TITLE: Phase II Clinical Trial of Pazopanib to evaluate the activity and tolerability in patients with advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists

SPONSOR PROTOCOL NUMBER: GEIS-30

Nº EudraCT: 2012-002745-38

VERSION: H_V03F_2015-02-11

CLINICAL TRIAL SPONSOR:

GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS - GEIS

CLINICAL TRIAL CHIEF INVESTIGATOR:

[redacted]

CLINICAL STUDY COORDINATOR IN GERMANY:

[redacted]

TRANSLATIONAL RESEARCH COORDINATOR:

[redacted]

PROTOCOL SIGNATURE FORM

Protocol: GEIS-30 Nº EudraCT: 2012-002745-38

Version: H_V03F_2015-02-11

I have read this protocol and I agree to conduct it in compliance with GCPs and the Helsinki Declaration.

Sponsor signature Chief Investigator Signature

PROTOCOL SIGNATURE FORM

Protocol: GEIS-30 Nº EudraCT: 2012-002745-38

Version: H_V03F_2015-02-11

Ich habe dieses Protokoll gelesen und stimme zu, die Studie in Übereinstimmung mit allen Festlegungen dieses Protokolls sowie der Deklaration von Helsinki, den ICH GCP Guidelines und den Deutschen Gesetzen und Bestimmungen durchzuführen.

Leiter der klinischen Prüfung

Name

Datum Unterschrift

SIGNATURE PAGE FOR GERMAN SITES

Ich habe dieses Protokoll gelesen und stimme zu, die Studie in Übereinstimmung mit allen Festlegungen dieses Protokolls sowie der Deklaration von Helsinki, den ICH GCP Guidelines und den Deutschen Gesetzen und Bestimmungen durchzuführen.

Prüfer

Name

Datum Unterschrift

Stellvertreter des Prüfers

Name

Datum Unterschrift

Ärztliches Mitglied der Prüfgruppe

Name

Datum Unterschrift

Ärztliches Mitglied der Prüfgruppe

Name

Datum Unterschrift

1. SUMMARY

1.1. Type of Request
A two cohort phase II, open-label, non-randomized, international multi-centre study of an IMP licensed but used for new indication.

1.2. Sponsor Data:
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS - GEIS
[redacted]

Contact Data:
[redacted]

1.3. Study Title
Phase II Clinical Trial of Pazopanib to evaluate the activity and tolerability in patients with advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists.

1.4. Sponsor Protocol Number: GEIS-30

1.5. Nº EudraCT: 2012-002745-38

1.6. Chief Investigator
[redacted]

1.7. Clinical Study Coordinator in Germany
[redacted]

1.8 Translational Research Coordinator

[redacted]

1.9. Monitoring Organization

MARKETING FARMACEUTICO & INVESTIGACION CLINICA – MFAR S.L.

[redacted]

For German sites:

[redacted]

1.10. Study Treatment

Single arm of Pazopanib 800 mg (2x400mg or 4x200 mg) given as a single agent once daily.

Presentation: The investigational product, 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 the Pazopanib SPC for information regarding the physical and chemical properties of Pazopanib and a list of excipients.

Pharmaceutical form: Film-coated tablet.

Route of administration: oral

1.11. Study phase and design

A two cohort Phase II, open-label, non-randomized, multi-centre study with 5 centres in Spain and 5 centres in Germany. Patients will receive oral Pazopanib, 800mg once daily and treatment will continue until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient or investigator decision.

1.12. Primary Objective

The primary objective of this study is to evaluate the activity of Pazopanib in patients with advanced and/or metastatic liposarcoma by means of progression-free survival (PFS) assessed 12 weeks after start of treatment. (According the RECIST criteria 1.1 and central radiology review).

1.13. Disease under investigation

Advanced and/or metastatic liposarcoma

1.14. Primary endpoint
The primary efficacy endpoint for this study is progression-free survival (PFS) assessed 12 weeks after start of treatment. (According the RECIST criteria 1.1 and central radiology review).

1.15. Patients to be included
Patients with advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists will be included.

1.16. Sample Size
74 patients (maximum of 37 patients in 2 different cohorts)

1.17. Treatment duration
Treatment will continue until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient or investigator decision.

1.18. Planned trial periods
Start date: Third quarter 2012.
First subject first visit (FSFV): Fourth quarter 2012.
Total duration of recruitment period: 30 months.
Last subject first visit (LSFV): Second quarter 2015.
Follow-up period: 12 months.
End of study date: Last patient last visit. Estimated second quarter 2016.

2. INDEX

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated PTT
AST	Aspartate aminotransferase
BP	Blood pressure
C24	Concentration at 24 hr following single-dose administration
CR	Complete response
CRF	Case Report Form
CrCl	Creatinine Clearance
CT	Computerized tomography
CYP	Cytochrome P450 (subtypes 3A, 3A4, 2D6)
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECO	Echocardiography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EIAC	Enzyme-inducing anticonvulsants
FDA	Food and Drug Administration
Flt-3	Fms-like tyrosine kinase-3
FU	Follow up
GCP	Good Clinical Practice
GISG	German Interdisciplinary Sarcoma Group
GSK	GlaxoSmithKline
HIF-1a	Hypoxia-inducible factor-1a
HRT	Hormone Replacement Therapy
IC_{50}	Half-maximal inhibition
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-treat
TKI	Tyrosine Kinase Inhibitor
LD	Longest diameter
LVEF	Left Ventricular Ejection Fraction

LLN	Lower Limit of Normal
MRI	Magnetic resonance imaging
msec	Millisecond(s)
MTD	Maximum tolerated dose
mTOR	mammalian Target of Rapamycin
MUGA	Multi-Unit Gated Analysis
NCI-CTCAE v4.0	National Cancer Institute-Common Toxicity Criteria for Adverse Events Version 4.0
OS	Overall survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PR	Partial response
PTT	Partial thromboplastin time
QD	Once daily
QTc	Corrected QT interval
RAP	Report and analysis plan
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SPC	Summary of Product Characteristic
STS	Soft Tissue Sarcoma
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor
µM	Micromolar

3. GENERAL INFORMATION

STUDY IDENTIFICATION

TITLE: Phase II Clinical Trial of Pazopanib to evaluate the activity and tolerability in patients with advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists.

PROTOCOL NUMBER: GEIS-30

Nº EudraCT: 2012-002745-38

3.1. Clinical Trial Type

A two cohort phase II, open-label, non-randomized, international multi-centre study of an IMP licensed but used for new indication.

3.2. Investigational drug description

Single arm (two cohorts) of Pazopanib 800 mg (2x400mg or 4x200 mg) given as a single agent administered once daily.

Presentation: The investigational product, 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 the Pazopanib SPC for information regarding the physical and chemical properties of Pazopanib and a list of excipients.

Pharmaceutical form: Film-coated tablet. Capsule-shaped, white, film-coated tablet with GS UHL debossed on one side.

Route of administration: oral

3.3. Sponsor Data

GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS - GEIS

[redacted]

Contact Data:

[redacted]

3.4. Study Monitoring Organization

MARKETING FARMACEUTICO & INVESTIGACION CLINICA – MFAR S.L.

[redacted]

For German sites:

[redacted]

3.5. Clinical Trial Chief Investigator

[redacted]

3.6. Clinical Study Coordinator in Germany

[redacted]

3.7. Translational Research Coordinator

[redacted]

3.8. Planned trial periods

Start date: Third quarter 2012.
First subject first visit (FSFV): Fourth quarter 2012.
Total duration of recruitment period: 30 months.
Last subject first visit (LSFV): Second quarter 2015.
Follow-up period: 12 months.
End of study date: Last patient last visit. Estimated Second quarter 2016.

4. RATIONALE AND OBJECTIVES

4.1 BACKGROUND AND RATIONALE

Soft tissue and bone sarcomas are rare malignant tumors, which encompasses 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, around half of patients 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 trabectedine have shown activity, with response rates of 20–40% in previously untreated patients. Recent and ongoing trials have investigated a variety of combination chemotherapeutic regimens (variously employing ifosfamide, doxorubicin, gemcitabine, temozolamide, vincristine, cisplatin, and dacarbazine, among others) as well as targeted therapies, which in some cases have yielded improvements in response rate but which have had little impact on survival. No other medical option is currently available, and the median survival of patients with soft-tissue sarcoma with non-resectable metastases is around 12-15 months, and approximately 8 months after second line chemotherapy[(1)].

Liposarcomas are STS which account for at least 20% of all STS in adults. They can be further classified into 3 histologically and biologically different subtypes: well-differentiated liposarcoma/de-differentiated liposarcoma (ALT-WD), myxoid or round cell liposarcoma and pleomorphic liposarcoma.

ALT-WD liposarcomas are locally aggressive rarely metastasising tumors characterized by ring or giant marker chromosomes on the cytogenetic analysis and by amplification of the 12q13-21 region on FISH (MDM2, CDK4 and HMGIC)[(2),(3)]. They account for about 40% [(4)] of liposarcomas with a 5 year OS around 80%. In a series of WD/DD treated with several regimens response rate was 12.5% OS 15 months and median PFS 3.6 months(95 CI: 3.3-5.9)[(5)]

Mixoid /round cell liposarcoma accounts for 45-50% of all liposarcomas. They tend to metastasise to unusual soft tissue and bone locations. High histologic grade with more than 5% of round cell component is associated with a 5-year OS of 50% approx. They are characterized by t(23;16)(q13-14;p11) which leads to the fusion of CHOP and TLS genes.[(6)]

Pleomorphic liposarcoma accounts for approximately 5-10% of all liposarcomas, characterized by high grade features with frequent and early lung metastasis and cytogenetically by high chromosome counts and complex structural rearrangements.

