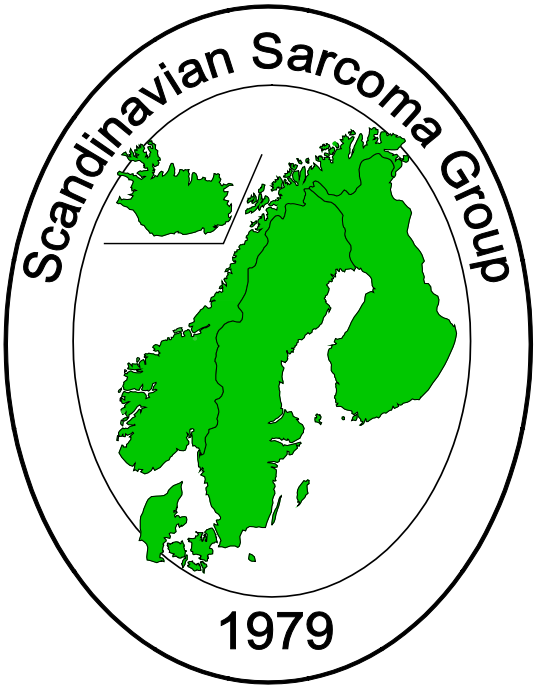

PAZOPANIB IN ADVANCED GASTROINTESTINAL STROMAL TUMORS REFRACTORY TO IMATINIB AND SUNITINIB

A Non-comparative Phase II Multicenter Study by the Scandinavian Sarcoma Group

(SSG XXI, "PAGIST")

Sponsor:
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PROTOCOL SYNOPSIS

Study Title	Pazopanib in Advanced Gastrointestinal Stromal Tumours Refractory to Imatinib and Sunitinib – A Non-comparative Phase II Multicenter Study by the Scandinavian Sarcoma Group
Study Number	SSG XXI
Study Short Name	PAGIST
Study Objectives	**Primary objective** The primary objective is to calculate the disease control rate (DCR=CR+PR+SD) at 12 weeks according to RECIST version 1.1. **Secondary objectives** - To calculate Overall response rate (ORR=CR+PR) at the time of best response since start of pazopanib - To calculate Progression free survival (PFS) for patients administered pazopanib - Assess the toxicity in patients treated with pazopanib **Subgroup analysis** - To calculate DCR in relation to mutational status of primary tumour sample - To calculate DCR in relation to plasma concentration at week 12
Study Endpoints	**Primary endpoint** Disease control rate (DCR=CR+PR+SD) at 12 weeks from start of pazopanib treatment according to RECIST version 1.1. **Secondary endpoints** - Overall response rate (ORR) defined as the fraction of patients ever achieving CR or PR during protocol treatment - Progression free survival (PFS) defined as the time from start of pazopanib to progressive disease according to RECIST, version 1.1 - Toxicity defined as adverse events and abnormal laboratory test results during protocol treatment **Subgroup analysis** - DCR in relation to mutational status of primary tumour sample - DCR in relation to plasma concentration at week 12
Study Design	Study SSG XXI is a non-comparative phase II multicenter trial evaluating the efficacy and safety of pazopanib in patients with GIST refractory to imatinib and sunitinib, and also to nilotinib if treated with that drug.
Study Drug	Pazopanib is a tyrosine kinase receptor inhibitor given as tablets of 400 mg, with the standard dose being two tablets given at one occasion at the same time each day without food at least one hour before and two hours after a meal.
Number of Patients	A total of 72 patients will be enrolled if an interim analysis performed after 22 patients shows that at least six patients achieve disease control as defined above.
Eligibility Criteria	a) Metastatic and/or locally advanced GIST, with diagnosis based on histology with positive c-kit and/or DOG-1, or with a GIST-typical mutation in KIT or PDGFRA, and confirmed by a

	specialized sarcoma pathologist b) Measurable disease on CT as defined by RECIST criteria; at least one measurable lesion not given radiotherapy c) History of progressive disease on CT according to RECIST criteria after both imatinib and sunitinib treatment, and *also* after nilotinib if this drug has been given d) No other TKIs given than imatinib, sunitinib and nilotinib e) Age at least 18 years at the time of diagnosis of GIST f) WHO performance status 0-2 g) Resolution of all toxic side effects from earlier TKI treatment and any other potential non-TKI treatment to grade 1 or below; however, without toxicity ≥ grade 2 there is no mandatory wash-out period from earlier TKI before start of pazopanib h) Sufficient organ functions as defined below: *Absolute neutrophil count (ANC)* ≥ 1.0 x 10^9/L *Platelets* ≥ 50 x 10^9/L *Prothrombin time (PT) or international normalized ratio (INR)* ≤ 1.2 x ULN (subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation) *Activated partial thromboplastin time (aPTT)* ≤ 1.2 x ULN *Bilirubin* ≤ 1.5 x ULN or direct (conjugated) bilirubin ≤ 2 x ULN if considered due to the tumour *Alanine amino transferase (ALT) and aspartate amino transferase (AST)* ≤ 3 x ULN or ≤ 5 x ULN if considered due to the tumour *Alcalic phosphatase (ALP)* ≤ 2 x ULN *Serum creatinine* ≤ 150 μmol/L *Dip-stick urinalysis* (if this test shows urine protein ≥ 2+, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value < 1 g to be eligible) *Left ventricular ejection fraction (LVEF)* ≥ 40%. *Corrected QT interval (cQT)* < 480 msec. Furthermore, patients with anamnestic QT prolongation or with QT prolonging comedication should be treated with caution. i) Absence of all following conditions: I) prior malignancy if presently claiming active treatment or in any other way is judged to be of significance by the investigator II) clinically significant gastrointestinal bleeding III) presence of uncontrolled infection of significance for the treatment IV) prior major surgery or trauma within 28 days prior to the

