STUDY No.: INT 70/09
EUDRACT No.: 2009-017093-20

Compound: Pazopanib

Phase 2 study with the multi-targeted tyrosine-kinase inhibitor Pazopanib (GW786034) for patients with relapsed or refractory urothelial cancer.

Sponsor:
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Principal Investigator:
Dr. Roberto Salvioni, MD
Chair, Department of Surgery, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Co-chairmen:
Dr. Andrea Necchi, MD
Department of Medicine, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Dr. Nicola Nicolai, MD
Department of Surgery, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Document type: Clinical Study Protocol
Development Phase: Phase II

Document status:

<table>
<thead>
<tr>
<th>Draft version No. 01</th>
<th>1st Release: 9 November 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft version No. 02 (1st Amendment – Centralized CT scan revision)</td>
<td>Release: 22 July 2010</td>
</tr>
</tbody>
</table>
SIGNATURE PAGE FOR INVESTIGATORS

Compound: Pazopanib
Protocol No.: INT 70/09
EudraCT No.: 2009-017093-20

I, the undersigned, have reviewed this protocol, including Appendices. I will conduct the study as described and will adhere to the Ethical and Regulatory considerations stated.

Dr. Roberto Salvioni
Principal Investigator
Center:
Department of Surgery, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian 1
20133 Milan

Dr. Andrea Necchi
Study co-chairman
Center:
Department of Medicine, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian 1
20133 Milan

Dr. Nicola Nicolai
Study co-chairman
Center:
Department of Surgery, Urology Unit
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian 1
20133 Milan
TABLE OF CONTENTS:

SIGNATURE PAGE FOR INVESTIGATORS ........................................................................................................... 2

1. SYNOPIS .................................................................................................................................................. 5

2. PROTOCOL SUMMARY ......................................................................................................................... 13

3. INTRODUCTION ...................................................................................................................................... 13

4. BACKGROUND ...................................................................................................................................... 14

4.1. PAZOPANIB AS TREATMENT IN CANCER PATIENTS ............................................................................. 14

4.2. SUMMARY OF EXPOSURE TO PAZOPANIB .......................................................................................... 15

5. PRE-CLINICAL STUDIES ......................................................................................................................... 15

5.1. IN VITRO ACTIVITY .......................................................................................................................... 15

5.2. IN VIVO ACTIVITY .......................................................................................................................... 17

6. RATIONALE ............................................................................................................................................ 19

7. STUDY OBJECTIVES ............................................................................................................................. 20

7.1. CENTRALIZED REVISION OF IMAGES: ............................................................................................ 20

8. TRANSLATIONAL RESEARCH: CORRELATIVE STUDY ........................................................................... 21

9. RATIONALE FOR CORRELATIVE STUDY ............................................................................................... 22

10. INVESTIGATIONAL PLAN .................................................................................................................... 23

10.1. STUDY DESIGN .................................................................................................................................. 23

10.2. STUDY POPULATIONS .................................................................................................................... 23

10.2.1. Patient Population ......................................................................................................................... 23

10.2.2. Number of Patients ....................................................................................................................... 23

10.3. INCLUSION/EXCLUSION CRITERIA .................................................................................................... 23

10.3.1. Inclusion ...................................................................................................................................... 23

10.3.2. Exclusion .................................................................................................................................... 25

10.3.3. Other Eligibility Criteria Considerations ...................................................................................... 28

10.4. INTERRUPTION OR DISCONTINUATION OF TREATMENT ................................................................. 28

Dose Interruptions/Modifications for Hepatotoxicity .................................................................................. 32

10.5. INVESTIGATIONAL PRODUCT ......................................................................................................... 34

10.5.1. Packaging and Labeling ............................................................................................................... 34

10.5.2. Storage of Investigational Product ............................................................................................... 35

10.5.3. Pazopanib Dispensing and Accounting ......................................................................................... 35

10.6. TREATMENT PLAN ............................................................................................................................ 35

10.7. STUDY PROCEDURES: .................................................................................................................. 36

10.8. CONCOMITANT MEDICATIONS ....................................................................................................... 37

10.8.1. Permitted Medications .................................................................................................................... 37

10.8.2. Prohibited Medications ................................................................................................................... 40

11. VISIT SCHEDULE AND ASSESSMENTS ............................................................................................. 40

12. SAFETY MEASUREMENTS ................................................................................................................... 41

12.1.1. Adverse Events (AE) and Serious Adverse events (SAE) .............................................................. 41

12.2. REPORTING OF SAEs TO GSK ...................................................................................................... 44

12.3. REGULATORY REPORTING REQUIREMENTS FOR SAEs ............................................................. 48

12.3.1. Post-study AEs and SAEs ............................................................................................................. 48

12.3.2. SAEs Related to Study Participation ............................................................................................ 49

12.3.3. PREGNANCY ............................................................................................................................... 49

Version 2, 22 Jul 2010
13. STATISTICAL CONSIDERATIONS

13.1. STATISTICAL ANALYSES

13.1.1. Primary study variable

13.1.2. Secondary study variables

13.1.3. Analysis populations

13.1.4. Sample size

14. REFERENCES

APPENDIX A: ECOG PERFORMANCE STATUS
APPENDIX B: DECLARATION OF HELSINKI
APPENDIX C: ELIGIBILITY FORM
## 1. SYNOPSIS

<table>
<thead>
<tr>
<th>Title of the study</th>
<th>Phase 2 study with the multi-targeted tyrosine-kinase inhibitor Pazopanib (GW786034) for patients with relapsed or refractory urothelial cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study No.</td>
<td>INT 70/09</td>
</tr>
<tr>
<td>EUDRACT No.</td>
<td>2009-017093-20</td>
</tr>
<tr>
<td>ClinicalTrials.Gov No.</td>
<td>NCT01031875</td>
</tr>
</tbody>
</table>
| Principal investigator | Dr. Roberto Salvioni, MD  
Chair  
Department of Surgery, Urology Unit  
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano  
Email: roberto.salvioni@istitutotumori.mi.it |
| Co-chairmen        | Dr. Andrea Necchi, MD  
Department of Medicine, Urology Unit  
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano  
Email: andrea.necchi@istitutotumori.mi.it  
Dr. Nicola Nicolai, MD  
Department of Surgery, Urology Unit  
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano  
Email: nicola.nicolai@istitutotumori.mi.it |
| Sponsorship        | Fondazione IRCCS Istituto Nazionale dei Tumori, Milano                                                                         |
| Participating Centers | Urology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano (coordinating center).                                      |
| Disease            | Metastatic transitional-cell carcinoma of the bladder and the urinary tract. Patients eligible to receive pazopanib are those who have metastatic urothelial carcinoma (UC) and who have already undergone at least one prior cisplatin-containing chemotherapy regimen for metastatic disease (neoadjuvant/adjuvant chemotherapy excluded). |
| Background and Rationale | Angiogenesis appears to play an important role in the progression of cancer. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent regulator of both normal and pathologic angiogenesis. Increased expression of VEGF has been measured in most human tumors examined to date, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, ovary, cervix, angiosarcomas, glioblastomas and bladder as well. |
Clinical benefit of angiogenesis inhibitors have been convincingly demonstrated in randomized Phase III clinical studies of bevacizumab, a monoclonal antibody to VEGF in combination with chemotherapy [Hurwitz, Ramalingam, Schneider], and sunitinib and sorafenib, two multi-targeted small molecule tyrosine kinase inhibitors of the VEGF and other receptors [Motzer, Escudier].