VEGF is expressed in many STS in which increased expression is associated with higher grade and worse prognosis. [(7)]

Pazopanib is an oral angiogenesis inhibitor that targets mainly VEGFR, PDGFR and c-kit. Recently the results of a phase II trial [(8)] of Pazopanib in STS have been published. It was a four-cohort 2-stages study. The liposarcoma stratum was closed after the first stage because of a PFS at 12 weeks of 17% (3 out of 17 patients did not progressed after 12 weeks). After central pathologic review, 2 other patients initially classified as other STS were found to have liposarcoma with stable disease at 12 weeks (5/19: 26% PFS12w), thus fulfilling criteria for cohort expansion. Phase II study had been completed and in phase III study patients with liposarcomas were excluded so therefore data on the liposarcoma cohort are inconclusive.

Furthermore the positive results of the phase III study PALETTE have been recently communicated, encouraging this treatment in other sarcomas: progression-free survival (PFS) per independent review was significantly prolonged with Pazopanib (median: 4.6 vs 1.6 months; HR=0.31, 95% CI 0.24-0.40; P<0.0001). The interim analysis for overall survival shows a statistically non-significant improvement of Pazopanib vs placebo (median: 12.5 vs 10.7 months, HR=0.83, 95% CI 0.67 – 1.11 p=0.25) [9].

Soluble factors associated with efficacy and toxicity of Pazopanib in these patients had been also reported [10]. Decreases in VEGFR2 and increase in PlGF were both associated with toxicity (HTA and TSH elevation) and poorer prognosis.

4.2 Rationale for the Pazopanib Dose

The Pazopanib dose to be used in this study is 800 mg daily, based on the following consideration:

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.

4.3. Study Objectives

4.3.1. Primary Objective:

The primary objective of this study is to evaluate the activity of Pazopanib in patients with advanced and/or metastatic liposarcoma by means of progression-free survival (PFS) assessed 12 weeks after start of treatment. (According the RECIST criteria 1.1 and central radiology review).

4.3.2. Secondary Objectives:

- Overall progression-free survival (median PFS)
- Objective tumor response (confirmed complete response [CR] and partial response [PR] using modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)
- Time to onset of response
- Duration of response
- Overall survival (OS)
- Clinical benefit rate (CBR)
- Growth Modulation Index (GMI).
- Safety profile (according CTCAE, version 4.0)

4.3.3. Translational Study Objectives

PRIMARY OBJECTIVES:

- To evaluate the influence of the angiogenic status of the tumor on the response to Pazopanib.
- To evaluate the serum profile of serum cytokine markers as indicator of response to Pazopanib.

SECONDARY OBJECTIVES:

- To evaluate microvessel density (MVD) and p53, MDM2, PTEN and VEGF/PDGF pathways by IHQ expression and their correlation with prognosis as well as their role as predictive factors to treatment with Pazopanib (Response, PFS and OS).
- To evaluate serum levels of several angiogenic factors/cytoquines using Luminex XMAP Technology at baseline, after the first 3 weeks of treatment, at maximum response and at progression and their predictive value for survival and response to treatment: 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 analyse PIK3CA mutations in order to demonstrate if those liposarcomas with PIK3CA mutations defines a subgroup of patients with differential response to Pazopanib.

5. STUDY DESIGN

5.1. Development Phase

A two cohort Phase II, open-label, non-randomized, multi-center study with 5 centres in Spain and 5 centres in Germany to evaluate the activity and tolerability of Pazopanib in patients with advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists.
The drug will be separately investigated in the following liposarcoma subtypes (cohorts):

- Well-differentiated liposarcoma/de-differentiated liposarcoma (ALT-WD)
- Myxoid/round cell liposarcoma.

A total of 17 eligible and treated patients will be included (in each stratum) in the first step of the study. If ≤ 3 successes are observed in a stratum, the trial will be stopped in this stratum with the conclusion that the drug should not be further investigated in this histology. Otherwise, patients will continue to be accrued. Each cohort will independently recruit a maximum of 37 patients. The statistical analysis will be performed in each stratum.

5.2. Patient Screening Identification

Informed consent should be obtained prior to start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol. Once both clinical and biological samples informed consent forms are signed a trial screening number will be assigned to each patient. Each site will receive inside the Site Investigator File a screening log form in which pre-determined screening numbers will be assigned. This document should be always at site under Investigator staff custody. This screening number will identify patients throughout the procedures needed to confirm the subjects' suitability for the trial Protocol (clinical laboratory tests, imaging, central pathological review, etc.).

An additional document will be provided in the Investigator Site File with detailed Patient Screening Identification procedures.

5.3. Central pathological review

Once a patient has signed the biological samples consent form, at least one representative formaline fixed paraffin embedded tumour block and H/E (haematoxylin/eosin) slides from all the different areas of the tumor will be collected for central pathological review. Patients may be included in the study with H/E slides only, but just if the tumor block is not available (all efforts should be done to send a representative tumor block). Representative histological sections should be sent for review in those cases without paraffin block, including H/E and other necessary stains. The diagnostic report, including macroscopic description of the specimen should be shipped together with the samples in all cases. First diagnosis sample or another more recent available sample obtained during the routine care previous to study entry will be acceptable. Tumour biopsy at study entry will NOT be

compulsory but recommended if clinically acceptable (ex. superficial or easily accessible locations). All the samples from Spain and Germany will be sent by courier to the central laboratory and diagnosis will be available in approximately one week. The central pathological review is a pre-requisite for entering the trial. The study treatment should not be initiated unless the diagnosis is confirmed by means of the central pathological review.

All the slides will be returned to the patient site with a formal report as per specific form after pathological central review. The paraffin blocks will be sent first to the translational research coordinator. All remaining samples will also be returned after the end of the project.

Central Review of diagnosis will be carried out by:

For sending the biological samples, please contact to:

A central review report will be generated as per specific form and will be replied to sites.
For sending the biological samples, please contact to:

All samples will be shipped codified as is specified in the detailed tumour collection and shipment procedures.

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

5.4. Patient Inclusion

After confirming that the patient is suitable for inclusion in this trial (inclusion/exclusion criteria), a patient trial number will be centrally assigned to each subject.
The procedure for patient inclusion is as follows:

- Complete and sign the patient inclusion forms (the patient registration forms should be signed by a clinician identified at signature list and delegation of responsibilities log.
- Please, send completed and signed patient inclusion form to:

- [redacted] will proceed with patient inclusion procedure, and
- Will reply site, sending the confirmation of patient inclusion form, both by fax and email. The confirmation of patient inclusion will contain the patient trial number.
- The treatment with Pazopanib should be started **only** if site has received the confirmation of inclusion forms.

The patient trial number will identify patients throughout the participation in the study.

An additional document will be provided in the Investigator Site File with detailed Patient Inclusion procedures.

5.5. Treatment description

The treatment with Pazopanib should be started **only** if site has received the confirmation of inclusion forms as per section 5.4 of this protocol.
Pazopanib 800 mg (2x400mg or 4 x 200 mg) per day, once a day, should be taken orally without food at least one hour before or two hours after a meal until disease progression, the development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient, or investigator decision.
Pazopanib should be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Pazopanib does not require any special storage conditions. Investigational product (Pazopanib) should begin within 7 days of inclusion (longer delays must be discussed with Study Chair).

For Pazopanib dose modifications, please, see in section 7.6 of this protocol.

Stock of Pazopanib will be centrally managed by [redacted], in case of any issue regarding Pazopanib, please contact to:

5.6. Patient Scheduled Visits

For more information, please, see in Table 5: Table of Assessments (section 8 of this protocol).

5.6.1. Before treatment:

Informed consent must be obtained prior to start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

Screening: To determine patient eligibility, within 14 days prior treatment start, it should be performed the following assessments: consent form signature, inclusion/exclusion criteria, medical history, physical exam (with Blood pressure assessment and vital and cancer signs and symptoms), ECOG, concomitant medication, clinical laboratory test, ECG, LVEF (MUGA ECO), Baseline imaging CT/MRI, tumor specimen collection, serum collection.

5.6.2. During treatment:

In general, physical exam with BP, concomitant medication, clinical laboratory test and ECOG status, and adverse event collection (diarrhoea, liver toxicity, etc.), should be performed in each schedule visit.

First 12weeks of treatment:

Week 0 (day 1): Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests, treatment control and dispensing.

Week 1 (day 8): Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests and adverse events.

Week 3 (day 22): Physical exam (with Blood pressure assessment), ECOG concomitant medication, clinical laboratory tests, adverse events and serum collection at the end of 3 weeks (day 22 of treatment), treatment control and dispensing.

Week 5 (day 36): Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests, adverse events, treatment control and dispensing.

Week 7 (day 50): Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests, ECG, Imaging (CT scan /MRI), adverse events, treatment control and dispensing.

Week 9 (day 64): Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests, adverse events and treatment control and dispensing.

