

7.5 Laboratory assessments

Laboratory assessments should be performed as indicated in the trial calendar of activities. These assessments may be carried out within 3 days before the actual visit to allow flexibility in scheduling. Assessments may be performed more frequently if clinically indicated. Correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges should take place prior to study entry and during study conduct as clinically indicated.

All laboratory tests with values that become abnormal and clinically significant while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline. See Section 5 of this protocol for guidance on subject follow-up and dose management in response to specific laboratory abnormalities.

Results for all unscheduled clinical laboratory assessments (e.g. hematology, TSH/T_4, coagulation parameters) should be recorded on appropriate e-CRF forms.

Table 6: Clinical Laboratory Assessments

Clinical Chemistry	
Renal function	Urea, Creatinine[a]
Liver function test (LFT) Panel[b]	Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Bilirubin (total)[c]
Electrolytes and others	Calcium, Potassium, Sodium, Magnesium, Inorganic phosphate, Glucose, and Lactate Dehydrogenase (LDH)
Hematology	Hematocrit, Hemoglobin, White Blood Cell Count, Red Blood Cell Count, Neutrophils, and Platelets

Coagulation Tests	Activated partial thromboplastin (aPTT) and International Normalization Ratio (INR)[d]
Urinalysis for Proteinuria	UPC[e]
Thyroid Function Test	TSH[f]
Pregnancy Test	Pazopanib should not be administered to pregnant or breast feeding women. For women in fertile age, a negative serum or urine pregnancy test must be confirmed (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadatropin [β-HCG]) within 7 days prior to enrollment. Thereafter, the pregnancy test only needs to be repeated if clinically indicated or as required by local regulations. A female is eligible to enter and participate in this study if she is of: Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had a hysterectomy, a bilateral oophorectomy (ovariectomy), a bilateral tubal ligation, or is post-menopausal. Female subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L). Female subjects using HRT must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to the first dose of study treatment. All patients (male and female) must agree to use adequate contraception methods. The acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows: • Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product • Oral contraceptive, either combined or progestogen alone • Injectable progestogen • Implants of levonorgestrel • Estrogenic vaginal ring • Percutaneous contraceptive patches • Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year • Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject • Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository) Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

a. Estimated creatinine clearance should be calculated using the Cockroft and Gault method (Appendix A). Alternatively, creatinine clearance can be measured directly by 24-hour urine collection.
b. Monitoring of LFTs pre and post enrollment. Monitor serum liver tests: Before initiation of treatment with pazopanib. Weeks 3, 5, 7 and 9. Month 3. Month 4. Subsequently, as clinically indicated. Periodic monitoring should continue after Month 4.
c. A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 X upper limit of normal (ULN). See treatment section for stopping criteria and dose modification guidelines for treatment-emergent liver function abnormality.
d. Coagulation tests may also be performed in response to an AE/SAE of bleeding and as clinically indicated.
e. UPC should be evaluated as described in Appendix B or by 24-hour urine protein. If UPC ≥ 3 or if urine protein is ≥3g, then the dose modification table guidelines should be followed.
f. Unscheduled thyroid function tests [TSH and thyroxine (free T_4)] should be performed if clinically indicated (e.g. if a subject develops signs and symptoms suggestive of hypothyroidism).

7.6 Safety assessments

Any patient included in the study receiving at least a single dose of study medication will be evaluable for the toxicity analysis. Safety profile will be characterized by treatment-emergent adverse events, vital signs and laboratory abnormalities. Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), timing, seriousness, and relatedness; and laboratory abnormalities. Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency. In each study visit all adverse events will be registered.

Physical examination and vital signs

Pre-treatment (screening): Evaluation by body system, height, weight, body surface area (BSA) and measurement of vital signs (blood pressure and body temperature).

During treatment and follow-up: Evaluation by body system, weight, body surface area (BSA) and verification of patient blood pressure measurements, at every treatment visit (before study drug administration) and at every follow-up visit.

Adverse events

The CTC-AE version 4.0 will be used to evaluate the clinical safety of the treatment in this study. Subjects will be assessed for AEs at each clinical visit and as necessary throughout the study.

Concomitant medication

The use of any natural/herbal products or others “folk remedies” should be discouraged but use of these products, as well as use of vitamins or nutritional supplements and all others concomitant medications must be recorded in the electronic case report form (e-CRF). Any medications, with the exceptions noted in section 5 of this protocol, which are considered necessary for patient´s welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator, registering the medication, doses, dates and reasons for administration in the e-CRF.

ECG

A baseline ECG is to be obtained within 14 days prior to inclusion. Then, every 4 weeks in the first 6 months of treatment, and every 8 weeks after 6 months, until end of treatment.

LVEF

MUGA or echocardiogram will be performed at baseline and at the end of treatment. A MUGA scan is the preferred method for left ventricular ejection fraction (LVEF) measurement. If a MUGA scan cannot be performed, an echocardiogram should be done. The same type of LVEF assessment must be performed at baseline and at all subsequent points in the study. A MUGA scan should be performed sooner if a subject develops signs and symptoms of congestive heart failure (e.g. shortness of breath during mild exertion or when lying down, feeling very tired, cough -especially at night-, swelling of the feet and/or ankles).

7.7 Efficacy assessments

Thoracic-abdominal CT scan / MRI

Imaging tests will be performed with thoracic-abdominal CT scan (contrast enhanced, biphasic) or MRI as appropriate. Imaging methods will be employed consistently during the course of each patient's evaluation along the study. Disease should be captured and target/non-target lesions identified at baseline. All the baseline disease assessments should be completed within 28 days prior to the date of inclusion in the trial. Subsequently, imaging studies required to investigate known disease should be done every 8 weeks (until tumor progression is documented in patients with complete response, partial response or stable disease). Patients who have not progressed but discontinued treatment due to toxicity or other reasons (unrelated to tumor progression) will still be re-evaluated every 8 weeks, unless they have started a new anti-cancer therapy.