Pazopanib (GW786034) is a potent and selective, orally available, small molecule inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor receptor-alpha (PDGFR-α), PDGFR-β, and cKit tyrosine kinases. Pazopanib is currently being evaluated as a monotherapy, in combination with lapatinib, and in combination with chemotherapy for the treatment of patients with various advanced solid and hematologic malignancies including renal cell, ovarian, breast, lung carcinomas and multiple myeloma. Clinical activity has been demonstrated with pazopanib in ongoing studies in patients with solid tumors [Kumar, Sonpavde].

Despite promising results obtained with cisplatin-based combinations in advanced urothelial cancer, long-term survival is only about 5%.

Prognosis of patients with relapsed-refractory disease is quite dismal.

No standard second-line therapy for patients with advanced chemotherapy-resistant carcinoma of the bladder and urinary tract can be recommended at the present time. Novel treatment strategies are then needed.

We suggest that Pazopanib may increase the progression-free survival of the patients with advanced urothelial cancer due to the anti-angiogenic and tumor cell apoptotic effects.

Therefore, Pazopanib monotherapy might represent a clinically relevant therapy whose efficacy for urothelial cancers warrants further study.

Traditional anatomic tumor response criteria are based on uni- or bidimensional changes in tumor size, and do not take into account changes in tumor metabolism or tumor density.

These changes however demonstrated to be all indicative of response to a targeted therapy (imatinib) in specific subset of patients with solid tumors (GIST). In these patients, metabolic responses seen on positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (18FDG) have been shown to be closely related to clinical benefit.

Furthermore, these metabolic changes usually precede by weeks or months significant decrease in tumor size as assessed by computed tomography (CT). Conversely, lack of metabolic response on 18FDG-PET indicates primary resistance to the drug and may help identify patients who would benefit from another therapy.

Newly proposed CT criteria using either no growth in tumor size or a combination of tumor density and size criteria have shown a close
correlation with the predictive value results of 18FDG-PET in GIST.

Thus, the integration of 18FDG-PET and CT, as in the combined hybrid PET/CT scanners now available (provided that TC is diagnostic), would not only optimize the evaluation of patients with urothelial cancer undergoing pazopanib treatment but may ultimately help shorten clinical trial, accelerating drug development in this disease.

The novelty of our project consists in the unexplored multitarget treatment approach associated with the incorporation of 18FDG-PET as a new tool to implement staging and response assessment of urothelial cancers, together with current imaging modalities.

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>To evaluate the activity of the drug in patients with relapsed/refractory transitional cell tumors receiving the following treatment program: daily oral doses of Pazopanib monotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Objectives</td>
<td>To evaluate the safety and tolerability of Pazopanib monotherapy in a population of chemotherapy pretreated patients.</td>
</tr>
</tbody>
</table>
| Primary Endpoint | Assessment of response-rate by RECIST 1.1 criteria. RR (%) = CR + PR.  
- CR = Disappearance of all target lesions; any pathological lymph-nodes must have reduction in short axis to < 10 mm  
- PR = At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. |
| Secondary Endpoints | Assessment of the safety and tolerability  
- incidence, nature and severity of treatment-related adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0.  
Progression-free survival (PFS). |
| Objective correlative study | To evaluate the ability of whole-body 18FDG-PET to image metastases and monitor tumor response and to determine the rate of concordance with CT imaging and RECIST response criteria.  
To evaluate the relationship existing between tumor response measured by 18FDG-PET and progression-free survival. |
| Study design | Open label, multicenter, non-randomised, phase II trial. |
| Number of patients | Total number of patients will be **41**. |
| Study drug | Pazopanib, supplied as capsules for oral administration at the strenght of 200 or 400 mg each. |
| Treatment plan & Study procedures |  
- Treatment will be administered on an outpatient basis.  
- For the purposes of this study, one cycle of therapy is defined as 4 weeks (28 days). |
At study entry, patients will receive one cycle of oral Pazopanib at the dose of 800 mg once daily.
- Response will be evaluated by RECIST criteria v.1.1.
- At the end of the first cycle, patients will undergo clinical assessment as well as disease evaluation by CT scan of the thorax and abdomen (or further sites if indicated) and whole body 18FDG-PET.
- All patients with at least a stable disease and without significant adverse events will continue investigational drug assumption.
- Patients with less than SD and those with significant toxicity probably related to the drug will be taken off study and will be considered for further alternative treatments outside of the clinical trial.
- Patients who experience toxicity may continue treatment with dose delayed or reduced according to the protocol indications.

**Study procedures:**
- Baseline radiological tumor measurements should be performed preferably within 14 days, but in any case no more than 28 days before the first dose of pazopanib.
- A detailed flow-chart of timing for patients and disease assessments is provided in the full version of the protocol.
- Patients will undergo disease evaluation, including the evaluation of all radiological, physical and laboratory abnormalities present at baseline, at the end of every cycles until treatment discontinuation thereafter and whenever is clinically indicated during treatment.

**Inclusion criteria**
- Age > 18 years.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Life expectancy of at least 12 weeks.
- Histologically confirmed diagnosis of transitional cell tumors of the bladder or the urothelium. Metastatic disease.
- Measurable disease criteria, defined as ≥ 1 unidimensionally measurable lesion ≥ 2 cm by conventional techniques or ≥ 1 cm by spiral CT scan.
- Failure of at least one cisplatin-based conventional chemotherapy regimen for metastatic disease (neoadjuvant/adjuvant therapy excluded).
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:
  - Hemoglobin ≥ 9.0 gr/dL
  - Absolute neutrophil count (ANC) ≥ 1,000/μL
  - Platelet count ≥ 75,000/μL
  - Total bilirubin ≤ 1.5 times the ULN
- ALT and AST ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer)
- Alkaline phosphatase ≤ 4 x ULN
- Serum creatinine ≤ 1.5 mg/dL
- PT-INR/PTT < 1.5 x ULN [Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.]
- Written informed consent.