	first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer V) evidence of active bleeding or bleeding diathesis VI) uncontrolled hypertension , i.e. systolic blood pressure ≥ 150 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg VII) known endobronchial lesions and/or lesions infiltrating major pulmonary vessels VIII) 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 IX) unable or unwilling to discontinue use of prohibited medications (see appendix!) for at least 14 days prior to the first dose of study drug and for the duration of the study X) any treatment for GIST within 14 days prior to the first dose of pazopanib with the exception of imatinib, sunitinib or nilotinib, which may be used up to the day before start of pazopanib treatment j) No pregnancy or lactation; negative serum or urine pregnancy test mandatory in women with childbearing potential k) Women with childbearing potential must accept the use of adequate contraception throughout the study period, meaning one of the following: - An intrauterine device with a documented failure rate of less than 1% per year; - Vasectomized partner who is sterile prior to the female patient´s entry; - Complete abstinence from sexual intercourse from two weeks before start of treatment and to three weeks after stop of treatment; - Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide). *Note: Oral contraceptives are not reliable due to potential drug-drug interactions.* l) Written informed consent
Statistical Methods	Demographic and prognostic variables will be presented by means of descriptive statistics. Whenever appropriate, results will be illustrated with a graph. For the analysis of the primary endpoint, Simon's two stage analysis will be used [14, especially Table 2]. Simon's method is implemented as follows: Since sample size calculation is an integral part of Simon's method, no separate section on sample size will be written.

	The study tests the null hypothesis H_0: $p \leq 20$ % against the complementary hypothesis H_1: $p>20$ %, where p is the probability of clinical benefit. The type I error probability should be less than 5 %. If the true value of p is 35 %, the type II error probability should be less than 20 %. In order to achieve this with Simon's optimal two-stage design, a maximal number of 72 patients should be enrolled with an interim analysis after 22 patients. If five or less of these patients experience clinical benefit defined as disease control (CR + PR + SD), the study is stopped for futility. Otherwise all 72 patients are enrolled and H_0 is rejected if more than 19 of these experience clinical benefit. If the study has not been stopped for futility, a two-sided 90 % confidence interval for *p* will be produced with the method of inverting a series of hypothesis tests. The reason for using a 90 % confidence interval is that it then will be congenial with Simon's method – so that the confidence interval covers *p = 20 %* if and only if H_0 is not rejected with Simon's method. The analysis of the secondary endpoints will be performed only if the study has not been stopped for futility. This should, strictly speaking, be accounted for in the calculation of P-values and confidence intervals. This subtlety is however ignored, and P-values and confidence intervals for the secondary endpoints should only be considered as approximate. 1. ORR will be calculated and a 90 % confidence interval will be produced 2. Kaplan-Meier estimates of disease-free survival will be produced together with 90 % confidence intervals. The results of this calculation will be accounted for in a graph. 3. DCR will be calculated separately within each mutational status group, and a P-value will be computed using Fisher's exact test. 4. Only descriptive statistics, means, medians, standard deviation and a box- and whiskers plot will be used to describe the plasma concentration between the groups with DCR = 0 and DCR = 1.

1. Introduction

1.1 Gastrointestinal stromal tumors (GIST)

GISTs are mesenchymal tumors which form a specific entity of soft tissue sarcomas (STS), and they are probably arising from a pre-stage of the interstitial cells of Cajal, the gastrointestinal "pacemaker cell". The predominant localizations for GISTs are the stomach and the small intestine, but they may also occur in the rectum, esophagus or colon, and occasionally also in the omentum or the mesenterium. Surgery is the most important treatment whenever possible, with exception of very small lesions that may be followed. Locally advanced or metastatic GIST is regarded as not curable, with a possible exception of localized tumors that may be resectable after medical treatment (see 1.2).

GIST is in the vast majority of cases characterized by the expression of the receptor tyrosine kinase KIT (CD117), and about 90% of GIST tumors contain mutations in the KIT receptor leading to constitutive activation of KIT. A small fraction of GISTs instead contain mutations in another tyrosine kinase, PDGFR-α. The mutations are of "gain-of-function"-type and their critical role in tumorogenesis has been demonstrated. However, about 10-15 % of GISTs lack mutations in these genes. The mutational status has been shown to correlate with the natural prognosis and also with responsiveness to modern treatment. For review, see e.g., [1].