Week 12 (day 85): Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests, ECG, LVEF determination, Imaging (CT scan /MRI),.adverse events, treatment control and dispensing.

From week 12 up to the End of Treatment Visit:

Every 4 weeks thereafter: Physical exam (with Blood pressure assessment), ECOG, concomitant medication, clinical laboratory tests and adverse events. Treatment control and dispensing

Every 8 weeks thereafter: ECG and Imaging (CT scan /MRI).

LVEF determination: (MUGA/ECO) will be performed at baseline and every 12 weeks +/-2 weeks (3 months) thereafter or more frequently if clinically indicated.

Serum collection: Within 72 hours after radiological response is documented.

5.6.3. After End of Treatment:

End of treatment Visit (to be performed 28 days after end of treatment): Physical exam (with Blood pressure assessment and vital and cancer signs and symptoms), clinical laboratory test, ECG, adverse events.

After discontinuation of protocol treatment in patients who have not progressed, will still be re-evaluated by imaging every 8 weeks, unless they have started a new anti-cancer therapy.

After progression disease: follow up for survival, patient status (alive/dead/lost to follow up) and new anti-cancer therapy.

5.7 Response evaluation

Informed consent must be obtained prior to start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

Response evaluation will be done by means of RECIST version 1.1 criteria.

Imaging Studies: CT Scan or MRI will be used for response evaluation. Disease should be captured and target/non-target identified at baseline, CT scan or MRI as appropriate. Subsequently, imaging studies required to investigate known disease should be performed on week 7, on week 12 and every 8 weeks thereafter. Imaging methods will be employed consistently during the course of each patient's evaluation during the study. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 8 weeks, unless they have started a new anti-cancer therapy.

5.8. Translational sub-study

For those patients that have consented for the participation in the translational sub-study, the biological samples will be collected as follows:

- Paraffin-embedded samples from original tumor and if clinically acceptable (ex. superficial or easily accessible locations), tumour biopsy at study entry.
- Serum from peripheral blood will be performed (4 per subject):
    1. Within 72 hours prior starting the treatment (basal).
    2. Within 72 hours after the first 3 weeks of treatment (Day 22).
    3. Within 72 hours after radiological response is documented.
    4. Within 72 hours after progressive disease is documented.

Translational sub-study will be carried out by:

[redacted]

[redacted]

All samples will be shipped codified as is specified in the detailed tumour collection and shipment procedures. For more information regarding translational sub-study, please see section 13 of this protocol.

For sending the biological samples, please contact to:

[redacted]

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

5.9. Central Images Review

All images assessments will be central reviewed through on-line platform by:

[redacted]

It is strongly recommended to upload the baseline MRI/CT scan before patient inclusion, if it is not possible, it should be done as soon as possible after patient inclusion.

All images assessments, performed during the clinical trial, should be uploaded to the specific 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 identified *only* by the specific codification detailed in the radiologic guidelines.

A central review report will be generated as per specific form.

For any issue regarding central images review, please contact to:

[redacted]

An additional document will be provided in the Investigator Site File with detailed central images review loading information.

6. PATIENT SELECTION

TYPE OF PATIENTS:
Patients with high or intermediate grade malignant liposarcoma with metastatic or locally advanced disease that fulfil all eligibility criteria will be included.

6.1. Inclusion Criteria

A subject will be considered eligible for inclusion in this study if all the following criteria are met:

1. Subjects 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 specified screening window.
    - Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.
2. Age ≥ 18 years or legal age of consent if greater than 18 years
3. Histological confirmed diagnosis of high or intermediate grade malignant liposarcoma with metastatic or locally advanced disease. Formaline fixed paraffin embedded tumour block and/or representative H/E (haematoxylin/eosin) slides must be available for central pathologic review to classify tumors in the 2 eligible subtypes:
    - Well-differentiated liposarcoma/de-differentiated liposarcoma (ALT-WD)
    - Myxoid/round cell liposarcoma
4. Patient must have documentation of disease progression within 6 months prior to study entry.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
6. Measurable disease by RECIST v1.1 criteria. At least one measurable lesion located outside of a previously irradiated area. If the only measurable lesion is in a previously irradiated area, RECIST progression should be documented after radiotherapy, in the previous 6 months before study entry.

7. The patient should not be considered eligible for surgery or radical radiotherapy. e.g. Patients to whom surgery/radiotherapy cannot be performed with a curative intent due to the extension of the disease. In the case of radiotherapy, it may also be limited due to a previous treatment with radiotherapy in the same area.
8. The patient must have either been considered ineligible for systemic chemotherapy or received at least one previous regimen for relapsed, refractory or metastatic disease. A maximum of three previous lines for advanced/metastatic disease are allowed.

   Patients not eligible for systemic chemotherapy:

   - Because of age, a biological condition or patient-refusal
   - Generally, patients that received anthracyclines in the adjuvant setting are not eligible for first line therapy with this agent for advanced disease.
   - Patients with a solitary kidney or >60 years old are usually not the best candidates for treatment with regular doses of ifosfamide.
9. Tumour tissue must be provided for all subjects for biomarker analysis before/during treatment with investigational product.
10. The patient should be able to swallow and retain study drug
11. Adequate organ system function as defined in Table 1

Table 1: Definitions for Adequate Organ Function

System	Laboratory Values
Hematology	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Haemoglobin	≥ 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}) (reference appropriate appendix)	≥ 30 mL/min to ≥ 50 mL/min
Urine Protein to Creatinine Ratio (UPC; appropriate appendix)[d]	<1
Or, 24-hour urine protein	<1g

a. Subjects may not have had a transfusion within 7 days of screening assessment.
b. Subjects 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. Subjects must have a 24-hour urine protein value <1 g to be eligible. Use of urine dipstick for baseline renal function assessment is not acceptable.

12.. 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
- 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

Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. 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

13. LVEF above the lower limit of normal for the institution, based on ECHO or MUGA.

Deviations from inclusion criteria are not allowed because deviations can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

6.2. Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Prior history of malignancies other than liposarcoma.

   subjects who have had another malignancy and have been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.

2. Clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.
3. 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.
4. 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.
5. Corrected QT interval (QTc) > 480 msecs
6. 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 III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)
7. 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, if this criterion is approved by Safety Review Team) in order for a subject to be eligible for the study.

8. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.

   Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible

9. 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 (procedures such as catheter placement not considered to be major surgery).
10. Evidence of active bleeding or bleeding diathesis.
11. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage.

    Lesions infiltrating major pulmonary vessels (contiguous tumour 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).

12. Recent hemoptysis (≥ ½ teaspoon of red blood within 8 weeks before first dose of study drug).
13. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.
14. Unable or unwilling to discontinue use of prohibited medications listed in section 7.4 of this protocol or at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.
15. Treatment with any of the following anti-cancer therapies:
    - radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of Pazopanib
    - 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
16. 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
17. Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity, except alopecia.

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

6.3. Patient Withdrawal Criteria

6.3.1. Permanent Discontinuation of Investigational Product

Subjects will receive investigational product until any of the following occur:

- Subject experiences disease progression according to RECIST V 1.1
- Subject experiences unacceptable toxicities or an adverse experience that would, in the judgement of the investigator, make continued administration of the study regimen an unacceptable risk.
- Subject is considered by the investigator or the sponsor to be significantly non-compliant with the requirements of the protocol
- A more than 3 weeks delay in treatment administration
- Study is closed or terminated
- Subject withdraws consent for study participation

The reason for discontinuing investigational product must be clearly recorded on the case report forms (CRF).
A temporary interruption in study medication due to an AE is not considered to be permanent discontinuation from investigational product.

6.3.2. Withdrawal from Study

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator may also, at his/her discretion, withdraw the subject 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 CRF 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 CRF. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.
Patients withdrawn the trial for any reason, cannot enter again.

6.4. Screening and Baseline Failures

A subject is considered to be a screening/baseline failure if the subject signs the informed consent, but withdraws before study randomization. All potential subjects who are screened for enrolment in this study including screening/baseline failures will be listed on the Subject Screening Log/Identification List but will not be entered in the study database. Reasons for exclusion will be recorded for potential subjects who do not enter the study.

7. TREATMENT DESCRIPTION

7.1. Study Medication

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.
The investigational product, Pazopanib monohydrochloride salt is produced as tablets containing Pazopanib monohydrochloride salt equivalent to 200 mg or 400 mg of the free base. Refer to the Pazopanib SPC for information regarding the physical and chemical properties of Pazopanib and a list of excipients.
Investigational product 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 investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.
Investigational product (Pazopanib) should begin within 7 days of inclusion (longer delays must be discussed with Study Chair by email: [redacted]).
Pazopanib 800 mg (2x400mg or 4x200 mg) per day (once a day) should be 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 does not need to be recorded on the 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 will be provided to sites by the Sponsor trough [redacted]. The contents of the investigational product label will be in accordance with all applicable regulatory requirements.

7.2. 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 Sponsor, when applicable. Product accountability records must be maintained throughout the course of the study.

7.3. Treatment Compliance

A record of the number of Pazopanib tablets dispensed to and returned by each subject must be maintained and reconciled with the 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.

7.4. Concomitant Medication

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.

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.

Permitted medications
Patients 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 ≤ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Use with cautions
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 pharmacological 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

Substances that induce or inhibit CYP3A4 may alter the pharmacological 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, troglitazone

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

7.4.1. 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.

7.4.2. 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 [(11)] (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.