Table 7: Choi/RECIST Criteria for Response Evaluation

	Choi	**RECIST**
Complete Response (CR)	Disappearance of all lesions. No new lesions.	Disappearance of all lesions
Partial Response (PR)	Decrease in size ≥ 10% of SLD or decrease of density ≥ 15% UH. No new lesions. Absence of progression of non-measurable disease.	Decrease of 30% of the sum of the diameters of target lesions
Stable Disease (SD)	Does not fulfill CR, PR or DP. There is no symptomatic deterioration attributable to tumor progression.	Between PR and DP
Disease Progression (DP)	A tumor increase ≥ 10% of SLD and without PR criteria for the radiological density in the CT scan. New lesions. New intra-tumor nodules or increase of existing nodules or increase of tissue part of a hypodense lesion	Increase of 20% of the total diameter or appearance of new lesions

* SLD: Sum of longest diameter (based on RECIST 1.1).

To perform the radiological studies, the following protocols will have to be applied:

Computed Tomography

- Pre-contrast examination.
- Contrast examination: To be performed using 120 ml of a conventional iodinated contrast agent, administered intravenously by an automated injector at a rate of 4 ml/sec; the contrast examination will be done in: arterial phase (delay: bolus tracking), portal phase (60 sec), delayed phase (6 min).
- Coronal mpr in delayed phase.
- Tumor density will be determined by measuring CT attenuation coefficient in Hounsfield Unit (HU) by drawing a region of interest around the margin of the entire tumor, using section thickness of 5 mm in the portal and delayed phase. Two-dimensional regions of interest of the entire lesion will be drawn, and all axial sections encompassing the lesion will be included. Software will calculate semiquantitatively the mean tumor attenuation in HU defined as the average of all the pixels enclosed in the volume of interest.
- It is strongly recommended to use CT scan when feasible, instead of MRI.

Magnetic Resonance

- Morphological pre-contrast examination: Always Axial T1 SE, and T2 FSE (with or without fat pre-saturation) or STIR, other sequences depending of local practice.
- Diffusion study: Axial b50, b400, b800, b1000.
- Dynamic examination:
  Before contrast injection: GE 3D TR less than 1 min Variable Flip angle (5, 10, 15, 20, 25, 28).
  During contrast injection: GE 3D TR less than 1 min (if possible 4 sec) for 5 min.
- Morphological post-contrast examination: Coronal or sagittal T1W sequence with fat sat; Axial T1 SE without fat sat.

- Tumor enhancement after contrast will be determined by measuring MR signal by drawing a region of interest around the margin of the entire tumor in the subtracted series from Axial-T1-SE after CE minus Axial-T1-SE before contrast (parameters and position must be identical in both sequences). Two-dimensional regions of interest of the entire lesion will be drawn, and all axial sections encompassing the lesion will be included. Software will calculate semi-quantitatively the mean tumor signal as the average of all the pixels enclosed in the volume of interest.

Bone scintigraphy

Bone scintigraphy is to be performed (if clinically indicated) in the screening stage and every 6 months up to progression.

Central imaging review

All imaging tests will be centrally reviewed (at international level) by using a web-based platform. The person in charge of performing these reviews will be a radiologist designated by the GEIS Group.

It is strongly recommended to upload the baseline CT/MRI scan before patient enrollment. If this is not feasible, it should be done as soon as possible. All tumor imaging tests performed during the clinical trial should be uploaded to the imaging platform as soon as possible. All scans generated should be exportable in electronic format (DICOM) to enable secure and rapid electronic transmission to the designated central imaging laboratory.

All scans will be anonymized before upload and identified only with the patient's unique trial number. A central radiology review report will be generated as per specific form.

For any issue regarding central imaging reviews, please contact:

Sofpromed Investigación Clínica, SLU
Ctra. Valldemossa, Km. 7,4, ParcBit - Edifici Disset
2nd Floor - Office C-7, 07121 Palma de Mallorca, Spain
Telephone: +34 971439900
Mobile: +34 648414261
Fax: +34 971570222
E-mail: ensayos@sofpromed.com

An additional document will be provided in the Investigator Site File with detailed central imaging upload information.

7.8 Treatment control

Medication dispensation

At the pharmacy service of each hospital sufficient pazopanib tablets are to be dispensed to patients in order to complete 4-week treatment periods.

Treatment fulfilment

In the medical diary of the patient the total number of pazopanib tablets taken and returned by the patient must be written. This information is to be entered in the e-CRF.

7.9 Biological sample collection

Tumor block collection

A paraffin-embedded block will be collected during the screening period for central pathological review. First diagnosis sample or another more recent available sample obtained during the routine care previous to study entry will be acceptable. Tumor biopsy at study entry will not be compulsory but recommended if clinically acceptable (e.g. superficial or easily accessible locations). It is strongly recommended if the previous histological material of the patient stems from more than one year in cases with pauci-symptomatic disease or in any fast growth rate tumor, before enrollment. The main reason is that in some surgical series there were focal poorly differentiated areas (which could be absent in the shipped block) in cases that ultimately died after metastatic recurrence of the anaplastic component. A post-treatment tumor sample will be collected when possible (selected patients for whom post-treatment biopsy could be performed). Please see the translational research section for more details on tumor block collection.

Blood sample collection

Serum will be collected as described:

- Three 5-mL tubes within 72 hours prior to starting the treatment (baseline).
- Three 5-mL tubes within 72 hours after radiological response is documented.
- Three 5-mL tubes within 72 hours after progressive disease is documented.

7.10 Survival

All patients should be followed until death, if possible. The date and cause of death must be evaluated and documented in the e-CRF. Follow up visits should take place every 12 weeks after tumor progression. In these visits patient status will be assessed (alive, dead, lost to follow up), as well as any new anti-cancer treatments.