### Exclusion criteria

<table>
<thead>
<tr>
<th>Excluded Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History of any one or more of the following cardiovascular conditions within the past 6 months:</td>
</tr>
<tr>
<td>- Cardiac angioplasty or stenting.</td>
</tr>
<tr>
<td>- Myocardial infarction.</td>
</tr>
<tr>
<td>- Unstable angina.</td>
</tr>
<tr>
<td>- Coronary artery by-pass graft surgery.</td>
</tr>
<tr>
<td>- Symptomatic peripheral vascular disease.</td>
</tr>
<tr>
<td>- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA).</td>
</tr>
<tr>
<td>- Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted).</td>
</tr>
<tr>
<td>- Uncontrolled hypertension.</td>
</tr>
<tr>
<td>- History or 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.</td>
</tr>
<tr>
<td>- History of HIV infection or active chronic hepatitis B or C.</td>
</tr>
<tr>
<td>- Active clinically serious infections (&gt; grade 2 NCI-CTC version 4.0).</td>
</tr>
<tr>
<td>- Patients with seizure disorder requiring medication (such as steroids or anti-epileptics).</td>
</tr>
<tr>
<td>- History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.</td>
</tr>
<tr>
<td>- Patients with evidence or history of bleeding diathesis.</td>
</tr>
<tr>
<td>- Known endobronchial lesions or involvement of large pulmonary vessels by tumor</td>
</tr>
<tr>
<td>- Hemoptysis within 6 weeks of first dose of study drug.</td>
</tr>
<tr>
<td>- Patients undergoing renal dialysis.</td>
</tr>
<tr>
<td>- Gastro-intestinal abnormalities that may increase the risk of GI bleeding or may affect the absorption of investigational study drug.</td>
</tr>
<tr>
<td>- Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study EXCEPT cervical carcinoma in situ, treated basal cell cancer.</td>
</tr>
</tbody>
</table>
carcinoma or any cancer curatively treated > 5 years prior to study entry.
- Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must use adequate barrier birth control measures during the course of the trial and three months after the completion of trial.
- Substance abuse, medical, psychological or social conditions that may interfere with the patient’s participation in the study or evaluation of the study results.
- Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer.
- Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study.
- Patients unable to swallow oral medications.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug.

**Excluded therapies and medications, previous and concomitant**

- 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 OR
  - chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib.
- (Palliative radiotherapy will be allowed).
- Use of biologic response modifiers, such as G-CSF, within 3 week of study entry. [G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator, however they may not be substituted for a required dose reduction.] [Patients taking chronic erythropoietin are permitted provided no dose adjustment is undertaken within 2 months prior to the study or during the study].
- Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity.
- Prior exposure to study drug.

**Treatment duration and follow up**

Patients who experience AEs or serious adverse events (SAEs) will be monitored until their recovery.

Trial expected duration (comprehensive of accrual, treatment and follow-up): **24 months**.

**Statistical design**

The study is planned according to the optimal two-stage Simon
design having overall response as the primary efficacy end-point, with a maximum overall accrual of 41 patients. The first stage is designed for 21 patients; with one or no responses, the trial will be terminated and the experimental treatment will be considered inactive. With 2 or more responses in the first stage, the trial will continue and accrue 20 additional patients. The treatment will be considered active if ≥ 5 patients will respond. Type I and type II error rates were set at the 5% and 10% level, respectively, assuming response rates of 5% and 20% under the null and alternative hypotheses, respectively.

Descriptive statistics and frequency tabulation will be used to summarize patient characteristics and toxicity profile.

PFS time will be calculated as the interval between the date of enrollment and that of first disease progression or death regardless of the cause, with censoring at the date of last follow-up visit for patients alive and without progression. The PFS curve will be estimated by means of the Kaplan-Meier method.

### Main References


2. PROTOCOL SUMMARY

Despite promising results obtained with cisplatin-based combinations in advanced urothelial cancer, only 15-20% of patients benefit of a durable survival. Prognosis of patients with relapsed or refractory urothelial cancer (UC) is quite dismal and new treatment modalities (alternative to chemotherapy) which spare quality of life while being active are needed. UC represent at the same time a fascinating model to test new targeted compounds. With these premises we are starting a phase II study to evaluate the activity and safety profile of a new multi-targeted oral tyrosine kinase inhibitor (TKI) in patients with advanced UC who have already undergone at least one prior platinum-based regimen for metastatic disease.

Moreover, tumor response evaluation may be very problematic when using targeted drugs in a novel context. Thus we aim to evaluate the role of fluorine-18-fluorodeoxyglucose-positron emission tomography (18FDG-PET), combined with standard computed tomography (CT), both at staging and disease restaging during treatment and to correlate 18FDG-PET results with progression-free survival if compared with current diagnostics.

Pre-treated patients with advanced UC will undergo the continuous administration of Pazopanib 800 mg orally once daily until disease-regression/unacceptable toxicity. A 4-weekly (every 1 cycle) restaging will be done in order to assess tumor response and quickly discover tumor progressions and eventually switch to standard conventional drugs.

3. INTRODUCTION

Conventional cisplatin-based upfront chemotherapy for advanced urothelial cancer includes the two combinations of methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) or gemcitabine and cisplatin (GC) with comparable results. Despite initial high response rates (RR) of 40–70% in advanced disease, chemotherapy is generally not curative and the overall 5-year survival is quite dismal, of about 5%. A recently reported randomized trial showed no improved overall survival (OS) with the addition of paclitaxel to GC. While neoadjuvant cisplatin-based combination chemotherapy before radical cystectomy for muscle-invasive UC improves the outcome, there is recurrence in about half the patients.

When relapse/progression occurs, no standard second-line chemotherapy regimen exists and actually depends on single center experience. Heterogeneity of disease characteristics and
patient population of small phase II studies with new drug combinations is one of the major pitfalls when interpreting results in this setting of treatment. Hence the need of a new trend in the management of recurrent/refractory UC in order to get active compound as well as reliable tools to treat these patients and properly to evaluate response.

4. **BACKGROUND**

4.1. **Pazopanib as treatment in cancer patients**

Pazopanib 800 mg once daily has shown encouraging efficacy signals in the following contexts:

- **RCC:** In Study VEG102616, there was a 35% overall response rate (78 of 225 subjects with complete response [CR] or partial response [PR]) based on investigator assessment; median duration of response was 68.0 weeks. The median progression-free survival (PFS) estimate adjusted for randomization to placebo was 11.9 months per Independent Review Committee (IRC) and 9.9 months per investigator [Hutson, 2008].

- **Ovarian cancer:** 11 of 36 subjects (31%) experienced a cancer antigen-125 (CA-125) response to pazopanib, with a median time to CA-125 response of 29 days and median duration of response of 113 days. Excluding one subject whose CA-125 decreased before she received the first dose, the biochemical response was 28% (10 subjects). Overall response rate based on modified Gynecologic Cancer Intergroup (GCIG) criteria (incorporating CA-125, Response Evaluation Criteria in Solid Tumors (RECIST), and clinical assessment) was 18% in subjects with measurable disease at baseline, and was 21% in subjects without measurable disease at baseline. Median PFS was 84 days.