7.4.3. 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 pharmacological 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.

7.4.4. 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 pharmacological 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

7.5. Treatment of Investigational Product Overdose

No maximum tolerated dose (MTD) 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), the investigator should contact [redacted] and additional monitoring of the subject for AEs/SAEs and laboratory abnormalities should be considered. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the GEIS Study Chair based on the clinical evaluation of the subject. Information regarding the quantity of the excess dose should be documented in the CRF.

7.6. Criteria for regimen modification during the study

7.6.1. Dose Interruptions/Modifications for Specific, Non-liver Related, Toxicities

As a general rule, if dose reduction of IP 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 IP 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 contact the Trial Chief Investigator by email [redacted] to review the subject's condition in order to resume the treatment.

Recommendations for investigational product dose interruptions/modifications in case of specific treatment-emergent AEs are provided in the following Table

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 (IP) 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 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 IP, 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 IP dose-reduced by 200 mg if IP was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt IP 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 IP dose-reduced by 200 mg.

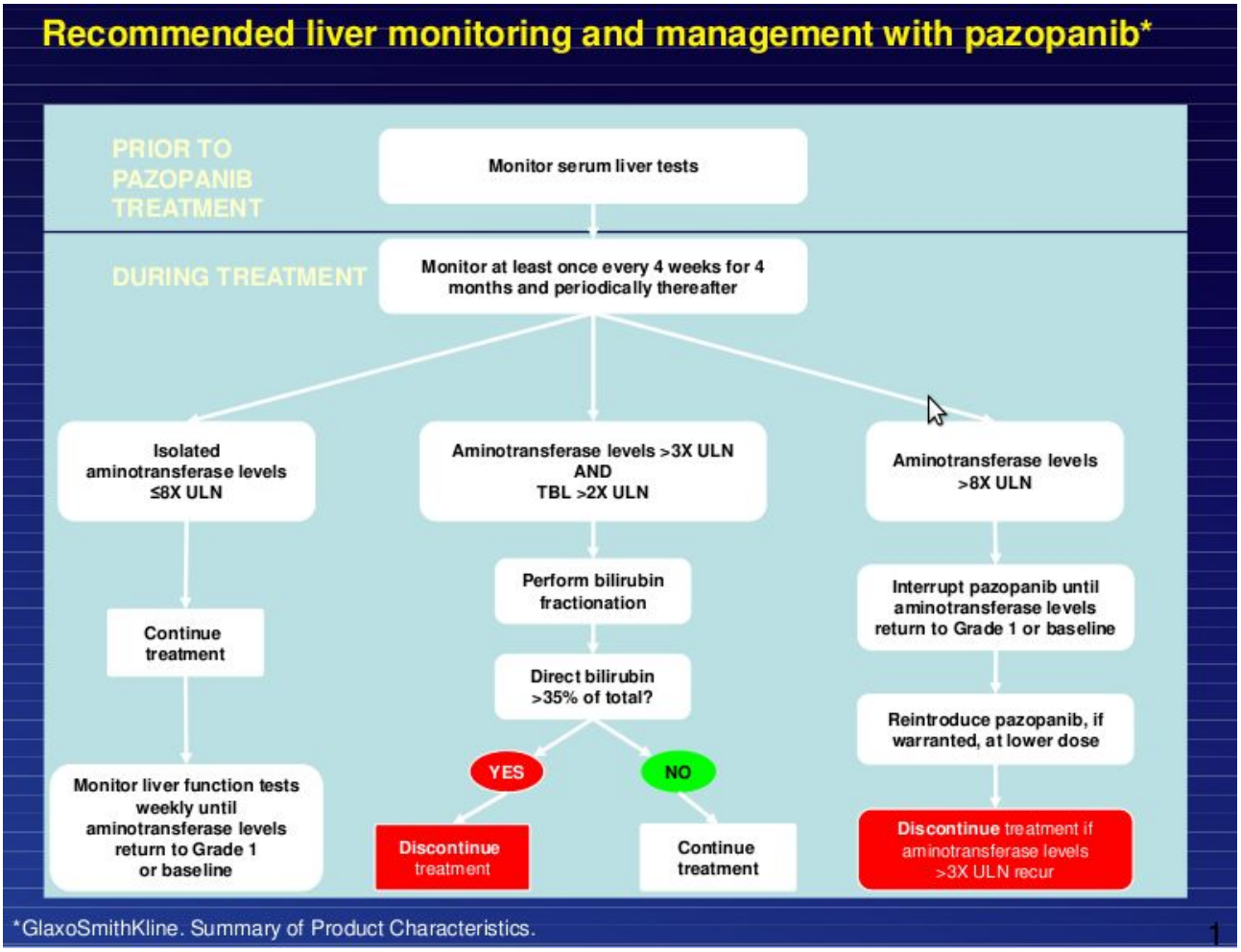
(D). Refractory hypertension unresponsive to above interventions.	Discontinue IP and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.	
QTc ≥ 480 < 500 msec	Continue IP; monitor as clinically indicated.
QTc ≥ 500 msec	Discontinue IP 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 IP. 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 Chief Study Physician to discuss whether further treatment with Pazopanib is appropriate. For other Grade I haemorrhage/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 IP and continue follow-up per protocol. Otherwise, interrupt IP until the AE resolved to ≤ Grade 1. Step 2. Restart IP; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue IP and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue IP at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt IP. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume IP 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 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 IP dosing (eg, re-initiating, escalating/de-escalating, or discontinuing IP), 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 IP and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue IP and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue IP with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 2. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue IP 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)	Continue IP at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold IP 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart IP 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	Discontinue IP
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue IP; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 1. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue IP and continue follow-up per protocol.

- Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
- AEs are graded according to NCI Common Terminology Criteria for Adverse Events

v4.0 (NCI CTCAE v4)
Abbreviations: BP, blood pressure; IP, investigational product.

7.6.2. Dose Interruptions/Modifications for Hepatotoxicity



Patients over 60 years of age have an increased risk of ALT > 3 x ULN.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring.

Recommendations for IP dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 3. 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 eCRF), 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 the liver event alcohol intake form in the eCRF. 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 LFT (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 Sponsor as an SAE **within 24 hours** of learning of its occurrence. 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 subject is benefiting from the study treatment, contact Study Chief Physician for possible re-challenge. Re-treatment 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. (5) Reintroduce Pazopanib, if warranted, at lower dose. **Recurrence – Liver Event Stopping Criteria:** If aminotransferase levels > 3xULN recur, 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.
(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 Sponsor as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 hours for 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(b) 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.

Abbreviations: ALT alanine aminotransferase; **AST** aspartate aminotransferase; **eCRF** electronic case report form; **IP** investigational product; **LFT** liver function tests; **SAE** serious adverse event; **ULN** upper limit of normal

7.6.3 Dose Modifications and Management of 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. [12]
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 litres) 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 Chief Trial Investigator 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.

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, phenothiazine (prochlorperazine); corticosteroids, (dexamethasone, prednisone); and cannibinoids (dronabinol).

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Study Development

Screening test for inclusion (lab tests and imaging) should have been performed ≤ 14 days before first dose administration.

Table 5: summarizes the assessments to be performed throughout the study as well as their schedule.

TABLE Of ASSESSMENT

	Before Treatment	During Treatment											After treatment	
	Screening (within 14 days prior treatment start)	Week 0 Day 1	W1 Day 8	W3 Day 22	W5 Day 36	W7 Day 50	W9 Day 64	W 12 Day 85	Every 4 weeks (after w12)	Every 8 weeks	Every 12 weeks	28 days after end of treatment	Before PD, every 8 weeks until PD	After PD every 12 weeks
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Medical history	X													
Physical Exam[a] (with vital and cancer signs and symptoms)	X	X	X	X	X	X	X	X	X			X	X	
ECOG	X	X	X	X	X	X	X	X	X				X	
Concomitant Medication	X	X	X	X	X	X	X	X	X					
Clinical Laboratory Tests [b,c]	X	X	X	X	X	X	X	X	X			X		
ECG[d]	X					X		X		X		X		
LVEF (MUGA/ECO)	X**							X			X			
Efficacy Assessment (Imaging/MRI) *	X**					X		X		X			X	
Adverse Events			X	X	X	X	X	X	X	X		X		
Tumor specimen collection [1]	X													
Serum collection [2]	X			X			x[2]							
Treatment control and dispensing		X		X	X	X	X	X	X					
Survival														

*Tumor assessment should be repeated in week 7 and week 12 and every 8 weeks thereafter until documented progression for patients with CR, PR, or SD and/or for patients who have discontinued study therapy due to toxicity or reasons other than progressive disease, unless they have started a new anti-cancer therapy.

**Both tumor assessment before treatment and LVEF can be done up to 28 days prior the start of the treatment.

[1] Tumor sample will be collected before treatment.

[2] Serum will be collected as described:

1. Within 72 hours prior starting the treatment (basal).
2. Within 72 hours after first 3 weeks of treatment (day 22).
3. Within 72 hours after radiological response is documented.
4. Within 72 hours after progressive disease is documented.

[a] Monitoring of BP: A measurement of BP should be taken the day of the visit +/- 3 days.

[b] Hematology Profile and Chemistry Profile (including liver Function) in every visit

[c] Thyroid function test (T4 and TSH):basal and every 12 weeks.