8. PHARMACOVIGILANCE

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. Any event involving adverse drug reactions, illnesses with onset during the study or exacerbations of pre-existing illnesses should be recorded. In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g. ECG) should also be recorded as adverse events. The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- test result is associated with clinically significant symptoms, and/or
- test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
- test result is considered to be an adverse event by the investigator.

8.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with the study treatment.

Adverse Reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

Any untoward medical occurrence or effect that at any dose:

- results in death (is fatal),
- is life-threatening,
- requires or prolongs inpatient hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect, or
- is medically significant.

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

Any suspected transmission of an infectious agent through the medication is also considered a SAE. Additionally, all hepatotoxicities as defined below are also considered SAEs for the purposes of this clinical trial:

- ALT > 3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin ≥ 2.0 x ULN, with direct bilirubin > 35%) or with hypersensitivity symptoms (e.g. fever, rash) —bilirubin fractionation should be performed if testing available.

- ALT > 8.0 x ULN without bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g. fever, rash) —bilirubin fractionation should be performed if testing available.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a SAR that is classified as 'unexpected' (i.e. a serious adverse reaction), the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics for that product.

The last version of Summary of Product Characteristic available in EMEA website will be the reference document to establish the AE expectedness for pazopanib.

Life Threatening Event

It is any event in which the subject 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.

Hospitalization / Prolongation of Hospitalization

Any event requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical study must be reported as a serious adverse event. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the investigator or treating physician.

Hospitalizations that do not meet criteria for serious adverse event reporting are:

a) Reasons described in protocol (e.g., drug administration, protocol-required investigations). Hospitalizations or prolonged hospitalization for a complication of therapy administration or procedures will be reported as Serious Adverse Event.
b) Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an adverse event.
c) Pre-planned hospitalizations (i.e., planned before study entry). Any surgery or procedure planned before study entry must be documented on the case report form.

Unexpected Adverse Reaction

An unexpected adverse reaction, the nature or severity of which is not consistent with the applicable product information.

The last version of Summary of Product Characteristic available in EMEA website will be the reference document to establish the AE expectedness for pazopanib.

AE Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the causality assessment is related to study drug or is unknown according to definitions listed below.

Causality Assessment

The investigator must provide an assessment of causality of the study drug according to the following criteria:

- **Yes.** There is a reasonable chance that the study drug caused the SAE.
- **No.** There is not a reasonable chance that the study drug caused the SAE and other causes are more likely.
- **Unknown.** It should only be used in special situations where the investigator has insufficient information (e.g. the patient was not attended in his/her center) and when none of the above options can be utilized.

8.2 Adverse event reporting

The Sponsor (through the appointed CRO in charge of pharmacovigilance) will collect AEs up to 30 days after administration of the last dose of study drug. All adverse events must be recorded using medical terminology in the source document and the electronic CRF. Investigators must assess the severity (grade) of the event

following NCI-CTCAE 4.0 criteria and assign a relationship to study therapy and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification. The investigator must provide any information as requested by the Sponsor in addition to that collected on the e-CRF.

Any serious adverse events which occur from patient informed consent signature, during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol-specific diagnostic procedures or interventions must also be reported. Beyond this period of time, only those SAEs suspected to be related to the study drug will be reported.

All SAEs suspected to be related to study treatment should be followed after the treatment/study withdrawal until the event or its symptoms have resolved or stabilized at a grade acceptable to the investigator, coordinating investigator and/or Sponsor.

Site investigation staff should notify the Sponsor (via the appointed CRO) all the pregnancies of female subjects that occurred during the clinical trial within 24 hours from becoming aware. Site investigation staff, should also communicate the outcome of the pregnancy within 24 hours since the awareness.

The cause of death of a deceased patient in a clinical trial, whether the case of an expected event or associated with the investigational agent, is considered an SAE and therefore must be communicated using the SAE form. The autopsy report should be sent to Sponsor identified only with the patient trial number.

Additionally, all hepatotoxicities as defined below are also considered SAEs for the purposes of this clinical trial:

- ALT > 3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin ≥ 2.0 x ULN, with direct bilirubin > 35%) or with hypersensitivity symptoms (e.g. fever, rash) —bilirubin fractionation should be performed if testing available.

- ALT > 8.0 x ULN without bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g. fever, rash) —bilirubin fractionation should be performed if testing available.

All SAEs and SUSARs, taking place in any country, must be directly communicated by fax or email within 24 hours to the study CRO in Spain:

Sofpromed Investigación Clínica, SLU
Telephone: +34 971439900
Mobile: +34 648414261
Fax: +34 971570222
E-mail: ensayos@sofpromed.com

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to the study CRO in Spain within 24 hours.

All SAEs suspected to be related to study drug must be followed up after the time of therapy discontinuation until the event or its consequences resolve or stabilize at an acceptable level for the investigator, the coordinating investigator and/or Sponsor.

8.3 SUSAR reporting

The Sponsor (through its appointed CRO) will be responsible for the reporting of SUSARs to regulatory authorities. The Sponsor will follow the procedure detailed in the current version of the document “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use” available at EMEA website.

All suspected unexpected serious adverse reactions (SUSAR) will be reported in accordance with current regulations on clinical trials in Europe, to the competent authority and ethics committees and investigators within the time and procedure established by the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" and following any local regulations.

Terms of SUSAR Expedited Notification to Regulatory Authorities

The maximum period for reporting shall be 15 calendar days from first knowledge by the Sponsor of the suspected adverse reaction. When the suspected serious unexpected adverse reaction is fatal or life-threatening, the Sponsor shall notify within a maximum of 7 calendar days from first knowledge by the Sponsor of the case. This information must be completed as far as possible within eight additional calendar days. This information should include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medication.