- **Advanced or metastatic soft tissue sarcoma:** Rate of PFS at 12 weeks, based on investigator assessment, was 18 of 41 subjects (43.9%) for leiomyosarcoma; 18 of 37 subjects (48.6%) for synovial sarcoma; and 16 of 41 subjects (39.0%) for other types of sarcoma [Sleijfer, 2008].

- **Early-stage Non-Small Cell Lung Cancer (NSCLC):** 30 of 35 subjects (86%) experienced a reduction in tumor volume after short-term use of pazopanib (median duration of 16 days) as assessed by high-resolution computed tomography (HRCT) after preoperative pazopanib treatment [Altorki, 2008].

- **ErbB2-positive advanced or metastatic breast cancer:** A higher response rate (36.2%
versus 22.2%) by independent review at Week 12 was observed in subjects on combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared with lapatinib 1500 mg once daily as a monotherapy, respectively (VEG20007, [Slamon, 2008]). Pazopanib has not shown signals of efficacy in Phase II studies conducted in multiple myeloma (VEG20006) or glioma (VEG102857).

4.2. Summary of exposure to Pazopanib

Approximately 2000 subjects with cancer have been enrolled in clinical studies of pazopanib (including studies conducted by the National Cancer Institute [NCI], part of the United States National Institutes of Health) as of 09 September 2008. Data collected to date show that oral pazopanib is absorbed after administration and that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings.

5. PRE-CLINICAL STUDIES

5.1. In vitro activity

Potency and selectivity of pazopanib against VEGFR, PDGFR, c-Kit, Flt-3 and Raf kinases

The in vitro activity of pazopanib was evaluated using recombinant kinase domain of various kinases (see Table 1).

Inhibition of receptor tyrosine kinase activity in cells

Pazopanib was able to inhibit ligand-induced phosphorylation of various tyrosine kinase receptors in cells (see Table 2).
Table 1: Summary of Pazopanib in-vitro activity.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>(K_{\text{app}}) (nM)</th>
<th>Enzyme</th>
<th>(IC_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-1</td>
<td>15</td>
<td>Human VEGFR-1</td>
<td>10</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>8</td>
<td>Human VEGFR-2</td>
<td>30</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>10</td>
<td>Human VEGFR-3</td>
<td>47</td>
</tr>
<tr>
<td>PDGFR-(\alpha)</td>
<td>30</td>
<td>Mouse VEGFR-2</td>
<td>42</td>
</tr>
<tr>
<td>PDGFR-(\beta)</td>
<td>14</td>
<td>Rat VEGFR-2</td>
<td>17</td>
</tr>
<tr>
<td>FLT3</td>
<td>230</td>
<td>Dog VEGFR-2</td>
<td>17</td>
</tr>
<tr>
<td>c-KIT</td>
<td>2.4</td>
<td>PDGFR-(\alpha),</td>
<td>71</td>
</tr>
<tr>
<td>B-Raf (Wild Type)</td>
<td>68</td>
<td>PDGFR-(\beta)</td>
<td>84</td>
</tr>
<tr>
<td>B-Raf V600E</td>
<td>160</td>
<td>c-KIT</td>
<td>74</td>
</tr>
<tr>
<td>C-Raf</td>
<td>109</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Kev: \(K_{\text{app}}\) = apparent inhibition constant

Table 2: Inhibition of ligand-induced receptor activation by Pazopanib

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Cells</th>
<th>(IC_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-2</td>
<td>Human umbilical vein endothelial cells</td>
<td>8</td>
</tr>
<tr>
<td>c-Kit</td>
<td>NCI-H526 (human small cell lung carcinoma cells)</td>
<td>3</td>
</tr>
<tr>
<td>PDGFR-(\beta)</td>
<td>Human foreskin fibroblasts</td>
<td>3</td>
</tr>
<tr>
<td>Flt-3</td>
<td>RS4;11 (human acute myelogenous leukemia cells)</td>
<td>(\geq1000)</td>
</tr>
</tbody>
</table>

Effects on cell proliferation

The ability of pazopanib to inhibit proliferation of various cell types was evaluated in an in vitro assay for 3 days. Pazopanib selectively inhibited the proliferation of human umbilical vein endothelial cells (HUVEC) stimulated with VEGF (\(IC_{50} = 21\) nM) compared to basic fibroblast growth factor (bFGF)-stimulated proliferation (\(IC_{50} = 21\) nM).

Pazopanib was further evaluated in a cell proliferation assay using a panel of 282 human cell lines. Only 7 tumor cell lines showed an \(IC_{50}\) value of < 1000 nM, suggesting that pazopanib is a weak or inactive inhibitor of proliferation in the majority of human cell lines tested in vitro.

Since pazopanib inhibits c-Kit and Flt-3 receptors, which are expressed on hematopoietic progenitor cells and have a pleiotropic role during progenitor cell proliferation and differentiation of various hematopoietic lineages, the effects of pazopanib on bone marrow progenitor growth were investigated in multiple growth factor formats in standard colony forming assays in vitro.

Pazopanib had weak activity in the colony forming unit assay induced by granulocyte-macrophage colony stimulating factor (GM-CSF) and Flt-3 ligand alone. However, addition of stem cell factor (ligand for c-Kit) enhanced the ability of pazopanib to inhibit colony formation, consistent with its activity against c-Kit kinase.
One of the circulating metabolites of pazopanib, GSK1268997, inhibited VEGF-induced endothelial cell proliferation with similar potency to that of pazopanib. The other 3 circulating metabolites, GSK1268992, GSK1071306 and GW700201, showed at least 10- to 20-fold less activity than pazopanib.

In summary, pazopanib potently inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β and c-Kit kinases. Consistent with its kinase activity, pazopanib selectively inhibited proliferation of endothelial cells stimulated with VEGF compared to bFGF stimulated proliferation and it had no direct anti-proliferative effect against the majority of the large number of tumor cell lines evaluated.

5.2. In vivo activity

Inhibition of VEGFR2 phosphorylation
In vivo effects of pazopanib on VEGFR-2 phosphorylation, angiogenesis and tumor growth have been investigated in a variety of animal models. Inhibition of VEGFR-2 phosphorylation was studied in naïve mice given an intravenous bolus administration of VEGF. The lungs of mice that received VEGF showed increased phosphorylation of VEGFR-2 compared to untreated control mice. Pre-treatment of mice with a single oral dose of pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in lungs in a dose- and time-dependent manner. The results from the time course and dose response experiments together suggest that plasma concentrations of ~40 μM or higher are required for the optimal inhibition of VEGFR-2 phosphorylation in mice.