[d] ECG: Baseline, week 7 and 12 and every 8 weeks thereafter.

Unless otherwise indicated, during treatment the marge for visits / explorations is +/- 4 days and after completion of treatment +/- 7 days

8.2 Assessments description:

1. Informed Consent: Written permission will be given by each patient prior to undergoing protocol-specific evaluations and prior to receiving treatment. The patient should sign 2 separate informed consents: one for the clinical trial and another for the biological samples.

2. Inclusion/Exclusion criteria: Will be reviewed by each patient prior to undergoing protocol-specific evaluations and prior to receiving treatment.

3. Medical History: Past or current medical conditions and treatments, current medications, medications taken within 30 days of randomization, date of diagnosis, prior cancer therapy and surgery, pathological confirmation of malignancy, and staging of liposarcoma at the time of diagnosis and study entry. Any pre-existing toxicity (eg, Grade 1 fatigue) should be documented and recorded at this time.

4. Physical Exam:

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

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

5. ECOG Performance Status (PS): PS will be assessed at screening, at day 1 before the study drug is administered, and in week 1, 3, 5, 7, 9 and week 12. Thereafter, every treatment visit before the study drug is administered (4 weeks).

If subjects discontinue study treatment without disease progression (e.g., withdrawal of study treatment due to unacceptable toxicity), continue the assessments of ECOG PS in accordance with the disease assessments until subjects experience disease progression.

6. 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 Case Report Form (CRF). Any medications, with the exception noted in the section (additional details), 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, providing the medication, doses, dates and reasons for administration in the CRF.

7. 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.

8. Clinical Laboratory Tests:

8.1 Hematology Profile: includes a complete blood count with differential and platelet count.

8.2 Coagulation Profile: includes INR, prothrombin time, and PTT.

8.3 Chemistry Profile: includes total protein, albumin, blood urea nitrogen,

creatinine, AST, ALT, alkaline phosphatase, total bilirubin, phosphorus, sodium, potassium, calcium, chloride, magnesium, amylase, lipase, and lactate dehydrogenase.

8.4 Urinalysis: routine analysis (UPC) or dipstick measurements and, if clinically indicated, microscopic analysis. If dipstick or routine urinalysis (UPC) indicates proteinuria ≥ 2+, a 24-hour urine collection (to assess protein) must be obtained. Use of urine dipstick for baseline renal function assessment is not acceptable.

8.5 Pregnancy Test (for Women of Child-bearing Potential): serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadatropin [β-HCG]) within 7 days prior to randomization. Thereafter, the serum pregnancy test only needs to be repeated if clinically indicated or as required by local regulation

8.6 Thyroid function test: TSH monitoring; if abnormal, free T4 testing: basal and every 12 weeks thereafter.

Hematology Profile, Coagulation Profile and Chemistry Profile (including liver function) will be assessed at screening, at day 1 before the study drug is administered, in weeks 1, 3, 5, 7, 9 and week 12. Thereafter, every treatment visit before the study drug is administered (every 4 weeks).

9. Electrocardiogram (ECG): A baseline electrocardiogram (ECG) value is to be obtained within 14 days prior to randomization. ECG should be done in week 7 and week 12 and every 8 weeks thereafter. Another determination will be performed at end of treatment visit (28 days after end of treatment).

10. LVEF determination: (MUGA/ECO) will be performed at baseline and every 12 weeks thereafter or more frequently if clinically indicated. 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 (ie, shortness of breath during mild exertion or when lying down, feeling very tired, cough (especially at night), swelling of the feet and/or ankles).

11. Tumor specimen collection: Tumor specimen 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 (ex. superficial or easily accessible locations)

12. Serum from peripheral blood: Serum will be collected from the patient considering the following scheme:

1. Within 72 hours prior starting the treatment (basal).
2. Within 72 hours after the first 3 weeks of treatment (day 22).
3. Within 72 hours after radiological response is documented.
4. Within 72 hours after progressive disease is documented

Serum specimens will be kept at each centre and sent at the end of the study to a central laboratory for translational studies.

13. Efficacy Assessment (imaging): TC or MRI as appropriate. Disease should be captured 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 repeated in week 7 and week 12 and every 8 weeks thereafter. Imaging methods will be employed consistently during the course of each patient's evaluation during the study. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 8 weeks, unless they have started a new anti-cancer therapy.

Table 6: Acceptable Imaging Assessment Methods and Technical Requirements

Anatomic region	Preferred / Alternative methods	Technique requirements	
		Mandated	**Strongly recommended**
Chest, abdomen and pelvis: ***Note:*** **Scan must cover lung apices to diaphragm, diaphragm through entire liver and to below the pubic symphysis.**	CT – preferred for chest, abdomen and pelvis	● Slice thickness: ≤7.5 mm (reconstruction interval equal to slice thickness, i.e. no gap) although ≤5mm is strongly recommended ● Use intravenous (i.v.) contrast for abdomen/pelvis unless contraindicated.	● Multi-slice CT ● Slice thickness: ≤5mm (reconstruction interval) ● Iodine contrast: 100-150 ml (300 mg Iodine/ml) at 2–3 ml/second ● Oral contrast: use institutional standard
	MRI – alternative for abdomen and pelvis [use CT for chest coverage]	● Use 1.0T and above scanner ● Use gadolinium based i.v. contrast (dose = 0.1mmol/kg) unless contraindicated ● Include both T1 and T2-weighted sequences with T1-weighted both pre and post-contrast.	● 1.5T or 3.0T scanner, phased-array coil ● 5-8mm scanning ● T2-weighted FSE with fat suppression pre-contrast. ● T1W (2D or 3D) pre and post contrast with fat suppression.
Brain	MRI - preferred	● Use of 1.0T and above scanner ● Use gadolinium based i.v. contrast (dose = 0.1mmol/kg) unless contraindicated	● 1.5T or 3.0T scanner with head coil ● T1 weighted (pre and post contrast) and T2 weighted (pre contrast) axial scans. ● Further details as per institutional standard.
	CT - alternative	● Use i.v. contrast unless contraindicated	● Per institutional standard
Bone	● Bone scintigraphy is preferred, although PET (18F-fluoride NaF or FDG) and 99m Technetium SPECT is acceptable as an alternative. ● Hotspots indicative of metastases must be investigated with X-ray, CT or MRI.		

- All scans generated should be exportable in electronic format (DICOM) to enable secure and rapid electronic transmission to the designated central imaging laboratory.
- The same modality for a given anatomical coverage and the same scanning procedure (most

importantly: reconstruction slice thickness, anatomic coverage, use of i.v contrast) should be consistent between baseline and all subsequent follow up scanning. If possible, the same scanner or an equivalent scanner should be used throughout the study.

Table 7: Disease Assessment Scope and Schedules

Anatomic Region & Assessment Modality[1, 2]	Baseline[3]	Following First Dose[4]
Chest, abdominal and pelvic CT or MRI	To be performed on all subjects.	To be performed on all subjects in week 7 and week 12 every 8 weeks thereafter.
Head CT or MRI	Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases. **Note:** subjects with a positive scan must be excluded from the study with the exception of those subjects meeting criteria in footnote 5 [5]	To be performed only as clinically indicated.
Bone Scan	To be performed only as clinically indicated	1) To be performed only as clinically indicated (i.e. subject is symptomatic with bone pain).

- The following information must be documented: date of assessment, diagnostic technology used for each anatomic region (e.g. chest spiral CT), description of the type and site of a lesion (e.g. liver mass).
- The same method, technique should be used to characterize each identified lesion at baseline and subsequent disease assessments.
- All the baseline disease assessments should be completed within 28 days prior to the date of inclusion in the trial.
- Disease assessments should be performed at the indicated frequency following the first dose until documented disease progression, death or upon initiating another anti-cancer treatment, whichever occurs first.
- Subjects with CNS metastases at baseline will be excluded from the study with the exception of those subjects who have previously-treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and meet both of the following criteria: a) are asymptomatic and b) have no requirement for steroids or EIACs.

14. Treatment control and dispensing:

- **Treatment control:** A record of the number of Pazopanib tablets taken and returned by each subject should be recorded in patient's medical record and register in the CRF.
- **Treatment dispensing:** At Pharmacy Service. Adequate number of Pazopanib tablets for 3 weeks of treatment during the first 12 weeks and for 4 weeks of treatment thereafter, should be dispensed.

15. Survival: patient status (alive/dead/lost to follow up) and new anti-cancer therapy. All subjects should be followed until death, if possible. The date of death and cause of death should be evaluated and documented in the eCRF.

9. ADVERSE EVENTS

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.
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., x-ray, ECG) should also be recorded as AE. The criteria for determining whether an abnormal objective test finding should be reported as an AE 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 SAE, and/or
- test result is considered to be an AE by the investigator.

9.1. Definitions

The definitions from ICH GCP apply in this trial protocol.

Adverse event (AE)
An adverse event is 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 judgement 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, for the purpose of this study it will be consider as SAEs, all hepatotoxicities as follows:

1) 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

2) 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.

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.

Last version of Summary of Product Characteristic available in EMEA website, will be the reference document to establish the AE expectedness for Pazopanib.

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 each study drug, including products in combination and comparators, according to the following criteria:
Y There is a reasonable chance that the study drug(s) caused the SAE.
N There is not a reasonable chance that the study drug(s) caused the SAE and other causes are more likely.
UK 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 centre) and when none of the above options can be utilized.