Expedited Reporting, Other Relevant Safety Information

The Sponsor shall notify (as soon as possible and no later than 15 days) any information which would alter the risk/benefit of the investigational drug, or to determine changes in dosage schedule or conduct of trial, for example:

- A qualitative change or an increase in the percentage of occurrence of the SAR expected, it is considered clinically significant.
- The SUSAR occurring after completion of a clinical trial reported by the investigator to the Sponsor.

New information concerning the conduct of the trial and likely to affect the safety of subjects, should be reported, including:

- Serious adverse events that may be associated with the test procedures and can modify the performance thereof.
- A significant risk to subjects such as lack of efficacy of the investigational drug used to treat a life threatening illness.
- Relevant safety new findings from animal studies (as formation of cancer).
- Any premature termination or temporary closure of a clinical trial with the same investigational drug for safety reasons, made in another country and by the same Sponsor.
- The Severe Adverse Reaction related solely to non-IMP considered relevant (as they are not subject to the general rules for expedited reporting of individual cases of SUSAR).

Furthermore, if relevant information is obtained, it will be notified as soon as possible.

Notification to Investigators

The Sponsor shall report the investigators any information that may affect the safety of trial subjects, as soon as possible. In addition, the Sponsor shall inform the researchers of the safety issues that impact the conduct of the clinical trial.

9. DATA MANAGEMENT

9.1 Electronic case report form (e-CRF)

In this protocol the term electronic case report form (e-CRF) refers to a web-based electronic data record in which the patient data will be collected.

An e-CRF is required to be completed by each participating site for each recruited patient. Only duly authorized and trained staff of each center will be granted access to enter and modify data in the e-CRF. Staff in charge of e-CRF usage will be given a unique user name and password.

The completed original electronic CRF files are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or regulatory authorities, without written permission from the Sponsor.

The investigators have the ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the e-CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic, attributable, complete, consistent, legible, timely, enduring and available when requested. The e-CRF must be signed electronically by the investigator or by an authorized staff member to attest that the data contained in the e-CRF is true. Any changes to entries made in the e-CRF will be tracked by an audit trail system that will identify the old and new values of the data fields, the person who made the change and the reason of modification (if necessary), thus not obscuring the original entry.

The data will be recorded in the e-CRF GCP-compliantly at the study center. The e-CRF application (FDA and EMEA compliant) is designed to be entirely server-based. All stages in the processing, with the exception of the actual data entry and display, are performed centrally on a web/database server. All the data will be stored in the central server. The server will be securely housed at a professional hosting provider hired by the study CRO in Spain, guaranteeing effective security and backup mechanisms.

For data entry and print-outs, the e-CRF system is based fully on the so-called “web interface”. Entry forms and reports are displayed on the client computer as HTML pages via any Web browser (IE 6+, FireFox 2+, Chrome, Safari 3+). No additional software is necessary to operate the e-CRF on the investigator’s client computer (no plugin installations or software/hardware adaptations needed). The e-CRF is operating system independent (Win/Mac).

The data will be checked for correctness by validity and consistency checks. Implausible or missing data can be corrected or supplemented following discussion with the investigator. All corrections will be tracked and stored by the audit trail system.

Other than the investigator, only expressly authorized persons trained for the study may complete the e-CRF. Access control will be implemented by an auditable registry of user logins and logouts. Automatic session logouts will be implemented after predefined periods of inactivity for security reasons. The e-CRF will not show patient personal identification data (each subject will be identified by a unique trial number only).

A comprehensive Data Management Plan will be developed by the study CRO specifying e-CRF/Database design and data-related procedures and policies.

9.2 Record keeping

To permit evaluations, audits and/or inspections from regulatory authorities or the Sponsor, investigators agree to keep records, including the identity of all participating patients (e.g. enough information to link records), all original signed informed consent documents, safety reporting forms, source documents and appropriate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be kept by the investigator according to International Conference on Harmonisation (ICH) and local regulations. In case an investigator becomes unable for any reason to continue the retention of study records for the required period, the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor. Investigators must receive the Sponsor’s written permission before disposing of any records.

10. MONITORING

The study will be monitored by regular onsite visits (two monitoring visits during the study and one closing visit), telephone calls and periodic inspection of the e-CRF with enough frequency to ascertain the following:

- Investigational medicinal product (IMP) storage conditions, sufficiency of drug supply for the trial.
- Compliance with approved protocol and all approved amendments, if any.
- That the investigator receives all documents and all trial supplies needed to conduct the trial properly and to comply with the applicable regulations.
- That the investigator and trial staff is adequately informed about the trial.
- Integrity and accuracy of data (as per monitoring plan):

    i. Informed consent (version, signature and date)
    ii. Eligibility criteria
    iii. Baseline tests
    iv. Adverse event collection
    v. SAE and SAE reporting
    vi. Biological samples storage and collection
    vii. Drug stock reconciliation in pharmacy

- e-CRF completion
- Reporting of protocol deviations according GCPs and the applicable regulatory local requirements. Taking appropriate action to prevent recurrence to the detected deviations.

The study appointed CRO will review the e-CRFs for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be sent to the relevant center for resolution. Any systematic inconsistencies identified may trigger monitoring visits to centers. Following the required reviews, the e-CRF data items will be exported into the clinical study database for further analysis.

The onsite monitoring visits of the trial will be carried out by the CRO Sofpromed Investigación Clínica, SLU in Spain, and in some cases by duly appointed monitoring agents/partners in the other participating countries.

Monitoring visits will be done by qualified study monitors. It is understood that these monitors will have access to the clinical records after asking the investigators. Adequate time for these visits should be allocated by the investigators. The investigators will also ensure that the monitor is given direct access to the relevant documents.

When a monitoring visit is required, monitors will contact the center to discuss dates of proposed visit. Once a date has been confirmed, the center should ensure that the relevant patient source documents are available for monitoring.

If any problems are detected in the course of the monitoring visit, the study CRO (or the delegated agent/partner in the country) will work with the Principal Investigator to resolve issues and, if necessary, to determine the center's future participation in the study.