1.2 Non-surgical treatment of GISTs

GIST was generally accepted as a specific entity in the 90´s, and it became then soon obvious that chemotherapy was of little or no use in this disease. Radiotherapy has also been regarded as a modality without any beneficial effect, but this has not yet been studied in a formalized way and a palliative effect in late stage disease can not be excluded.

However, a dramatic shift in the management of GIST evolved since it by the turn of the century was shown that the tyrosin kinase inhibitor imatinib mesylate (Gleevec/Glivec), developed for the treatment of bcr-abl mutated chronic myeloic leucemia, also effectively inhibited the KIT mutation. Thus, a phase II-trial in 147 patients with advanced GIST showed a 54 % objective response rate by RECIST (Response Evaluation Criteria in Solid Tumors)[2]. Follow-up from this trial subsequently demonstrated a median progression-free survival (PFS) of 2.5 years [3]. Only about 15 % of GISTs seem to be primarily resistant to imatinib. KIT mutations in exon 11 seem to result in the best responses, whereas mutations in exon 9 seem to need the double standard dose of imatinib to respond (800 vs 400 mg per day). GISTs lacking mutations, so called wild type (WT), have an even less chance to respond to imatinib.
When a responsive GIST progress, it has been shown that the tumor harbour one or several secondary mutations that inhibits binding of imatinib to the KIT or PDGFR-α. About 5 – 10% of patients in this situation seem to respond temporarily to imatinib dose escalation.

In 2006, another tyrosine kinase inhibitor, sunitinib malate, which inhibits also the angiogenic genes of the VEGF class, was shown to give another 5-6 months PFS in imatinib refractory patients, even if few responses were reported [4]. This drug has therefore been approved as second-line treatment in GIST.

However, there is so far no established treatment for patients failing both imatinib and sunitinib, a situation that will face most patients with a median time from diagnosis of about 3 years. Some

patients are by then only treated with symptomatic options, even if it is strongly recommended that TKIs must be given as long the patient can tolerate the drug to hinder a dramatic progression.

Some patients are, however, offered other experimental drugs, within or outside clinical trials, most often new TKIs with somewhat different binding capacities and toxicity profile. Thus, there are some experiences with other TKIs as nilotinib, sorafenib, masatanib, valatanib, dasatanib etc., but there are no systematic or convincing results of effective third line activity presented so far. Furthermore, some of these drugs seem to be more toxic than at least imatinib.

1.3 Pazopanib

Pazopanib is a novel adenosine triphosphate competitive tyrosine kinase inhibitor of VEGF1, 2 and 3, PDGFR -α and –β, and KIT [5]. More than 2000 patients with malignant tumours have been enrolled in clinical studies of pazopanib, and it has been shown that a daily dosage of 800 mg orally is associated with a reasonable safety profile and encouraging efficacy in various tumours [6].

Most common side effects reported in clinical studies have been diarrhea (52%), hypertension (40%), hair color depigmentation (38%), nausea (26%), anorexia (22%), and vomiting (21%). Most of these events were grade 1 or 2 according to NCI CTCAE version 3.0. However, rare but severe events previously seen with other VEGFR inhibitors have also been observed with pazopanib treatment, e.g., cardiac/cerebral ischemia, hemorrhage, and bowel perforation.

The most common laboratory abnormalities include elevations of ALT, AST and bilirubin, hypophosphatemia, hypomagnesemia, hypoglycaemia, and hypokalemia. These disturbances were seldom more than grade 1/2.

Pazopanib was recently approved by FDA (brand name: Votrient^{TM}) for metastatic renal cell carcinoma with or without earlier treatment with cytokines [7,8]. The drug is under exploration for ovarian cancer, breast cancer and non-small cell lung cancer.

A phase II-study by EORTC and GlaxoSmithKline on non-GIST soft tissue sarcoma demonstrated a 12 week progression free survival (PFS) for leiomyosarcoma of 43.9%, for synovial sarcoma of 48.6% and for a group of various sarcomas 39.9%, whereas the effect in liposarcoma was less convincing [9]. Based on this study, a phase III placebo-controlled multicentre study has been performed, results not yet published.