9.2. Reporting of Adverse Events

The sponsor 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 CRF. Investigators must assess the severity (grade) of the event following NCI-CTCAE V 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 sponsor in addition to that on the 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, Chief investigator and/or Sponsor.
Site investigation staff should notify the sponsor, all the pregnancies of female subjects and female partners of male subject 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 communicate using the SAE form. The autopsy report should be sent to Sponsor identified only with the patient inclusion number.

For the purpose of this study it will be consider as SAEs, all hepatotoxicities as follows:

1) 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

2) 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 serious adverse events must be reported by fax within 24h to MFAR, S.L.

[redacted]

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 MFAR S.L. 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 Trial Chief Investigator and/or Sponsor.

9.3 SUSAR Expedited reporting by the Sponsor

The Sponsor will be responsible for the reporting of SUSARs to regulatory authorities. The Sponsor will follow the procedure detailed in 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 EC 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.

9.3.1 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.

9.3.2 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 or investigational drug development and likely to affect the safety of subjects, 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 an 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.

9.3.3 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 clinical trials or product development, including development program interruption or changes to safety-related protocol issues.

10. STATISTICAL CONSIDERATIONS

10.1. Study Endpoints

10.1.1. Primary Efficacy Endpoint

The primary end-point of the study is progression free survival 12 weeks after start of therapy, measured as a binary variable. This will be based on the disease evaluation performed 12 weeks after start of treatment with central radiology review. Patients who are alive and progression free at this time will be considered as successes. Patients who have progressed or are dead at this time will be considered as failure. Patients with an unknown progression status will be considered as failure. The diagnosis of progression should be based on tumor measurements, according to the RECIST 1.1 criteria.

10.1.2. Secondary Endpoints

Overall progression free survival (median PFS)
Overall progression free survival will be computed from the date of start of treatment to the first documented date of progression or the date of death, whatever the cause. Patients alive and free from progression at the time of the analysis will be censored at the date of last follow-up.

Objective tumor response
Objective tumor response, measured according to the RECIST 1.1 criteria, will be used as secondary end-point in this trial.

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and followed until disease progression.

Time to onset of response
It will be computed from the date of start of treatment to the time of first documented response.

Duration of response
It will be computed from time of attaining response to the time of first documented progression or death.

Overall survival (OS)
It will be computed from the date of start of treatment to the date of death, whatever the cause. Patients alive or lost for follow-up at the time of the analysis will be censored at the date of last follow-up.

Clinical benefit rate
Patients who achieve CR, PR, or SD for 6 months or more and an improvement of symptoms will be considered as having derived clinical benefit.

Growth Modulation Index (GMI)
GMI is the ratio between time to progression (TTP) with pazopanib (TTPp) divided by the

TTPp-1 with the previous line of therapy.

Safety profile (according CTCAE, version 4.0)

The safety and tolerability of Pazopanib will be determined by means of type, incidence, severity, timing, seriousness, and relatedness; of reported AEs, physical examinations, and laboratory tests. Toxicity will be graded and tabulated by the NCI-CTCAE v 4.0.

10.2. Efficacy assessment

Disease should be captured and target/non-target identified at baseline by CT or MRI as appropriate. Subsequently, imaging studies required to investigate known disease should be performed on week 6/7, on week 12 and every 8 weeks thereafter. Imaging methods will be employed consistently during the course of each patient's evaluation during the study. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 8 weeks, unless they have started a new anti-cancer therapy, withdrawal of consent or death, whichever occur first. 10.2.1. 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 received at least 3 weeks of treatment with Pazopanib with no major protocol deviations will be included in the analysis of efficacy.

10.3. Safety assessment

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

10.4. Sample Size and Statistical analysis

The drug will be separately investigated in the following liposarcoma subtypes:

- Well-differentiated liposarcoma/dedifferentiated liposarcoma (ALT-WD)
- Myxoid/round cell liposarcoma.

The Simon two-stage design will be separately applied in each stratum. A total of 17 patients will be included in each stratum for the first step of the trial. For the second step, 20 (up to 37) additional patients will enter in each stratum provided the results of the first step were positive. A total of 37 patients could enter the study in each stratum.

Success will be defined as documented disease stabilization or response after at least 12 weeks of therapy.

The following design characteristics and decision rules apply separately to each stratum. The Simon optimal one sample two stages testing procedure (optimal design) will be used with the following hypotheses:

- Success in 20% of the cases or less in one of the strata will be considered as unacceptable, and would not warrant further investigation (null hypothesis). Therefore, the value of P0 will be taken as 20%.
- Success in 40% of the cases or more in one of the strata will be considered as an acceptable result warranting further investigation of the drug in this histology (alternative hypothesis). Therefore, the value of P1 will be taken as 40%.

These two reference values are based on a retrospective analysis of the EORTC STBSG database of patients treated with 2nd line therapy [13].

Under those hypotheses, a total of 37 eligible and treated patients will need to be recruited in each stratum and followed for at least 12 weeks. The size of the type I and type II errors is 10% (alpha=beta=0.1).

A total of 17 eligible and treated patients will be included (in each stratum) in the first step of the study.

1. If ≤ 3 successes are observed in a stratum, the trial will be stopped in this stratum with the conclusion that the drug should not be further investigated in this histology.
2. Else, patients will continue to be accrued until 37 eligible patients have been recruited and have started therapy. If 11 or more successes are observed in those 37 patients, we will conclude that the results of this trial warrant further investigation in this histology.

In addition, sequential tests for each cohort combined with overall futility test will be performed after the first stage accrual is achieved, as described by LeBlanc et al[14]. This procedure allows for stopping a subgroup for futility keeping error rates.

PFS and OS will be calculated from the date of treatment initiation and will be estimated by the Kaplan-Meier method in each stratum. Due to the rarity of the disease, patients will be allowed to get in the study while the first stage analysis is being performed unless otherwise advised by safety or futility sequential test for each cohort.

11. LEGAL AND ETHICS CONSIDERATION

11.1. Ethic Committee

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 (Annex XII); 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.

11.2. Authorities

The study protocol and/or related documents will be submitted to regulatory authorities before commencement of the clinical trial, as national authorities on the country where the trial is taking place require.

11.3. Informed consent

The patient should sign 2 separate informed consents: one for the clinical trial and another for biological samples studies.
The clinician will have to explain the nature, objectives and possible consequences of the clinical trial in a manner that is understandable by the patient.
The patient must give his/her consent before being admitted into the study and before biological samples are taken.
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 investigator will not start any investigation related with the study until the consent has been obtained.
The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the Ethics Committee.

11.4. Confidentiality

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 centre, and pertinent Health Authorities.
The investigator should facilitate access to the source documents and data for monitoring and auditing purposes.
The content of the case report forms (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.

11.5. Insurance Policy

The insurance or indemnity in accordance with pertinent regulatory requirements will be provided.
All patients in this study are insured through the Insurance Company HDI International with an insurance policy that satisfies the conditions stipulated by the RD 223/2004 in Spain.

11.6. End of the 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.

11.7. Early study termination

This study can be terminated prematurely if in the opinion of the sponsor there is a reasonable and sufficient cause. The investigator 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 (blank or totally or partially filled out CRF, study drugs, etc) must be returned to GEIS.

12. PRACTICAL CONSIDERATIONS

12.1. Diagnostic Criteria for the Study Disease

Patients included on this trial should have histological confirmed diagnosis of high or intermediate grade malignant liposarcoma with metastatic or locally advanced disease. Patient must have documentation of disease progression within 6 months prior to study entry documented as progressive by CT scan or MRI. Prior scans will be used to classify the patient as having progressive disease at baseline according to RECIST 1.1 criteria.
Paraffin embedded tumour blocks/slides will be collected for all patients for a central pathological review. First diagnosis sample or another more recent available sample obtained during the routine care previous to study entry will be acceptable. Tumour biopsy at study entry will NOT be compulsory but recommended if clinically acceptable (ex. superficial or easily accessible locations). The central pathological review is a pre-requisite for entering the trial; the study treatment should not be initiated unless the diagnosis is confirmed by means of the central pathological review.

12.2. Responsibilities according to Good Clinical Practice

Investigator Responsibilities
Responsibilities of the principal investigator of each participating centre include:

- To sign the study protocol.
- To know in depth all study drugs characteristics.
- To obtain informed consent of subjects before inclusion in the trial.
- To ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory valued, related to the trial.
- Collect, register and notify data in a correct way.
- To notify immediately to the sponsor all SAE and unexpected adverse events.
- To take responsibility that all people involved in the trial will respect the confidentiality of any information about the study subjects.
- To keep the Ethics Committee regularly informed on the facts of the study.
- To take responsibility on the elaboration of the final study report, providing his/her agreement and signature.

For German Investigator Responsibilities see also Annex VII

12.3. Instructions for e-CRF completion

The data will be recorded GCP-compliantly by means of the electronic documentation system (electronic CRFs) at the study centre.
The application 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. In particular, data storage will be undertaken exclusively centrally. The server is housed at "Centro de Proceso de Datos de InterHost en Madrid, calle Albasanz, 71"
For data entry and print-outs, the system is based fully on the so-called "web interface", i.e. entry forms and reports are displayed on the client computer as HTML pages (Hyper Text Markup Language = standard page description language on the Internet) within a Web browser. No user-specific software is necessary to operate the system on the investigator's client computer. There is the possibility of direct access to the raw data by means of ODBC for further processing of the data.