Monitors will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol, and to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 (and its subsequent amendments).

11. STUDY DESIGN AND STATISTICS

11.1 Study design

GEIS-32 is a phase II, open-label, non-randomized, multicenter clinical trial with three strata (1-a typical SFT, 1-b malignant/dedifferentiated SFT and 2 EMC). The study will be developed at international level with 8 sites in Spain, 5 sites in Italy and 5 sites in France, during a recruitment period of 36 months. Patients will receive oral pazopanib at 800 mg once daily continuously. Patients will continue to receive treatment until there is evidence of progressive disease, unacceptable toxicity, non-compliance, withdrawn consent or investigator decision. The IMP will be investigated separately in the cohorts.

11.2 Study endpoints

Primary endpoints

- Objective response rate (ORR) (confirmed complete response [CR] and partial response [PR]), measured using Choi and RECIST 1.1 criteria. Response criteria will be based on the baseline identification of target lesions and follow-up until tumor progression.

Secondary endpoints

- Efficacy measured by the progression-free survival (PFS) rate assessed by median time
- Overall survival (OS) measured since treatment start date until date of death, whichever the cause.
- Clinical benefit rate (CBR). Patients who have reached CR, PR or SD during 6 months or more, presenting clinical improvement of symptoms, will be considered as having experienced clinical benefit.
- Long term safety profile of pazopanib, through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well physical explorations and laboratory tests. Toxicity will be graded and tabulated by using NCI-CTCAE 4.0.

11.3 Sample size and analytical methodology

To estimate the sample size for stratum 1 (typical SFT), a 1-stage phase II design has been used, having considered the published response rate based on Choi criteria in SFT patients which correspond to 40% in monotherapy. For a design with P0=0.40, P1=0.60; α=0.1 and β=0.2. Thus, 30 patients should be enrolled into the study, and to reject the null hypothesis for the typical SFT stratum 16 responses or more (Choi criteria), out of the 30 patients, are needed.

To estimate the sample size for stratum 2 (malignant-dediferentiated SFT), a Simon 2-stage phase II design has been used, having considered the published response rate based on Choi criteria in SFT patients which correspond to 40% in monotherapy. For a design with P0=0.40, P1=0.60; α=0.1 and β=0.2. At the first stage, 23 patients should be enrolled into the study, if there are fewer than 12 responses (11 or less) the trial will be terminated and it will be concluded that pazopanib is not sufficiently active. At the second stage, another 8 patients (total 31 patients) would be enrolled into the study. To reject the null hypothesis for the SFT stratum 16 responses or more (Choi criteria), out of the 31 patients, are needed.

To estimate the sample size for stratum 3 (EMC), a 1-stage phase II design has been used, having considered the published response rate based on RECIST criteria. For a design with P0= 0.05, P1= 0.20, α=0.1 and β=0.2. Thus, 21 patients should be enrolled into the study, and to reject the null hypothesis for the EMC stratum 3 responses or more (RECIST criteria), out of the 21 patients, are needed.

For variables that follow binomial distributions (i.e. response rate) frequency and percentages will be calculated, together with their correspondent exact 95% confidence intervals. For time-to-event variables (i.e. PFS or OS) Kaplan-Meier estimations will be used. To analyze the reduction of risk and the influence of other variables on time-to-event variables Cox Regression will be applied. To correlate pharmacodynamics markers and biomarkers with clinical response standard methods for bivariate and multivariate regression and correlation will be used. Multivariate methods will be used only if the required assumptions are verified.

11.4 Efficacy analysis

Disease should be captured (with CT or MRI scan) and target/non-target identified at baseline. All the baseline disease assessments should be completed within 28 days prior to the date of inclusion in the trial. Subsequently, imaging studies required to investigate known disease should be done every 8 weeks (until tumor progression is documented in patients with complete response, partial response or stable disease). Patients who have not progressed but discontinued treatment due to toxicity or other reasons unrelated to tumor progression will still be re-evaluated every 8 weeks, unless they have started a new anti-cancer therapy.

Efficacy assessment populations:

- Intent to treat (ITT) analysis: Efficacy analysis will be carried out in the ITT population. All patients participating in the study will be included in the analysis of efficacy.
- Per Protocol (PP) analysis: Efficacy analysis will be carried out in per protocol population. All patients participating in the study and having received at least 3 weeks of treatment with pazopanib with no major protocol deviations will be included in the analysis of efficacy.

11.5 Safety analysis

Any patient included in the study receiving at least a single dose of study medication will be evaluable for the toxicity analysis. Safety profile will be characterized by treatment-emergent Adverse Events (TEAE), vital signs and laboratory abnormalities. Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), timing, seriousness, and relatedness; and laboratory abnormalities. Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency. In each study visit all adverse events will be registered according to NCI-CTC version 4.0.

12. TRANSLATIONAL STUDY

12.1 Rationale

SFTs show a well-developed and characteristic pattern of thin-walled branching hemangiopericytoma-like vessels under the microscope. There is a strong clinical benefit of antiangiogenic therapy in relapsed SFT. Nevertheless, the mechanisms regulating neoangiogenesis in SFT have not been described. Pazopanib is a tyrosine kinase inhibitor (TKI) that targets many angiogenic factors, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFRa, PDGFRb and c-KIT. Then, the impact of pazopanib on the angiogenic process in SFT will be investigated. EMC is a very rare soft tissue sarcoma little responsive to standard cytotoxic chemotherapy. There are preliminary data on the activity of sunitinib in this histotype. The mechanism of action of antiangiogenic in this sarcoma is still to be defined.

12.2 Translational objectives

SFT cohorts:

- To perform a central pathologic review (diagnosis confirmation) of paraffin-embedded tumor blocks for each recruited patient with SFT, including (exploratory) STAT6 immunohistochemistry.