1.4 Rational for exploring pazopanib in GIST

The molecular targets for pazopanib have all a potential role for pathogenesis in GIST. Many researchers have found increased expression of VEGF in GIST, e.g., a Japanese group which showed positivity for VEGF with immunohistochemical staining in 26/33 (79%) GIST[10]. Furthermore, they found positivity for VEGFR-1 in 73% and for VEGFR-2 in 91%. In another work, a correlation with prognosis is found, demonstrating that patients with GIST expressing high VEGF levels had inferior PFS (7 vs 29 months) and OS (20 vs not reached >50 months) compared to weak or non-expressors of VEGF [11]. Sunitinib is also targeting VEGF, and has shown to be effective in many patients with imatinib refractory GIST [4], which has lead to the approval of this drug in imatinib refractory GIST. Other tyrosine kinase inhibitors with similar targets have also been tested in small clinical studies, e.g., sorafenib, with promising effects in

3rd [12] and 4th line [13]. In the latter study, 20% of patients achieved a partial remission and about a quarter of the patients received treatment for more than four months. In comparison with these other TKIs, pazopanib seem to be at least as safe and tolerable, as elucidated in clinical studies on different tumours. There is an obvious need for more tools in GIST patients refractory to imatinib and sunitinib, and pazopanib fulfils the criteria to be evaluated.

2. Study objectives and overview

2.1 Primary objective

The primary objective is to calculate the disease control rate (DCR=CR+PR+SD) at 12 weeks according to RECIST version 1.1.

2.2 Secondary objectives

- To calculate Overall response rate (ORR=CR+PR) at the time of best response since start of pazopanib
- To calculate Progression free survival (PFS) for patients administered pazopanib
- Assess the toxicity in patients treated with pazopanib

2.3 Subgroup analysis

- To calculate DCR in relation to mutational status of primary tumour sample
- To calculate DCR in relation to plasma concentration at week 12

2.4 Overview of the study

The study is a non-randomized open label phase II multicentre study to evaluate efficacy and tolerability of pazopanib in metastatic and/or locally advanced GIST with disease progression according to RECIST criteria after treatment with imatinib and sunitinib, i.e., intolerance to one or both of these drugs without evidence of progression is not enough. Nilotinib, a TKI with similar targets as imatinib and presently investigated in a phase III randomized trial against imatinib as first line in advanced GIST, is also allowed to have been used, but if so, the patient must also have shown progression during this therapy, i.e., from all the three mentioned TKIs. The use of any other TKIs before inclusion in this trial is not allowed, however. There is no mandatory wash-out period from last TKI until start of pazopanib. The standard dose is 800 mg orally once a day at least one hour before or two hours after a meal. Dose reductions, if needed, will be done according to section 3.2.3. The treatment will continue as long as no criteria for stopping treatment, as specified in 3.2.4, occurs. Follow-up will be done until 30 days after end of treatment for all patients (see section 5!). The study will thus come to an end 30 days after end of treatment for the last patient.

3. Study procedures

3.1 Eligibility criteria

a) Metastatic and/or locally advanced GIST, based on histology with positive c-kit and/or DOG-1, or with a GIST-typical mutation in KIT or PDGFRA, and confirmed by a specialized sarcoma pathologist

b) Measurable disease on CT as defined by RECIST criteria; at least one measurable lesion not given radiotherapy

c) History of progressive disease on CT according to RECIST criteria after both imatinib and sunitinib treatment, and *also* after nilotinib if this drug has been given

d) No other TKIs given than imatinib, sunitinib and nilotinib

e) Age at least 18 years at the time of diagnosis of GIST

f) WHO performance status 0-2

g) Resolution of all toxic side effects from earlier TKI treatment and any other potential non-TKI treatment to grade 1 or below; however, without toxicity ≥ grade 2 there is no mandatory wash-out period from earlier TKI before start of pazopanib

h) Sufficient organ functions as defined below:
Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
Platelets ≥ 50 x 10^9/L
Prothrombin time (PT) or international normalized ratio (INR) ≤ 1.2 x ULN (subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation)
Activated partial thromboplastin time (aPTT) ≤ 1.2 x ULN
Bilirubin ≤ 1.5 x ULN or direct (conjugated) bilirubin ≤ 2 x ULN if considered due to the tumour
Alanine amino transferase (ALT) and aspartate amino transferase (AST) ≤ 3 x ULN or ≤ 5 x ULN if considered due to the tumour
Alcalic phosphatase (ALP) ≤ 2 x ULN
Serum creatinine ≤ 150 μmol/L
Dip-stick urinalysis (if this test shows urine protein ≥ 2+, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value < 1 g to be eligible)
Left ventricular ejection fraction (LVEF) ≥ 40%. *Corrected QT interval (cQT)* < 480 msec. Furthermore, patients with anamnestic QT prolongation or with QT prolonging comedication should be treated with caution

i) Absence of all following conditions:
I) prior malignancy if presently claiming active treatment or in any other way is judged to be of significance by the investigator
II) clinically significant gastrointestinal bleeding
III) presence of uncontrolled infection of significance for the treatment
IV) prior major surgery or trauma within 28 days prior to the first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer
V) evidence of active bleeding or bleeding diathesis
VI) uncontrolled hypertension, i.e. systolic blood pressure ≥ 150 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg
VII) known endobronchial lesions and/or lesions infiltrating major pulmonary vessels
VIII) 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
IX) unable or unwilling to discontinue use of prohibited medications (see appendix 1) for at least 14 days prior to the first dose of study drug and for the duration of the study