The data are checked for correctness by ranks and validity and consistency checks. Implausible or missing data can be corrected or supplemented following discussion with the investigator. The correction documents are stored (audit trail).
Other than the investigator, only expressly authorised persons trained for the study may complete the e-CRF.
All data in the e-CRF should be able to be documented in measurement records or by entry in patient records.

12.4. Supply of Study Drugs

Pazopanib will be supplied by the Sponsor.

12.5. Packaging and labelling

The study drugs labels will contain all the information to comply with standing regulatory requirements.

12.6. Final report and Publications

12.6.1. Clinical Trial Publication

The final publication of the trial results will be written by the Chief Investigator on the basis of the final analysis performed at the [redacted]

A draft manuscript will be submitted by the Chief Investigator, other co-authors (including the Clinical Study Coordinator in Germany) and [redacted] for review no later than six months after receiving the Data Center report (final analysis). After revision by the Data Center, other co- authors (including the Clinical Study Coordinator in Germany) and [redacted], 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 pathologist, radiologist and statistician, who have contributed to the trial, will be included in the authorship of the final manuscript.

The sequence of the authors in publication will be: Chief investigator (first), subsequent authors according to the number of patients, Clinical Study Coordinator in Germany (last).

The title of all manuscripts will include [redacted], and all manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the trial, the data centre staff involved in the study, as well as supporting bodies (Sponsor's Partner, etc...).

All publications (papers, abstracts, 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 [redacted] allowing a period of at least 30 days for review (at least 5 working days for abstracts). They will not include either [redacted] confidential information other than the study results or personal data on any patient, such as name or initials.

The Chief Investigator and the Clinical Study Coordinator in Germany must approve all publications, abstracts and presentations of data pertaining to patients included in this

study.

This is applicable to any individual patient registered/randomized in the trial, or any subgroup of these.

Such a publication cannot include any analysis of any of the study end-points unless the final results of the trial have already been published by the Chief Investigator.

12.6.2. Translational Research Publication

Results of the translational research project will be published in major scientific journals, after the publication of the main results of the clinical study.

The first author will be the Translational Study Coordinator. All centres that have contributed to at least 5% of the analysed material will be represented in the publication by one co-author; centres that have contributed to at least 15% of the analysed material will be represented by two co-authors; this(these) author(s) will be selected by each centre internally (pathologist, molecular biologist, clinician...). All centres that have provided material for the analysis will be acknowledged. The list of authors will also include the Chief Investigator and the Clinical Study Coordinator in Germany.

The clinical trial will be registered in "clinicaltrials.gov", database of National Institute of Health of United States of America.

12.7. Monitoring

The study will be monitored by regular site visits, telephone calls and periodic inspection of the CRF with enough frequency to ascertain the following:

- Investigational Products (IPs): storage conditions, that the supplies are sufficient throughout the trial.
- Rate of patient inclusion.
- Compliance with approved protocol and all approved amendment, if any.
- That the investigator receives all documents and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory regulations.
- That the investigator and trial staff is adequately informed about the trial.
- Integrity and accuracy of data (as per monitoring plan):
    - Consent Informed (version, signature and date)
    - Eligibility criteria
    - Baseline tests
    - SAE and SAE reporting
    - Primary endpoint
    - Biological Samples storage and collection
    - Stock reconciliation in pharmacy.
- CRFs completion and adverse events collection.
- Reporting of protocol deviations according GCPs and the applicable regulatory local requirements. Taking appropriate action to prevent recurrence to the detected deviations.

Monitoring visits will be done by study monitors. It is understood that these monitors will have access to the clinical records after asking the investigator. Adequate time for these visits should be allocated by the Investigator. The Investigator will also ensure that the

monitor is given direct access to the documents.

12.8. Protocol Amendments

Supplements and changes to the protocol can be performed exclusively by the Sponsor, who must submit them to the Ethics Committee and the local Regulatory Authority protocol amendments.

12.8.1 Amendment 1

The 1st amendment modify the schedule in the monitoring of plasma hepatotoxicity and therefore in the schedule of visits. It does not increase the number of visits. These modifications are implemented in Protocol version 2.0 April 8, 2013.

12.8.1 Amendment 4

New safety information about pazopanib is included in the protocol version 3.0 February 11, 2015.

12.9. Data Handling

All data (personal, clinical, economic, derived from biologic material) obtained from patients will be handled according to the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data. According to such legislation, patients will be able to exert their rights to access, modification, opposition and cancellation of their data, for which the clinical trial physician must be addressed. The content of the CRFs, as well as the documents generated during the study will be considered strictly confidential and not revealed to third parties.

12.10. Documentation

The Investigator/Institution should maintain trial documents according to ICH Topic E6 Section 8, and as required by pertinent regulatory requirements.
Essential documents should be stored according to ICG GCP guidelines or for a longer period of time, if required by pertinent regulations.
The original patient data (clinical record) must be kept archived for the time stipulated by the study centre regulations. This period should not be less than 15 years.

13. TRANSLATIONAL STUDY

PRIMARY OBJECTIVES:

- To evaluate the influence of the angiogenic status of the tumor on the response to Pazopanib.
- To evaluate the serum profile of serum cytokine markers as indicator of response to Pazopanib.

SECONDARY OBJECTIVES:

- To evaluate microvessel density (MVD) and p53, MDM2, PTEN and VEGF/PDGF pathways by IHQ expression and their correlation with prognosis as well as their role as predictive factors to treatment with Pazopanib (Response, PFS and OS).
- To evaluate serum levels of several angiogenic factors/cytoquines using Luminex XMAP Technology at baseline, after the first 3 weeks of treatment, at maximum response and at progression and their predictive value for survival and response to treatment: 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 analyse PIK3CA mutations in order to demonstrate if those liposarcomas with PIK3CA mutations defines a subgroup of patients with differential response to Pazopanib.

STUDY OF BIOMARKERS:

Paraffin-embedded samples from 74 original tumors and if clinically acceptable (ex. superficial or easily accessible locations), tumour biopsy at study entry will be collected and the following analysis will be carried out:

- Microvessel density on full sections of the tissue.
- Immunohistochemical profile of angiogenic markers and p53, MDM2 and PTEN.
- Quantitative RT-PCR of a panel of angiogenic markers.

Serum from peripheral blood will be performed (4 per subject):

1. Within 72 hours prior starting the treatment (basal).
2. Within 72 hours after the first 3 weeks of treatment.
3. Within 72 hours after radiological response is documented.
4. Within 72 hours after progressive disease is documented.

Methodology:
a) Microvessel density and immunohistochemistry: Full sections of paraffin-embedded material will be stained with anti-CD34 or anti-CD31 and evaluated using a light microscope and specific software for measuring microvessesls with no muscular walls.
Tissue microarrays (TMA) will be constructed containing at least two cores (1.0 mm in diameter) from each tissue sample.
At least the following antibodies will be tested: VEGF, PDGF, VEGFR-1 (flt-1), VEGFR-2 (flk-1/KDR), PDGFR-alfa, PDGFR-beta, HIF-1, TSP-1, VE-cadherin, p53, MDM2 and PTEN.
Additional tests could be considered depending of new findings or evidences in the field of tumor angiogenesis.

b) RT-PCR Low density arrays for the expression of angiogenic factors: We will perform an RNA extraction from paraffin embedded material and an RT-PCR low density expression array containing 94 angiogenesis-related genes will be analysed. These arrays include known angiogenesis growth factors like VEGF, and known matrix derived inhibitors such as endostatin. Additionally, the panel contains markers and targets for angiogenesis and lymphangiogenesis.
List of genes included:
- Angiogenic growth factors (28): ANG, ANGPT1, ANGPT2, ANGPT4, CSF3, CTGF, CXCL12, ECGF1, EDIL3, EPHB2, FGF1, FGF2, FGF4, FST, GRN, HGF, IL8, LEP, MDK, PDGFB, PROK1, PTN, TGFA, TGFB1, TNF, VEGF, VEGFB, VEGFC.
- Angiogenesis inhibitors (37): ADAMTS1, ANGPTL1, BAI1, CHGA, COL15A1, COL18A1, COL4A1, COL4A2, COL4A3, CXCL10, CXCL2, F2, FBLN5, FGA, FLT1, FN1, HSPG2, IFNB1, IFNG, IL12A, ITGA4, LECT1, PF4, PLG, PRL, SEMA3F, SERPINB5, SERPINC1, SERPINF1, THBS1, THBS2, TIMP2, TIMP3, TNFSF15, TNMD, TNNI1, VASH1.
- Angiogenesis markers (10): AMOT, ANGPTL2, ANGPTL3, ANGPTL4, CEACAM1, HEY1, ITGAV, PECAM1, PGK1, XLKD1.
- Angiogenesis targets (13): EDG1, ENPP2, FLT3, FLT4, ITGB3, KDR, KIT, NRP1, NRP2, PDGFRA, PDGFRB, TEK, TIE1
- Lymphangiogenesis markers (5): CD44, CDH5, FIGF, FOXC2, PROX1
- Controls (2): 18S, GAPDH

c) Serum cytokine markers: 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].

d) Analysis of PIK3CA mutations: DNA extraction, amplification of exons 4, 7, 9 and 20 of PIK3CA by PCR and direct sequencing will be performed.