- To evaluate the serum profile of serum cytokine markers as indicator of response to pazopanib. The Luminex technology will be employed for the analysis of 12 cytokines [VEGF-A, PlGF-1, SDF-1 alpha (CXCL12), TNF alpha, IL-8, IL-6, PDGF –beta, HGF, E-Selectine, ICAM1, MMP-9 and FGFb].

- To evaluate the profile of angiogenic markers in the primary tumor and/or in the subsequent biopsies. Microvessel density (MVD) and VEGF/PDGF pathways will be evaluated by IHQ expression as well as their correlation with prognosis and their role as predictive factors to treatment with pazopanib (response, PFS and OS).

- To evaluate pharmacodynamic markers (MVD, VEGF/PDGF) only in patients with paired samples (in the biopsies taken after treatment).

EMC cohort:

- To perform a central pathologic review (diagnosis confirmation) of paraffin-embedded tumor blocks for each recruited patient with EMC, including FISH analysis and/or RT-PCR NR4A3 and its partners (EWSR1, TAF15).

- To evaluate the expression and activation profile of angiogenic targets (VEGFR, PDGFR, RET, MCSR1) in the primary tumor and/or in the subsequent biopsies by immunohistochemistry, pRTK array and IP/WB respectively.

12.3 Biological sample collection

The samples to be collected for both SFT and EMC patients are:

1. One representative paraffin-embedded tumor block of the diagnostic biopsy/resection (mandatory) taken at pre-treatment stage (screening).

2. Three 5-mL tubes of peripheral blood within 72 hours prior to starting treatment (baseline).

3. One representative paraffin-embedded tumor block (selected patients for whom post-treatment biopsy could be performed).

4. Three 5-mL tubes of peripheral blood within 72 hours after radiological response is documented.

5. Three 5-mL tubes of peripheral blood at the end of treatment (within 72 hours after progressive disease is documented).

12.4 Translational analytical methods

In the case of serum, the kinetic profile of each biomarker will be considered (increased, constant, decreased). All parameters analyzed will be correlated with progression-free survival (PFS), objective tumor response, overall survival (OS) and histopathological parameters.

For the statistical analysis, binary variables will be used, which will reflect the positivity status of measurements (yes/no; presence; absence).

The association with histopathological parameters and objective tumor response, all categorical, will be calculated through chi-squared test in order to determine the homogeneity or lineal tendency for the ordinary variables.

The statistical significance level will be of 5%. With the aim of studying the impact of histology, immunohistochemistry and molecular factors on PFS and OS, the proportional method Kaplan-Meier (log rank) will be used. The evidence of relative risk for each patient will be provided by means of a Cox proportional hazards model, by using a stepwise selection to identify the independent predictors of poor outcome.

Multivariate analysis will be performed for the biomarker study if the number of cases available for the study is at least 10-fold the number of variables involved. Otherwise, standard univariate pre and post tests will be used.

For the shipment of biological samples, please contact:

Sofpromed Investigación Clínica, SLU
Ctra. Valldemossa, Km. 7,4, ParcBit - Edifici Disset
2nd Floor - Office C-7, 07121 Palma de Mallorca, Spain
Telephone: +34 971439900
Mobile: +34 648414261
Fax: +34 971570222
E-mail: ensayos@sofpromed.com

An additional document will be provided in the Investigator Site File with detailed guidelines regarding biological sample management.

13. ETHICS AND REGULATORY ASPECTS

13.1 Institutional review board / ethics committees

The study protocol and/or related documents will be submitted to institutional review boards/ethics committees, according to local regulations in each country, before commencement of the clinical trial. These approvals are indispensable for study start-up.

13.2 Regulatory authorities

The study protocol and/or related documents will be submitted to regulatory authorities before commencement of the clinical trial, as national authorities on each country require. These authorities are the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) of Spain, the Agenzia Italiana del Farmaco (AIFA) of Italy and the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) of France.

13.3 Ethical conduct of the study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki adopted by the 18th World Medical Association General Assembly, Helsinki, Finland.

The study will be carried out in conformity with the requirements of the "Declaration of Helsinki" adopted by the 18th World Medical Association General Assembly held in Helsinki, Finland, June 1964 and revised by the 29th World Medical Association General Assembly held in October 1975 in Tokyo, the 35th World Medical Association General Assembly held in Venice in October 1983, the 41st World Medical Association General Assembly celebrated in Hong Kong in 1989, the 48th World Medical Association General Assembly held in Somerset West, South Africa in October 1996, the 52nd World Medical Association General Assembly celebrated in Edinburgh, Scotland in October 2000, the 59th World Medical Association General Assembly held in Seoul, Korea, October 2008, the 64th World Medical Association General Assembly held in Fortaleza, Brazil, October 2013; the Good Clinical Practice (GCP) norms issued by the working group on the Efficacy of Medicinal Substances of the European Union (1990) (CPMP/ICH/135/95) and applicable regulatory requirements and laws on the country where the Trial is taking place.

According to Directive 95/46 of the European parliament and 2001/20/EC by which the requirements to perform a clinical trial are established, the information obtained in the course of the clinical trial, will only be able to be used by the clinical trial Sponsor to evaluate the results according to the mentioned regulation.

13.4 Patient privacy

All parties involved in the study must ensure protection of patient personal data and will not include patient names on any Sponsor forms, reports, publications, or in any other disclosures, except when required by laws.

Patient names and other identifiable data will be replaced by an alphanumerical code provided by the Sponsor.

In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of patient personal data.

In order to warrant the confidentiality of study data according to Directive 95/46 of the European parliament and 2001/20/EC, personal and clinical data can only be accessed by the Sponsor of the study or its designated staff, for monitoring/auditing purposes, the investigator and team of collaborators, the Ethics Committee of the investigational site, or the one overseeing the center, and pertinent Health Authorities.

The investigator should facilitate access to the source documents and data for monitoring and auditing purposes.