X) any treatment for GIST within 14 days prior to the first dose of pazopanib with the exception of imatinib, sunitinib or nilotinib, which may be used up to the day before start of pazopanib treatment

j) No pregnancy or lactation; negative serum or urine pregnancy test mandatory in women with childbearing potential

k) Women with childbearing potential must accept the use of adequate contraception throughout the study period, meaning one of the following:
- An intrauterine device with a documented failure rate of less than 1% per year;
- Vasectomized partner who is sterile prior to the female patient´s entry;
- Complete abstinence from sexual intercourse from two weeks before start of treatment and to three weeks after stop of treatment;
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).
Note: Oral contraceptives are not reliable due to potential drug-drug interactions.

l) Written informed consent

3.2 Study drug

3.2.1 Provision

The study drug will be provided by GlaxoSmithKline as a financial support for the trial. It will be delivered through one hospital pharmacy per participating country. Study drug labelling is done by the company Aspen in Germany.

3.2.2 Dosage and administration

800 mg (two tablets à 400 mg) taken once daily orally without food at least one hour before and two hours after a meal.

3.2.3 Dose modifications

In the case of adverse events of CTCAE version 4.0 grade 3-4, or if laboratory limits for inclusion (see 3.1) is not any longer fulfilled at any sampling during the study period, the dose is reduced to 400 mg daily, and if the event is then reversed to grade 0-1 for toxicity according to CTCAE, and to acceptable limits (as for inclusion) for laboratory values, an increase is made to 600 mg daily (but not more). In the case of an adverse event of grade 2, a similar dose reduction may be made as a joint decision by the patient and the investigator. If a dose increase to 600 mg as described above lead to grade 3-4 adverse events again, the dose must be permanently decreased to 400 mg. If any grade 3-4 events occur at the dose level of 400 mg, the treatment must be stopped permanently. The same decision may be taken (as above) for grade 2 events.

3.2.3.1 Specifications for certain adverse events

a) Hypertension: In the case of hypertension of at least CTCAE v 4.0 grade 3, i.e. systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure of ≥ 100 mm Hg, the dose of pazopanib is decreased to 400 mg daily, and antihypertensive treatment is started or intensified. During the time of adverse event of at least grade 3, the blood pressure will be measured twice a week until the pressure is lowered to at least grade 2. When the blood pressure has returned to systolic < 160 mm Hg, and diastolic < 100 mm Hg, the pazopanib dose is increased to 600 mg daily, and the

blood pressure must be monitored twice weekly at least further two weeks. If a hypertension of at least grade 3 recurs, the dose of pazopanib must be permanently lowered to 400 mg daily, and if needed the antihypertensive treatment may be further intensified during intense monitoring as above. If a further grade 3 episode occurs, the treatment will be stopped permanently.

b) QT-prolongation: This is not specifically mentioned in CTCAE v 4.0, but may occur during pazopanib treatment. If corrected QT interval (cQT) exceeds 480 msec during the study (measured from ECG, which is done regularly according to the flow-sheet), this will be regarded in a similar way as a grade 3-4 toxicity with respect to dose reductions and stopping treatment.

c) Liver function tests: For ALT, AST, bilirubin and alcalic phosphatase, any value above the limit for eligibility as given in 3.1 h will lead to a decrease in pazopanib dose to 400 mg daily. These values will thereafter be measured weekly until stabilization. If the increased value(s) will decrease again under the limit for eligibility, the dose will be increased to 600 mg, but if the value(s) instead will increase further to a formal CTCAE v 4.0 grade 3-4, pazopanib will be permanently stopped. If an increase to 600 mg was done and the value(s) again exceeds the eligibility limits a decrease will again be done to 400 mg daily. If this dose is not tolerated, the treatment will likewise be stopped permanently.

d) Hypothyreoidism or electrolyte disturbances shall be treated/substituted/corrected according to common principles for such conditions

3.2.4 Criteria for stopping treatment
The treatment with pazopanib will be stopped immediately if any of the following events occurs: progressive disease, unacceptable toxicity, defined as grade 3-4 adverse events occurring at the dose level of 400 mg, intercurrent condition contraindicating pazopanib, patient´s wish.

3.2.5 Accountability Procedures
Dispensed pazopanib blister packs will be accounted for by study site nurse and kept at site until destruction is authorized by study monitor.
Pazopanib will be accounted for through hospital/pharmacy records and unused medication/empty vials may be destroyed as per institutional standard procedure.

3.2.6 Compliance
Patients will be asked to fill out a patient diary on a daily basis with information on the time dose was taken, number of tablets taken and if any dose was missed. The diary together with dispensed cartons/blister packs of pazopanib will be collected at every site visit.