The proposed biomarker study includes analysis of tumor tissue at diagnosis and serum cytokines and growth factors at different phases within the treatment schedule. In the case of serum, the kinetic profile of each biomarker will be considered (decreased, constant, increased). All analysed parameters will be correlated with: Progression-free survival (PFS) assessed 12 weeks after start of treatment (According the RECIST criteria 1.1); median PFS; objective tumor response; overall survival and histopathological parameters.
For the statistical analysis, we will use binary variables reflecting the positivity status of the measures (yes or no; presence/absence). Association with histopathological parameters, and objective tumor response, all categorical, will be also assessed using a chi-square test to determine homogeneity or linear trend for ordinal variables. The significance level will be set at 5%. To study the impact of the histological, immunohistochemical and molecular factors on progression-free survival (PFS) and overall survival (OS), the Kaplan-Meier proportional risk test (log rank) will be used. Evidence of the relative risk for each patient will be also provided by means of a Cox proportional hazards model using stepwise selection to identify the independent predictors of poor outcome.
We do not plan to use multivariate analysis to analyse biomarkers. Standard pre-post univariate tests will be used instead.
For the kinetic profile of the serum biomarkers, each variable will be considered as continuous. A correlation between the growth factor or cytokine levels with the different points of the treatment schedule will be considered and the slope value will be used in

order to distinguish those cases with no change, negative or positive trend. The threshold will be calculated after considering the behaviour of the whole series.
The slope value will be considered from baseline and using the nonparametric Wilcoxon signed-rank test. However other analysis will be undertaken depending of the behaviour of the measures.

For sending the biological samples, please contact to:

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

14. REFERENCES:

1. Minchom A, Jones RL, Fisher C et al. Clinical Benefit of Second-Line Palliative Chemotherapy in Advanced Soft-Tissue Sarcoma. Sarcoma, vol. 2010, Article ID 264360, 8 pages, 2010. doi:10.1155/2010/264360.
2. Mandahl N et al. Nonramdom pattern of telomeric associations in atypical lipomatous tumors with ring and giant marker chromosomes. Cancer Genet Cytogenet 1998; 103:25.
3. Meis-Kindblom JM et al. Cytogenetic and molecular genetic analyses of liposarcoma and its soft tissue simulators: recognition of new variants and differential diagnosis. Virchows Arch 2001; 439:141.
4. Jones RL, Fisher C, Al-Muderis et al. Differential sensitivity of liposarcoma subtypes to chemotherapy. Eur J Cancer. Dec 2005; 41(18):2853-60.
5. Toulmonde M, Italiano A, Penel N et al. Advanced well-differentiated/dedifferentiated liposarcomas: Role of chemotherapy and survival. J Clin Oncol 29: 2011 (suppl; abstr 10071). Data actualized in poster presentation.
6. Antonescu Cr et al. Specificity of TLS-CHOP rearrangement for classic myxoid/round cell liposarcoma: absence in predominantly myxoid well-differentiated liposarcoma. J Mol Diagn 2000; 2: 132.
7. Pakos EE et al. Expression of vascular endothelial growth factor and its receptor, KDR/Flk-1 in soft tissue sarcomas. Anbticancer Res 2005; 25: 3596.
8. Sleijfer S et al. Pazopanib, a multikinase angiogénesis inhibitor, in patients with relapsed or refractory advanced Soft Tissue Sarcoma: A phase II study from the EORTC- Soft Tissue and Bone Sarcoma Group (EORTC62043). JCO 2009; 27(19): 3126.
9. Van Der Graaf W, Blay JY, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomized, double-blind, placebo-controlled phase III trial. The Lancet 2012; 379 (9829): 1879.
10. Sleijfer S et al. Soluble factors associated with efficacy and toxicity of Pazopanib in advanced soft tissue sarcoma patients: An EORTC-STBSG. JCO 28;/ s, 2010 (abst 10040).
11. 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
12. 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.
13. Van Glabbeke M, Verweij J, Judson I et al. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. European Journal of Cancer 38 (2002) 543–549.
14. LeBlanc M, Rankin C and Crowley J. Multiple Histology Phase II Trials.Clin Cancer

Res 2009; 15: 4256-4262.

ANNEX I: Urine Protein Creatinine Ratio (UPC)

Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.
Normal protein excretion is <150 mg/24 hours and is similar for men and women.
Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.
Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

Calculating UPC
UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).
UPC ratio ≈ equivalent to grams of protein excreted in urine over 24 hrs.
Example: Patient has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.
UPC ratio= (90 mg/dL) / (30 mg/dL) = 3
The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

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

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: µmol/L	Multiply by 88.4
SI Units: µmol/L	Conventional Units: mg/dL	Divide 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. Available from http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm

ANNEX II: Determination of Creatinine Clearance (Cl_{CR})

Estimation of creatinine clearance using Cockroft and Gault method:

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

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

Cl_{CR} 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:

$$Cl_{CR} = \frac{C_U \cdot V}{C_{CR}}$$

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.

ANNEX III: Laboratory assessment recommendations

Clinical Laboratory Assessments

Laboratory assessments should be performed as indicated in the Time and Events Table (table 5). 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.
Results for all unscheduled clinical laboratory assessments (.e.g., hematology, TSH/T4, coagulation parameters) should be recorded on an unscheduled laboratory form in the eCRF.
Table 6 shows the clinical laboratory assessments that should be reported.

Table 6: Clinical Laboratory Assessments

Clinical Chemistry	
Renal function	Urea, [Creatinine]
Liver function test (LFT) Panel	Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Bilirubin (total)[b]
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)[c]
Urinalysis for Proteinuria	UPC[d]
Thyroid Function Test	TSH[e]

a) Estimated creatinine clearance should be calculated using the Cockroft and Gault method (Annex III). Alternatively, creatinine clearance can be measured directly by 24-hour urine collection.
b) A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 X upper limit of normal (ULN). See Section 7.6.2 for stopping criteria and dose modification guidelines for treatment-emergent liver function abnormality.
c) Coagulation tests may also be performed in response to an AE/SAE of bleeding and as clinically indicated.
d) UPC should be evaluated as described in Annex II or by 24-hour urine protein. If UPC ≥ 3 or if urine protein is ≥ 3g, then the dose modification table guidelines should be followed (Section 7.6.1).
e) Unscheduled thyroid function tests [TSH and thyroxine (free T4)] should be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

ANNEX IV Definition of Responsibilities in Trial Sites

Only valid for German sites

Am 26. Oktober 2012 trat das Zweite Arzneimittelrechtsänderungsgesetz in Kraft. Infolge dessen gelten neue Anforderungen hinsichtlich Prüfer, Stellvertreter, Prüfstelle und Prüfgruppe

§ 4 (25) AMG (*Prüfer*)

- **Prüfer ist** in der Regel ein für die Durchführung der klinischen Prüfung bei Menschen in einer Prüfstelle verantwortlicher Arzt oder in begründeten Ausnahmefällen eine andere Person, deren Beruf auf Grund seiner wissenschaftlichen Anforderungen und der seine Ausübung voraussetzenden Erfahrungen in der Patientenbetreuung für die Durchführung von Forschungen am Menschen qualifiziert.
- **Wird eine klinische Prüfung in einer Prüfstelle von einer Gruppe von Personen durchgeführt, so ist der Prüfer** der für die Durchführung **verantwortliche Leiter dieser Gruppe**.
- Wird eine Prüfung in mehreren Prüfstellen durchgeführt, wird **vom Sponsor ein Prüfer als Leiter der klinischen Prüfung benannt**.

§ 40 (1a) AMG (*Stellvertreter, Prüfgruppe*)

- Der **Prüfer bestimmt angemessen qualifizierte Mitglieder der Prüfgruppe**.
- Er hat sie **anzuleiten** und zu **überwachen sowie ihnen die für ihre Tätigkeit im Rahmen der Durchführung der klinischen Prüfung erforderlichen Informationen**, insbesondere den Prüfplan und die Prüferinformation, **zur Verfügung zu stellen**.
- Der Prüfer hat **mindestens einen Stellvertreter mit vergleichbarer Qualifikation zu benennen**.

§ 40(2) AMG (*Aufklärung der Patienten*)

- **Die betroffene Person ist durch einen Prüfer, der Arzt** oder bei zahnmedizinischer Prüfung Zahnarzt ist, **oder durch ein Mitglied der Prüfgruppe, das Arzt,** oder, bei zahnmedizinischer Prüfung, Zahnarzt **ist**, über Wesen, Bedeutung, Risiken und Tragweite der klinischen Prüfung sowie über ihr Recht aufzuklären, […]
- Der betroffenen Person ist ferner Gelegenheit zu einem **Beratungsgespräch mit Prüfer oder Mitglied der Prüfgruppe, das Arzt** oder Zahnarzt **ist**, über sonstige Bedingungen der klinische Prüfung […]

§ 67 (1) AMG (*Anzeigepflicht*)

- Ist […] eine klinische Prüfung bei Menschen anzuzeigen, so **sind der zuständigen Behörde** auch deren Sponsor, […] sowie **der Prüfer und sein Stellvertreter**, soweit erforderlich auch mit Angabe der Stellung Leiter der klinischen Prüfung, **namentlich zu benennen**.

ANNEX V: 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,
and the 59th World Medical Association General Assembly held in Seoul, Korea, October 2008

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.