The content of the electronic case report forms (e-CRF), as well as the documents generated during the study will be protected from non-permitted uses by persons not involved in the investigation, and will therefore be

considered strictly confidential and not revealed to third parties, except those specified in the previous paragraphs.

13.5 Patient information sheet and consent

The patient information sheet (PIS) and informed consent (IC) documents must be in compliance with ICH GCP guidelines, local regulatory requirements and legal requirements. The PIS/IC used in the study, and any changes made during its course, must be prospectively approved by the ethics committees before use. Site investigators must ensure that each patient, or the corresponding representatives, is well informed about the nature and the objectives of the study, including potential risks associated with the trial. Investigators, or the persons designated by them, will obtain written informed consents from each patient or from the patient's legal representative before any trial-specific activity begins.

The patient should sign two separate informed consents: one for the clinical trial and another for biological samples studies.

The study subject will provide his/her consent, signing by duplicate the appropriate model. For this purpose, each model must carry the signature of investigator and patient. The investigator will retain one copy of the original of each patient's signed consent form.

The patient must always give his/her written consent before being admitted into the study and before biological samples are taken.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the corresponding ethics committees.

13.6 Insurance policy

Clinical trial insurance policies, in accordance with pertinent regulatory requirements, will be provided for the study in each country (Spain, Italy and France). All patients in this study will be insured through the insurance Company HDI International with an insurance policy that satisfies the requirements of each country. These policies will be issued and funded by the Sponsor.

14. TRIAL GOVERNANCE AND RESPONSIBILITIES

14.1 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will include mainly the study coordinating investigators. The trial statistician would also attend and supply the committee with all applicable data and information, for all discussions with the exception of private discussions of the committee.

It is the role of the TSC to monitor progress of the trial and safety of participants, and to ensure there is adherence to the protocol and the principles of Good Clinical Practice.

The TSC's terms of reference, roles and responsibilities will be defined in a charter issued by the Sponsor.

The TSC should meet in confidence at regular intervals, and at least annually. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the Trial Management Group (TMG) and, if required, to the relevant ethics committees and competent authorities.

14.2 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the coordinating investigators and identified collaborators, the trial statistician and trial managers. Selected principal investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centers and professional groups. Notwithstanding the legal obligations of the Sponsor and coordinating investigators, the TMG have operational responsibility for the conduct of the trial.

14.3 Sponsor responsibilities

The international Sponsor of this clinical trial is the Grupo Español de Investigación en Sarcomas (GEIS). GEIS will delegate on the study CRO and on the national coordinating institutions in each country a series of responsibilities that will be indicated in specific agreements. The responsibilities of the Sponsor within the trial will also be specified in the contracts signed with each participating hospital.

14.4 Coordinating institutions in each country

There will be one national coordinating institution in each country in which the trial is conducted. Each national coordinating institution will be responsible for a number of country-specific trial coordination tasks, including ethics committees and regulatory approvals. Exact responsibilities including translation of essential documents and some local monitoring procedures will be detailed in a contract between the international Sponsor and each individual coordinating institution. The appointed coordinating institutions per country are as follows:

- Spain: Grupo Español de Investigación en Sarcomas (GEIS) (with a number of coordination responsibilities delegated on CRO Sofpromed Investigación Clínica, SLU, as per specific agreement)
- Italy: Italian Sarcoma Group (ISG)
- France: Centre Léon Bérard (CLB)

14.5 Principal investigators responsibilities

Responsibilities of each Principal Investigator and participating center will be detailed in a contract with the Sponsor or with the delegated country-specific coordinating institution with trial coordination responsibilities in that country.

Principal Investigator responsibilities include putting and keeping in place arrangements to run the trial at their site according to the trial protocol and applicable guidelines, local regulations and the principles of GCP. These responsibilities include, but are not limited to, ensuring that:

- The applicable ethical and institution specific approvals are in place before recruiting patients;
- Sufficient data is recorded for all patients to enable accurate linkage between hospital records and e-CRFs;

- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff involved with the trial are trained in and work to the applicable regulatory requirements;
- Original consent forms are personally signed and dated by both the patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents are retained in accordance with local regulations;
- Staff comply with the protocol and trial guidance notes for the trial;
- SAEs are reported to the study CRO within the required timelines.

15. STUDY DEVELOPMENT CONSIDERATIONS

15.1 Inclusion of the study in clinical trial registries

The clinical trial will be registered in the *clinicaltrials.gov* database of the National Institute of Health of the United States of America, as well as in *clinicaltrialsregister.eu*.

15.2 Quality control and quality assurance

During study conduct, the Sponsor, via its designated monitors, will perform periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. Monitors shall review source documents to verify that the data recorded on the electronic CRFs is accurate. The investigators and participating centers will permit the Sponsor's monitors (or its agent's), as well as regulatory authorities, direct access to source documents to carry out this verification.

Each study site may be subject to review by the Institutional Review Board (IRB)/ethics committees, and/or to quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

The investigators and their staff should be available during the monitoring visits and possible audits or inspections. Sufficient time is to be devoted to these processes.

15.3 Definition of end of study

The study will be considered closed from a normative point of view after data on primary and secondary variables are sufficiently prepared for its initial publication.

15.4 Sponsor discontinuation criteria

Premature termination of this study may occur due to regulatory authority decision, change in opinion of IRB/ethics committees, drug safety problems, or at discretion of the Sponsor. If the study is prematurely terminated, the Sponsor will notify the investigators. After notification, the investigator must contact all participating patients and the hospital. All study materials must be collected and all e-CRFs completed to the fullest extent possible.

This study can be terminated prematurely if in the opinion of the Sponsor there is a reasonable and sufficient cause. Investigators will receive a written notification in which the Sponsor motivates the interruption of the study. Reasons that justify are as follows, but not limited to:

- Finding of unforeseen, considerable or unacceptable risks for the patients.
- Impossibility to include an acceptable number of patients.
- Insufficient compliance with protocol requisites.
- Plans to modify halt or discontinue the development of study drug.
- In case of early termination of the study, all the study material (study drugs, etc.) must be returned to the Sponsor.