4. Pretreatment investigations

a) Pathological diagnosis confirmed by a specialized pathologist at a sarcoma centre (if the initial diagnosis was done by another pathologist)
b) CT scan of thorax, abdomen and pelvic region within 14 days of start of pazopanib
c) medical history and concomitant medication
d) physical examination including blood pressure
e) WHO performance status
f) Electrocardiography (ECG)
g) LVEF by echocardiography or MUGA scintigraphy
h) ANC, platelets, direct (conjugated) bilirubin, AST, ALT, ALP, serum creatinine, PT/INR, aPTT, dip-stick urinalysis, Ca, Mg, K, Na, TSH, T4
i) pregnancy test for women with childbearing potential
j) weight

5. Investigations during treatment

a) week 4 and 8: physical examination including blood pressure measurement, ECG, evaluation of toxicity, changes in medication, laboratory as in 4h). Blood pressure values will be noted in the patient´s diary.
b) week 12 and thereafter every 8 weeks as long as treatment continues: as week 4 + CT abdomen/pelvic region (and thorax only if involved at baseline).
However, if clinical signs of progression occur before week 12, e.g., aggravated symptoms or suspected findings at the physical examination, it is recommended to perform an extra CT of the abdomen and pelvic region. If a progression without doubt is demonstrated, the patient must stop the treatment with pazopanib.
c) week 12 and thereafter every 16 weeks as long as treatment continues: LVEF.
d) week 12 only: blood sample for measuring plasma trough level of pazopanib; the sample must be taken just before the daily dose of pazopanib supposed to be about 24 hours since the last dose, and shall be stored at the site until end of study when it will be sent to the SSG secretariat and further on to a laboratory in the USA for analysis (see instructions in appendix 2).
e) One month (30 days) after stopping treatment, a follow-up to check toxicity and adverse events will be done, either as a visit or by telephone.

6. Safety determination

6.1 Adverse Event

Definition:

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does *not necessarily have a causal relationship* with this treatment. Thus, any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product is classified as AE.

In SSG XXI, AEs will be documented on the case report forms (CRF) where a lot of AEs are listed including the most common described in relation with pazopanib treatment. For AEs not specifically listed, the spaces for "other" at the end shall be used, and if > 2 "other " AEs occur, more copies of the CRF must be used.

All AEs are graded for severity according to Common Terminology Criteria for Adverse Event v. 4.0 (CTCAE). All AEs occurring by the time of study completion (within 30 days of last study drug intake) must be recorded.

6.2 Serious Adverse Event or Reaction

Definition:

A serious adverse event (SAE) or serious adverse reaction (SAR) is defined as any untoward medical occurrence or effect that:

a) results in death regardless of its cause during protocol treatment and for 30 days after terminating protocol treatment
b) is life-threatening
c) requires hospitalization or prolongation of an existing hospitalization
d) results in persistent or significant disability or incapacity
e) is a congenital anomaly or birth defect
f) is a secondary malignancy during protocol treatment and for 30 days after terminating protocol treatment

In SSG XXI, specific SAE forms will be used to report the SAEs thus encompassing:

- *All deaths* including death due to disease progression, intercurrent diseases or accidents during protocol treatment and for 30 days thereafter. Death due to progression of disease will thus not constitute a SAE if it occurs at least 30 days after the last protocol treatment.

- All life threatening events. The term "life-threatening" refers to an event where the patient is at IMMEDIATE risk of death at the time of the event (e.g. requires IMMEDIATE intensive care treatment). It does not refer to an event which hypothetically might cause death if it was more severe.

- Unexpected hospitalization, defined as at least one unplanned overnight admission caused by an adverse event.

- Disability defined as a substantial disruption in a person's ability to conduct normal life functions (e.g. blindness, deafness). Disability resulting from tumor surgery does not constitute an SAE.

- Secondary malignancies are also considered as SAEs and are reportable on an SAE form during protocol treatment and for 30 days after the last protocol treatment.

Any SAE (and SUSARS) occurring until 4 weeks after study drug discontinuation must be reported.

If in doubt whether a SAE must be reported or not, please contact the national coordinator for SSG XXI.

All SAE reports must be sent to the SSG secretariat in Lund within one working day. If the outcome of the SAE is not clear by the time of reporting, a further report must be sent later. The secretariat will send a copy of all SAE reports to GlaxoSmithKline.

6.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Unexpected SAEs are those of which the nature or severity is not consistent with information in the relevant source documents. The approved Summary of Product Characteristics (SmPC) will serve as the source document in the respective countries.

6.3.1 SUSAR reporting

SUSARs including deaths and life-threatening SAEs must according to laws and GCP rules be further reported to the regulatory authorities in the participating countries.

Based on the SAE-CRF, the "safety unit" at the SSG secretariat will complete an SAE assessment sheet that documents the causal relationship between the SAE and the investigational medicinal product and the expectedness of the SAE.

In case of a SUSAR, this will be reported to the competent regulatory authorities directly to the EudraVigilance database by a person certified by EMA at the SSG secretariat. All deaths and life-threatening SUSARs will be reported within 7 days, all other within 15 days. Notification of the SUSAR will also be sent to the responsible ethics committee and to all main investigators at each participating trial site.