Inhibition of angiogenesis
Pazopanib given orally at ≥ 30 mg/kg inhibited bFGF- and VEGF-induced angiogenesis in a variety of animal models including the Matrigel plug and corneal micropocket models of angiogenesis in Swiss nu/nu or C57B1/6 mice. Pazopanib also showed generally dose-dependent inhibition of aberrant ocular angiogenesis in laser-induced choroidal neovascularization in C57B1/6J mice (≥ 8 mg/kg PO) and Brown Norway rats (2.25 mg/kg, eye drops) as well as corneal neovascularization in a suture-induced model in New Zealand white rabbits (≥ 0.3 mg/kg, eye drops). These results are consistent with the role of VEGFR and PDGFR signaling in angiogenesis and demonstrate the effectiveness of pazopanib in blocking angiogenesis induced by various approaches.

Anti-tumor activity in human tumor xenografts in mice
The anti-tumor activity of oral pazopanib has been investigated as a single agent and in
combination with various antineoplastic agents in various human tumor xenograft models in mice. Pazopanib was administered orally in these studies on a once or twice daily schedule and was well tolerated. Pazopanib inhibited the growth of different tumor xenografts to varying degrees. Pazopanib had no effect on the growth of prostate tumors in the transgenic prostate cancer mouse model, CR2-T-Ag. These data demonstrate that different tumors have varying dependence on angiogenesis and VEGFR/PDGFR signaling.

Since treatment with pazopanib alone does not eradicate tumors in mouse models, the effect of combining pazopanib with various antineoplastic agents was evaluated, including various signal transduction inhibitors using human tumor xenograft models in mice. In general, the combination of pazopanib with all agents was well tolerated in mice in these studies, with no significant increase in body weight loss or any overt clinical effects. The combination with lapatinib (a marketed epidermal growth factor receptor [EGFR/ErbB2] tyrosine kinase inhibitor) showed a modest increase in tumor growth inhibition of both BT474 and NCI-H322 xenografts compared to either agent alone, although the differences were not statistically significant. The combination of pazopanib with marketed anti-cancer drugs (topotecan, irinotecan, 5-fluorouracil, oxaliplatin or taxotere) did not show any significant increase in tumor growth inhibition of HT29 xenografts compared to the best single agent alone. The combination of pazopanib with paclitaxel and carboplatin also showed no improvement in tumor control compared to the most active monotherapy regimen.

Early combination experiments of pazopanib with taxotere in mice bearing HT29 human colon tumor xenografts showed no significant increase in tumor growth inhibition of combination compared to the best single agent. Thus, the effect of various dosing schedules and relative staggering of the initiation of administrations of the two agents in the HT29 model were evaluated and the time to reach two tumor doubling (4 times the initial tumor size) was monitored to more appropriately capture any potential advantage of the combination. The median time to reach two tumor doublings was longest in mice treated with both pazopanib and taxotere, with the concomitant treatment of both agents being superior to the staggered scheduling. These studies suggest that there may be a benefit of combining pazopanib with chemotherapy in controlling tumor growth, even though the effect on tumor size may not be significantly different during the treatment period. Pazopanib was also evaluated in combination with AKT and B-Raf kinase inhibitors.

Treatment of mice with pazopanib and GSK690693, a pan-AKT kinase inhibitor [Rhodes, 2008], was evaluated against human colon (HT29, Colo-205), ovarian (SKOV3) and renal (CAKI-1, 786-O) xenografts in mice. There was no increase in tumor growth inhibition in colon and renal
xenografts with the combination compared to the best single agent, although an increased tumor growth inhibition was observed in the SKOV3 ovarian carcinoma model at the highest dose of both compounds given together compared to either agent alone. Pazopanib was also tested in combination with a tool B-Raf inhibitor, SB-590885 [King, 2006], in mutant BRAFV600E (A375P and HT29) xenografts. A modest increase in tumor inhibition in both of these models was observed in mice treated with the combination of two agents compared to either agent alone. The anti-tumor effect of pazopanib in combination with bevacizumab (a monoclonal antibody against vascular endothelial growth factor) was investigated against human colon tumor xenografts, RKO, SW620 and HT29. A modest increase in tumor growth inhibition was observed when both agents were combined compared to either agent alone in all 3 models, suggesting a potential benefit of combining the two agents. The effect of pazopanib on the expression and secretion of Cancer Antigen-125 (CA-125) was tested in human ovarian cancer cells in vitro as well as in OVCAR-3 ovarian tumor xenograft in mice. Paclitaxel was used as a comparator as it is approved for use in patients with ovarian carcinoma. Pazopanib compared to paclitaxel exerted different effects on the expression and secretion of CA-125 as measured in vitro and in vivo and was not always associated with changes in tumor burden, suggesting that caution should be taken in using CA-125 as an independent marker of anti-tumor activity with pazopanib in clinical studies. Taken together, these data demonstrate that pazopanib inhibited VEGFR-2 phosphorylation, angiogenesis and growth of various tumor xenografts in animals. Plasma concentrations of pazopanib at ~ 40 μM or higher are required for optimal inhibition of VEGFR-2 phosphorylation in mice, which is also consistent with the anti-angiogenic and anti-tumor effects based on the mouse exposure studies.

6. RATIONALE

Salvage chemotherapy for advanced UC yields suboptimal response rates of 15-40% and a median survival of 6-9 months at best. Furthermore, toxicity is awaited and feared in these pre-treated patients and often limits the possibility to administer active drugs and at therapeutic doses. Renal dysfunction, poor performance status and old age are relatively common and preclude cisplatin chemotherapy. Carboplatin-based combined regimens are feasible in such patients, but appear to be worse than cisplatin-based ones. Schedules not including cisplatin (taxane-gemcitabine) also appear to be reasonable alternatives in these patients but with poorer results. Therefore, the development of novel and tolerable agents for UC is warranted, coupled
with the identification of reliable imaging modalities that not only quantify response but also are able to predict both tumor response and outcome. We suggest that Pazopanib may increase the response rate and progression-free survival of patients with advanced urothelial cancer due to the anti-angiogenic and tumor cell apoptotic effects. Due to the lack of reliable and reproducible predictors of response as well as of imaging tools to assess tumor response, the trial will provide incorporation of 18FDG-PET to stage and evaluate response of urothelial cancers, together with current imaging modalities (RECIST criteria).

7. STUDY OBJECTIVES

The primary objective of this trial is to evaluate the activity of the drug in patients with relapsed/refractory transitional cell tumors receiving Pazopanib. The primary endpoint is the overall response (complete or partial response).