15.5 Publication of results

The final publication of the trial results will be written by the international coordinating investigators on the basis of the final analysis performed.

The draft manuscript will be reviewed by the coordinating investigators, other co-authors and GSK. After revision the manuscript will be sent to a major scientific journal. Results obtained in the different strata may be separately published.

Regarding authorship, institutional entry of 5% of evaluable patients in the study results in qualification for one authorship (two names for 20% entry, up to the number of authors allowed by the journal). The reference pathologists, radiologists and statisticians, who have contributed to the trial, will be included in the authorship of the final manuscript.

All manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the trial, as well as supporting parties.

All publications (papers, abstracts, or presentations) including data from the present trial will be submitted for review to all co-authors prior to submission. They will also be submitted to GSK allowing a period of at least 30 days for review (at least 5 working days for abstracts). They will not include either GSK confidential information other than the study results or personal data on any patient, such as name or initials.

Results of the translational research will be published in major scientific journals, after the publication of the main results of the clinical study. The first authors will be the translational study coordinators. All centers that have contributed to at least 5% of the analyzed material will be represented in the publication by one co-author; centers that have contributed to at least 15% of the analyzed material will be represented by two co-authors; this(these) author(s) will be selected by each center internally (e.g. pathologist, molecular biologist, clinician). All centers that have provided material for the analysis will be acknowledged.

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APPENDIX A: DETERMINATION OF CREATININE CLEARANCE (Cl_{CR})

Estimation of creatinine clearance using Cockroft and Gault method:

$$Cl_{CR} \text{ for males (mL/min)} = \frac{[140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$$

$$Cl_{CR} \text{ for females (mL/min)} = \frac{(0.85) \times [140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$$

For SI units:

$$Cl_{CR} \text{ for males (mL/min)} = \frac{[140 - \text{age (years)}] \times [\text{weight(kg)}] \times (1.23)}{[\text{Serum creatinine (µmol/L)}]}$$

$$Cl_{CR} \text{ for females (mL/min)} = \frac{[140 - \text{age (years)}] \times [\text{weight(kg)}] \times (1.05)}{[\text{Serum creatinine (µmol/L)}]}$$

Calculation of creatinine clearance based on 24-hour urinary creatinine excretion and concurrent serum creatinine levels:

$$Cl_{CR} = (C_U \cdot V) / C_{CR}$$

Here, C_U is the concentration of creatinine in the urine (mg/dL or µmol/L, for SI units), V is the urine volume (in mL per minute of urine produced during the collection period), C_{CR} is the serum creatinine concentration (mg/dL or µmol/L, for SI units), and Cl_{CR} is the creatinine clearance in mL per minute.

APPENDIX B: URINE PROTEIN/CREATININE RATIO (UPC)

Clinical significance of UPC

There is a good correlation between the ratio of concentration of protein and the concentration of creatinine in any sample of urine and the quantity of protein excreted during 24 hours.

The expression of creatinine is practically constant throughout the day despite the emission of urine output may be variable.

The normal excretion of protein is < 150 mg/24 hours and it is similar for both men and women.

Men excrete between 20 mg and 25 mg of creatinine/kg of weight/day.

Women excrete between 15 mg and 20 mg of creatinine/kg of weight/day.

UPC Calculation

UPC ratio = Protein in urine (mg/dL) / Creatinine in urine (mg/dL).
UPC ratio ≈ equivalent to the grams of protein excreted in urine during 24 hours.

Example: Patient with protein in urine = 90 mg/dL and creatinine in urine = 30 mg/dL.
UPC ratio = (90 mg/dL) / (30 mg/dL) = 3
The UPC ratio is 3, and it correlates approximately with 3 g of excretion of protein in a period of 24 hours.

Units for UPC ratio

Note: To calculate UPC, the concentrations of proteins and creatinine must be expressed with the same units (mg/dL, g/L, or µmol/L). If, for example, the concentration of proteins is expressed in mg/dL and the concentration of creatinine is expressed through µmol/L, the conversion of concentration values is required. Conversion factors:

From	To	Conversion factor
Conventional units: mg/dL	Units of International System: µmol/L	Multiply by 88.4
Units of International System: µmol/L	Conventional units: mg/dL	Divide by 88.4

References:
Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.
NKF: NKF KDOQI Guidelines [Internet]. National Kidney Foundation; nd. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification.
Link: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm

APPENDIX C: DECLARATION OF HELSINKI, WORLD MEDICAL ASSOCIATION GENERAL ASSEMBLY

Adopted by the 18th World Medical Association General Assembly held in Helsinki, Finland, June 1964 and revised by the 29th World Medical Association General Assembly held in October 1975 in Tokyo,
the 35th World Medical Association General Assembly held in Venice in October 1983,
the 41st World Medical Association General Assembly celebrated in Hong Kong in 1989,
the 48th World Medical Association General Assembly held in Somerset West, South Africa in October 1996,
the 52nd World Medical Association General Assembly celebrated in Edinburgh, Scotland in October 2000,
Paragraph 29 Clarification note, added by the World Medical Association General Assembly, Washington 2002,
the 59th World Medical Association General Assembly held in Seoul, Korea, October 2008,
and the 64th World Medical Association General Assembly held in Fortaleza, Brazil, October 2013.

INTRODUCTION

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are under-represented in medical research should be provided appropriate access to participation in research.

In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

In medical practice and in medical research, most interventions involve risks and burdens. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

Participation by competent individuals as subjects in medical research must be voluntary.

Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

PRINCIPLES FOR MEDICAL RESEARCH WHEN COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

The possible benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or.

Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

The physician must fully inform the patient which aspects of the care are related to the research.

The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy.

In all cases, new information should be recorded and, where appropriate, made publicly available.