6.4 Annual Safety Report

An annual safety report will be written by SSG, comprising a detailed risk-benefit-analysis and a summary table containing all documented SARs in the course of the trial. The report will be submitted to the concerned ethics committees and to the National Competent Authorities.

7. Statistics

7.1 Endpoints

7.1.1 Primary endpoint

Disease control rate (DCR=CR+PR+SD) at 12 weeks from start of pazopanib treatment according to RECIST version 1.1.

7.1.2 Secondary endpoints

- Overall response rate (ORR) defined as the fraction of patients ever achieving CR or PR during protocol treatment
- Progression free survival (PFS) defined as the time from start of pazopanib to progressive disease according to RECIST, version 1.1
- Toxicity defined as adverse events and abnormal laboratory test results during protocol treatment

7.1.3 Subgroup analysis

- DCR in relation to mutational status of primary tumour sample
- DCR in relation to plasma concentration at week 12

7.2 Statistical analysis and sample size

Demographic and prognostic variables will be presented by means of descriptive statistics.

Whenever appropriate, results will be illustrated with a graph.

For the analysis of the primary endpoint, Simon's two stage analysis be used [14, especially Table 2]. Simon's method is implemented as follows.
Since sample size calculation is an integral part of Simon's method, no separate section on sample size will be written.

The study tests the null hypothesis
H_0: $p \leq 20$ %
against the complementary hypothesis
H_1: $p>20$ %,

where p is the probability of clinical benefit. The type I error probability should be less than 5 %. If the true value of p is 35 %, the type II error probability should be less than 20 %. In order to achieve this with Simon's optimal two-stage design, a maximal number of 72 patients should be enrolled with an interim analysis after 22 patients. If five or less of these patients experience clinical benefit defined as disease control (CR + PR + SD), the study is stopped for futility. Otherwise all 72 patients are enrolled and H_0 is rejected if more than 19 of these experience clinical benefit.

If the study has not been stopped for futility, a two-sided 90 % confidence interval for *p* will be produced with the method of inverting a series of hypothesis tests. The reason for using a 90 % confidence interval is that it then will be congenial with Simon's method – so that the confidence interval covers *p = 20 %* if and only if H_0 is not rejected with Simon's method.

The analysis of the secondary endpoints will be performed only if the study has not been stopped for futility. This should, strictly speaking, be accounted for in the calculation of P-values and confidence intervals. This subtlety is however ignored, and P-values and confidence intervals for the secondary endpoints should only be considered as approximate.

1. ORR will be calculated and a 90 % confidence interval will be produced
2. Kaplan-Meier estimates of disease-free survival will be produced together with 90 % confidence intervals. The results of this calculation will be accounted for in a graph.
3. DCR will be calculated separately within each mutational status group, and a P-value will be computed using Fisher's exact test.
4. Only descriptive statistics, means, medians, standard deviation and a box- and whiskers plot will be used to describe the plasma concentration between the groups with DCR = 0 and DCR = 1.

8. Data management

The study data management will follow the SSG standard operating procedure (SOP) for data management if nothing else is specifically stated in this protocol.

8.1 Patient registration

A registration form must be filled in and sent by fax to the SSG secretariat *before* treatment with study drug is initiated. At the secretariat, the registration form will be completed with a unique patient identification number and a returning fax will be sent to the participating institution. The local investigators will keep a confidential patient identification list connecting the patient identification numbers with the full patient name and ID codes.

8.2 Case report forms (CRF)
Data will be recorded on paper based case report forms (CRFs). The local investigator is responsible for the completion of CRFs.
CRFs must be filled out with ink. Corrections should be performed as follows: A single line should be drawn through the incorrect information, the correct information written next to it and dated and signed, if necessary giving reasons for the correction. Data fields that can not be completed because of lack of information should be commented, e.g. "NK" (Not Known), "NA" (Not Applicable) or "ND" (Not Done). When a CRF is completed, a copy of the CRF shall be kept at the participating institution, and the original shall be sent to the SSG secretariat.

8.3 Retention of documents
The study site must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms etc. All information on CRFs must be traceable to these source documents in the patients file.

8.4 Data processing
At the SSG secretariat, data will be entered into an electronic database. The study database will be implemented and tested according to the principles of SSG SOP for data management. Implausible or missing data detected during data entry, monitoring visit or data validation will be corrected or supplemented after contacting the local investigator through queries. Query resolutions will be stored together with the corresponding CRFs and a copy shall be kept at the participating institution. Before final analysis a decision must be taken on final closure of the database.

8.5 Data storage
The originals of all trial documents including e.g., the protocol, amendments, all CRFs and correspondence with ethical committees and regulatory agencies, will be stored at the SSG secretariat for the time period defined by national laws and regulations, but at least 10 years after publication of the final analysis.
Local investigators will store all necessary study documents, as advised by the SSG secretariat, including copies of the protocol, amendments and CRFs, the patient identification list, signed informed consents, CVs and signature list of all local investigators etc. Local investigators will also store the patient's hospital charts for as long as required by national laws and regulations, but at least 10 years after publication of the final analysis.