Definitions in brief (RECIST v1.1 criteria):
- CR = Disappearance of all target lesions; any pathological lymph-nodes must have reduction in short axis to < 10 mm.
- PR = At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

7.1. CENTRALIZED REVISION OF IMAGES:

A centralized revision of DICOM files of both baseline and restaging CT scans has been planned in agreement with GlaxoSmithKline S.p.A. Image transmittal will be made in electronic format by CD, provided that all patient personal informations has been carefully removed. One CD for each time point will be used containing DICOM files. CDs will be labeled with Study ID (e.g. INT 70/09), Subject number and scan date.

Files will be shipped to GlaxoSmithKline S.p.A. Clinical Imaging (blad/pazo), Building 21, Stockley Park West, Uxbridge, Middlesex, UB11 1BT.

Secondary objectives are to evaluate the safety and tolerability of Pazopanib monotherapy in a population of chemotherapy pretreated patients.

Secondary Endpoints are:
- Assessment of the safety and tolerability
incidence, nature and severity of treatment-related adverse events graded according to Common Terminology Criteria for Adverse Events v4.0.
- Progression-free survival (PFS).
- Overall survival (OS).

8. TRANSLATIONAL RESEARCH: CORRELATIVE STUDY

To develop the use of 18FDG-PET to determine objective response criteria in order to implement standard RECIST (CT-based) response criteria, thus facilitating the development of this as a further objective tool to assess tumor responses in patients with advanced and/or metastatic urothelial carcinoma.

Specific objectives:
1) To evaluate the ability of whole-body 18FDG-PET to image metastases and monitor tumor response and to determine the rate of concordance with CT imaging and RECIST response criteria.

Figure 1: Tumor response will be defined and quantified according to EORTC criteria for 18FDG-PET (Young, 1999):

<table>
<thead>
<tr>
<th>Progressive metabolic disease (PMD):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SUV increase &gt; 25%</td>
</tr>
<tr>
<td>- Visible increase in extent &gt; 20%</td>
</tr>
<tr>
<td>- New lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stable metabolic disease (SMD):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SUV increase &lt; 25% or decrease &lt; 15%</td>
</tr>
<tr>
<td>- No visible decrease in extent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partial metabolic response (PMR):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SUV reduction &gt; 15-25% after one cycle</td>
</tr>
<tr>
<td>- SUV reduction &gt; 25% after more than one cycle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete metabolic response (CMR):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Complete resolution of FDG uptake</td>
</tr>
</tbody>
</table>

2) To evaluate the relationship existing between tumor response measured by 18FDG-PET and progression-free survival/overall survival.

Furthermore, translational endpoint on circulating biomarkers are planned. Collection of 50mL of EDTA peripheral blood samples will be carried out in all individual patients at baseline and every 4 weeks thereafter for at least 4 times overall (T₀, T₁, T₂, T₃), together with disease restaging.
Angiogenesis-related markers will be studied to analyse drug-induced changes including, but not limited to, VEGF, soluble VEGFR-1, 2 and -3, soluble c-Kit, IL-6, 8, 12 and HGF by using multiplex ELISA plates.

The exploratory biomarker analysis will include:

- The investigation of the correlation between angiogenic biomarkers at baseline and after 4 weeks with response, PFS, and OS.
- Descriptive changes of soluble angiogenic biomarkers from T₀ to T₁.
- Correlation of changes from T₀ to T₁ samples with response (CT and PET) and PFS/OS.

Additional analyses may be conducted as appropriate.

9. RATIONALE FOR CORRELATIVE STUDY

Traditional anatomic tumor response criteria are based on uni- or bidimensional changes in tumor size, and do not take into account changes in tumor metabolism or tumor density. These changes however demonstrated to be all indicative of response to a targeted therapy (imatinib) in specific subset of patients with solid tumors (GIST). In these patients, metabolic responses seen on 18FDG-PET have been shown to be closely related to clinical benefit. Furthermore, these metabolic changes usually precede by weeks or months significant decrease in tumor size as assessed by computed tomography (CT). Conversely, lack of metabolic response on 18FDG-PET indicates primary resistance to the drug and may help identify patients who would benefit from another therapy.

Newly proposed CT criteria using either no growth in tumor size or a combination of tumor density and size criteria have shown a close correlation with the predictive value results of 18FDG-PET in GIST.

18FDG-PET is emerging as a new tool to stage patients with muscle-invasive UC who are candidates to radical surgery. Interesting results have been reported when it was compared to standard CT.

Thus, the integration of 18FDG-PET and CT, as in the combined hybrid PET/CT scanners now available (provided that TC is diagnostic), would not only optimize the evaluation of patients with urothelial cancer undergoing pazopanib treatment but may ultimately help shorten clinical trial, accelerating drug development in this disease.
10. INVESTIGATIONAL PLAN

10.1. Study Design

This is an open label, multicenter, non-randomized, phase II study. The promoter and Sponsor of the study is the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan.

10.2. Study Populations

10.2.1. Patient Population

Patients eligible to receive pazopanib are those who have metastatic UC and who have already undergone at least one prior cisplatin-containing chemotherapy regimen for metastatic disease (neoadjuvant/adjuvant chemotherapy excluded). Patients must meet the inclusion and exclusion criteria described below to receive pazopanib.

10.2.2. Number of Patients

Total number of patients will be 41. For further detail on sample size and statistical design see paragraph 10.

10.3. Inclusion/Exclusion Criteria

10.3.1. Inclusion

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. Procedures conducted as part of the subject’s routine clinical management (e.g., blood count, imaging study) 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 (paragraph 8).
Note: It is not necessary that informed consent be obtained within the protocol-specified screening window.

2. Age ≥ 18 years.

3. Life expectancy ≥ 12 weeks.

4. Histologically confirmed diagnosis of transitional cell tumors of the bladder or the urothelium.

5. Metastatic disease.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

7. Measurable disease criteria, defined as ≥ 1 unidimensionally measurable lesion ≥ 2 cm by conventional techniques or ≥ 1 cm by spiral CT scan.

8. Failure of at least one cisplatin-based conventional chemotherapy regimen for metastatic disease (neoadjuvant/adjuvant therapy excluded).

9. Adequate organ system function as defined in Table 3.

**Table 3:** Definitions for Adequate Organ Function

<table>
<thead>
<tr>
<th>System</th>
<th>Laboratory Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>≥ 1.0 X 10⁹/L</td>
</tr>
<tr>
<td>Hemoglobin¹</td>
<td>≥ 9 gr/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 7.5 X 10⁹/L</td>
</tr>
<tr>
<td>Prothrombin time (PT) or international normalized ratio (INR)</td>
<td>≤ 1.5 X upper limit of normal (ULN)*</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>≤ 1.5 X ULN</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>≤ 1.5 X ULN</td>
</tr>
<tr>
<td>AST and ALT</td>
<td>≤ 2.5 X ULN**</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>≤ 4 X ULN</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>≤ 1.5 mg/dL</td>
</tr>
<tr>
<td>Or, if greater than 1.5 mg/dL</td>
<td>≥ 50 mL/min</td>
</tr>
<tr>
<td>Calculated creatinine clearance</td>
<td></td>
</tr>
<tr>
<td><strong>Urine Protein to Creatinine Ratio (UPC)²</strong></td>
<td>&lt; 1</td>
</tr>
<tr>
<td>1</td>
<td>Subjects may not have had a transfusion within 7 days of screening assessment.</td>
</tr>
<tr>
<td>2</td>
<td>If UPC ≥ 1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value &lt; 1 gr to be eligible.</td>
</tr>
</tbody>
</table>

¹: Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.

**²**: ≤ 5 X ULN for patients with liver involvement by their cancer.

10. 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

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 < 40 pg/mL (< 140 pmol/L).

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. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject’s entry and is the sole sexual partner for that female.
- 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.

Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

10.3.2. Exclusion

1. Prior malignancy.

Note: Subjects who have had another malignancy and have been disease-free for 5 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
2. History or 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 (CT or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.

3. Patients with seizure disorders requiring medication (such as steroids or anti-epileptics).

4. Positive blood tests for HIV, HCV, or HCV.

5. Clinically significant gastrointestinal abnormalities that may increase the risk for GI bleeding including, but not limited to:
   - Active peptic ulcer disease.
   - Known intraluminal metastatic lesion/s with suspected 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.

6. 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.

7. Presence of uncontrolled serious infection (grade > 2 NCI-CTC v. 4.0).

8. Patients undergoing renal dialysis.

9. Prolongation of corrected QT interval (QTc) > 480 msecs.

10. 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 by-pass graft surgery.
• Cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted).
• Symptomatic peripheral vascular disease.
• Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA).

11. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥ 140 mmHg or diastolic blood pressure (DBP) of ≥ 90 mmHg].

Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. The mean SBP / DBP values from each blood pressure assessment must be < 140/90 mmHg in order for a subject to be eligible for the study. See Table 4 for details on blood pressure control and reassessment while on treatment.

12. History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
   Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible

13. Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).

14. Evidence of active bleeding or bleeding diathesis.

15. Known endobronchial lesions or involvement of large pulmonary vessels by tumor

16. Hemoptysis within 6 weeks of first dose of study drug.

17. 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.

18. Unable or unwilling to discontinue use of prohibited medications list in paragraph 7.7.2 for 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.

19. 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 OR
• chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib.

20. Use of biologic response modifiers, such as G-CSF, within 3 week of study entry. [G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator, however they may not be substituted for a required dose reduction.] [Patients taking chronic erythropoietin are permitted provided no dose adjustment is undertaken within 2 months prior to the study or during the study].


NOTE:
Any ongoing potentially reversible toxicity from prior anti-cancer therapy that is > Grade 1 or any toxicity from prior anti-cancer therapy that is progressing in severity will render the subject ineligible.

Current treatment with leuprolide or other GnRH agonists is permitted (this is more protocol specific for Phase I, breast and prostate studies).

22. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug.

10.3.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study: Clinical Investigator’s Brochure for pazopanib.[Investigator Brochure]

10.4. Interruption or Discontinuation of Treatment

Recommendations for investigational product (IP) dose interruptions/modifications in case of specific treatment-emergent AEs are provided in the following sections.

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 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 GSK Study Physician 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 Table 4:

| Table 4: Dose Modification Algorithms for Potential Treatment-Related Adverse Events |
|---------------------------------|-------------------------------------------|
| **AE Terms & Descriptions**    | **Dose Modification Algorithms**          |
| **Hypertension**               |                                           |
| (A). Asymptomatic and persistent SBP of $\geq 140$ and $< 170$ mmHg, or DBP $\geq 90$ and $< 110$ mmHg, or a clinically significant increase in DBP of $\geq 20$ 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 $\geq 170$ mmHg, or DBP $\geq 110$ 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 $\geq 170$ mmHg, or DBP $\geq 110$ mmHg, despite modification of | Step 1. Interrupt IP  
Step 2. Adjust current or initiate new antihypertensive |
<table>
<thead>
<tr>
<th>AE Terms &amp; Descriptions</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>antihypertensive medication(s)</td>
<td>medication(s).</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg.</td>
</tr>
<tr>
<td>(D). Refractory hypertension unresponsive to above interventions.</td>
<td>Discontinue IP and continue follow-up per protocol.</td>
</tr>
</tbody>
</table>

### Proteinuria

<table>
<thead>
<tr>
<th>24-hr urine protein $\geq$ 3 grams</th>
<th>Step 1. Interrupt IP.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 2. Test weekly the 24-hour urine protein until the level is $&lt; 3$ grams. Then, restart IP dose reduced by 200 mg.</td>
</tr>
<tr>
<td></td>
<td>Step 3. If 24-hour urine protein $\geq$ 3 grams recurs, repeat Steps 1 and 2.</td>
</tr>
<tr>
<td></td>
<td>Step 4. If 24-hour urine protein $\geq$ 3 grams recurs and the IP dose can no longer be reduced, discontinue IP and continue follow up per protocol.</td>
</tr>
</tbody>
</table>

### Haemorrhage /Bleeding

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Continue IP with current dose; monitor as clinically indicated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>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 $\leq$ Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Step 2. Restart IP; consider reducing dose and monitor as clinically indicated.</td>
</tr>
<tr>
<td>Grade 3 or 4, or</td>
<td>Discontinue IP and continue with follow-up per protocol.</td>
</tr>
<tr>
<td>Recurrent $\geq$ Grade 2 event after dose interruption/reduction.</td>
<td></td>
</tr>
</tbody>
</table>

### Venous Thrombosis (DVT, PE)

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Continue IP with same dose; initiate and monitor anticoagulation as clinically indicated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Step 1. Interrupt IP.</td>
</tr>
<tr>
<td>AE Terms &amp; Descriptions</td>
<td>Dose Modification Algorithms</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>Step 2. Initiate and monitor anticoagulation as clinically indicated.</td>
</tr>
<tr>
<td></td>
<td>Step 3. Resume IP at reduced dose only if all of the following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>- The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week.</td>
</tr>
<tr>
<td></td>
<td>- No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Grade 4 and/or PE</td>
<td>Discontinue IP and continue follow-up per protocol.</td>
</tr>
<tr>
<td>Arterial Thrombosis/Ischemia</td>
<td>Discontinue IP and continue follow-up per protocol.</td>
</tr>
<tr>
<td>Any Grade</td>
<td>Discontinue IP and continue follow-up per protocol.</td>
</tr>
<tr>
<td>Thrombocytopenia: Investigate and document underlying cause</td>
<td>Continue IP with current dose; monitor as clinically indicated.</td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>Step 1. Interrupt IP until toxicity resolves to ≤ Grade 2.</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated.</td>
</tr>
<tr>
<td></td>
<td>If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue IP and follow-up per protocol.</td>
</tr>
<tr>
<td>Anaemia:</td>
<td>No specific dose reduction rules are indicated for anaemia unless due to haemorrhage or bleeding as noted above.</td>
</tr>
<tr>
<td>Other Clinically Significant Adverse Events</td>
<td>Continue IP; monitor as clinically indicated.</td>
</tr>
</tbody>
</table>
### AE Terms & Descriptions

| 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. |

**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. |

a. Well-controlled BP defined as mean SBP <140 mmHg and mean DBP <90 mmHg.  
b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v. 4.0 (NCI CTCAE v 4.0).