9. Quality assurance
9.1 Monitoring
SSG XXI ("PAGIST") will be monitored by site visits to all participating institutions. For details, see separate Monitoring plan (appendix 3).

9.2 Validity checks
Validity checks will be performed at the SSG secretariat according to the principles of SSG SOP for data management.

10. Protocol ethics

The study will be conducted in accordance with the protocol, ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines (CPMP/ICH/135/95) and applicable regulatory requirements.

10.1 Patient information

Before entry into the trial all eligible patients referred to the trial sites will receive a written patient information describing the rationale for and the outline of the suggested therapy, as well as probable and possible side effects and risks. Oral information from one of the investigators at the institution will also be given, and the patient must have the opportunity to ask any question, and to consider participation together with her/his relatives. The written information will be constructed by the respective national coordinator of the study to be accepted by the respective ethics committees.

10.2 Informed consent

Prior to trial entry the patient must give her/his written consent after being informed as described above, and this must be stored at the institution. It is the right of the patient to withdraw her/his consent anytime during the study.

10.3 Risk/benefit consideration

The patients eligible for this trial have been progressing on the only two lines of therapy approved for this malignant disease, and their prognosis is obviously very poor. At the same time, there is a sound rational behind the suggestion that pazopanib may work based on its property to target both receptor kinases of importance for the pathogenesis of GIST, and VEGF, which probably also has a crucial role for the progression of this disease. Pazopanib has been used in clinical trials for different malignancies enrolling several thousand patients, and was recently approved for the use in renal cancer based on a reasonable safety profile. It is considered a much greater risk for death refraining from trials of new potentially useful drugs for these patients, compared to the risk associated with known or still unknown side effects of pazopanib.

11. Administrative matters

11.1 Sponsor

SSG is the sponsor of the study.

11.2 Necessary approvals

In each participating country a National Coordinator is appointed, who is responsible for ensuring that investigators, Ethical committee/-s and competent authorities in his/her country are informed of all relevant information and for answering any national queries.

Before start of the study in any country, an ethical approval must be given according to the regulations in the country. The protocol must also be approved by the National Competent Authority in each participating country through the EudraCT system.

11.3 Reasons for stopping the study

The sponsor may decide to stop the study if anything of the following occurs:

- New data will either make the value of pazopanib in GIST less likely or another available treatment option more attractive for immediate use for the patients

- Serious toxicity of a grade or frequency that could not be expected from earlier experience of the drug
- An unexpected low inclusion rate that is not in accordance with the possibility to answer the questions of the study in a reasonable time and/or the economy of the study

Furthermore, the study may be halted by a decision of the National Competent Authority in each country.

11.4 Protocol amendment

Any amendments to the protocol must be agreed upon by the members of the working group. Any modifications which may have an impact on the conduct of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample size, study procedures, or significant administrative aspects will require a formal amendment and must be approved by the concerned ethics committees and the National Competent Authorities.

11.5 Clinical trial report

A summary of the study will be written by the sponsor and provided to the national competent authorities within one year of the end of the trial. The report will comply with the ICH-GCP guidelines (CPMP/ICH/135/95) and guideline on the Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

11.6 Publication principles

The outcome of the study will be reported in a relevant peer reviewed medical journal. The SSG rules for authorship will be followed.

12. References

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Flow-sheet SSGXXI

	Pretreatment / Screening visit	Week 4 and 8	Week 12 and every 8 weeks thereafter
Informed consent	X		
GIST diagnosis confirmed by SSG pathologist	X		
CT of thorax, abdomen pelvic region	Within 14 days of start of trt		X[3]
ECG	X	X	X
Medical history	X		
Previous TKI treatment	X		
Concomitant medication	X		
Physical examination[6]	X	X	X
Pregnancy test[1]	X		
WHO PS	X		
Weight	X	X	X
LVEF[2]	X		X[4]
ANC	X	X	X
Platelets	X	X	X
Direct bilirubin	X	X	X
AST/ALT	X	X	X
ALP	X	X	X
Serum Creatinine	X	X	X
Ca, Mg, K	X	X	X
TSH, T4	X	X	X
PT/INR	X	X	X
aPTT	X	X	X
Dip-stick urinalysis	X	X	X
Plasma concentration			Week 12 only
Eligibility criteria	X		
Registration in study	X		
Toxicity and Adverse events		X	X[5]
Changes in study drug medication		X	X

[1]Only applicable for women with childbearing potential
[2]By echocardiography or MUGA scintigraphy
[3]CT thorax not needed if normal at baseline
[4]LVEF will be performed week 12 and every 16 weeks thereafter
[5]Will also be checked 30 days after treatment discontinuation either by a visit or a telephone call
[6]Blood pressure will also be measured at week 1, 2 and 3 after start of treatment by either a nurse in primary health care or by the patient him-/herself; the values to be noted in the patient´s diary.