Abbreviations: BP, blood pressure; IP, investigational product.

---

### Dose Interruptions/Modifications for Hepatotoxicity

Recommendations for investigational product dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 5. 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 (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary.

**Table 5:** Guidelines for Management of Treatment Emergent Hepatotoxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A). ALT of ≤ 3.0 x upper limit of normal (ULN)</td>
<td>Continue IP at current dose with full panel liver function tests (LFTs)¢ monitored as per protocol.</td>
</tr>
</tbody>
</table>
| (B). ALT > 3.0 x ULN to ≤ 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) | 1. Continue IP at current dose.  
2. Perform the following assessments for excluding hypersensitivity and other contributing factors:  
   - Eosinophil count  
   - Viral serology for hepatitis A, B and C  
   - Liver imaging  
3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1. |
| (C). ALT > 8.0 x ULN without bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%) | 1st occurrence  
1. Interrupt IP until toxicity resolves to ≤ Grade 1 or baseline |
<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Modification Algorithms</th>
</tr>
</thead>
</table>
| bilirubin ≤ 35%) and without hypersensitivity symptoms (e.g., fever, rash). | 2. Perform the following assessments for excluding hypersensitivity and other contributing factors:  
- Eosinophil count  
- Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus IgM antibody, or heterophile antibody, or monospot testing  
- Liver imaging  
3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1.  
4. If the subject is benefiting from the study treatment, contact GSK Study 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.  
If approval for retreatment is granted, the subject must be reconsented (with new informed consent specific to hepatotoxicity). |
| (D). 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). | 1. Discontinue IP immediately  
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, or heterophile antibody, or monospot testing  
- Anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody  
- Serum creatinine phosphokinase for possible muscle injury caused LFT elevation  
- Liver imaging (ultrasound or CT scan)  
3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until LFTs reduced to Grade 1. |
| For isolated total bilirubin elevation | 1. Isolated hyperbilirubinemia (ie in the absence of |
Event | Dose Modification Algorithms
--- | ---
without concurrent ALT increases (defined as ALT < 3 X ULN) | 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 > 2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue pazopanib at the same dose. 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, γ-GT and total bilirubin.

### 10.5. Investigational Product

Pazopanib is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β), and c-Kit [Kumar, 2007]. Pazopanib is being developed by GlaxoSmithKline (GSK) for the treatment of a variety of cancers. In nonclinical experiments, pazopanib has demonstrated encouraging potency and selectivity for VEGF receptors: for example, pazopanib demonstrated significant inhibition of VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells and was 3- to 400-fold selective for VEGF receptors compared to 23 other kinases tested. Pazopanib showed significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibited angiogenesis in several different models angiogenesis (e.g., the Matrigel plug assay, the cornea micropocket, and the laser-induced choroidal neovascularization models).

#### 10.5.1. Packaging and Labeling

Pazopanib monohydrochloride is supplied as a series of aqueous film-coated tablets containing 200 mg and 400 mg of the freebase:

- 200 mg, oval-shaped, white, packaged in bottles containing 34 tablets each
- 400 mg, oval-shaped, white, packaged in bottles containing 68 tablets each

Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib and a list of excipients.
10.5.2. **Storage of Investigational Product**

The investigational product will be stored at room temperature (15-30°C) in a secure location accessible only by authorized personnel. All drug supplies are to be used only for this protocol and not for any other purpose.

10.5.3. **Pazopanib Dispensing and Accounting**

The principal investigator or his/her designees must maintain an inventory record of study drug dispensed to patients to assure the regulatory authorities that pazopanib is not supplied to any person who is not enrolled in the present study. The study drug should be stored in a secure and locked area with limited access. The storage and custody of the study drug are responsibility of the principal investigator.

Study drug should be dispensed at the sites by the research coordinator or designee under the license of the physician or by a pharmacist at the site.

Patients should be provided with up to 28-day supply of the study drug. Patients should not be given more than 28-days supply at one time.

10.6. **Treatment plan**

- Treatment will be administered on an outpatient basis.
- For the purposes of this study, one cycle of therapy is defined as 4 weeks.
- At study entry, patients will receive one cycle of oral Pazopanib at the dose of 800 mg once daily.
- Response will be evaluated by RECIST criteria v.1.1.
- At the end of the first cycle, patients will undergo clinical assessment as well as disease evaluation by CT scan of the thorax and abdomen (or further sites if indicated) and whole body 18FDG-PET (see paragraph 8).
- All patients with at least a stable disease and without significant adverse events will continue investigational drug assumption (Figure 1).
- Patients with less than SD and those with significant toxicity probably related to the drug will be taken off study and will be considered for further alternative treatments outside of the clinical trial.
- Patients who experience toxicity may continue treatment with dose delayed or reduced according to the indications on paragraph 7.4.
10.7. Study procedures:

- Baseline radiological tumor measurements should be performed preferably within 14 days, but in any case no more than 28 days before the first dose of pazopanib.
- A detailed flow-chart of timing for patients and disease assessments is provided in paragraph 8.
- Patients will undergo disease evaluation, including the evaluation of all radiological, physical and laboratory abnormalities present at baseline, at the end of every cycles until treatment discontinuation thereafter and whenever is clinically indicated during treatment.

Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. If a dose is missed, the subject should take the dose as soon as possible, but not if there are 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.

If vomiting occurs after taking pazopanib another dose is not permitted on that day. The subject should resume taking pazopanib at the next scheduled dose. If vomiting persists, the subject should be instructed to notify the investigator.

Figure 1:
Legend: CT: computed tomography, PD: progressive disease, PET: positron emission tomography, PZP: pazopanib, SAE: serious adverse event.

10.8. Concomitant Medications

10.8.1. Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit. All concomitant medications taken during the study will be recorded in the case report form (CRF) with indication, dose information, and dates of administration. Subjects should receive full supportive care during the study, including transfusion of blood and blood products, 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 gr/day is permitted, it should be used with caution in subjects with impaired liver function.

Permitted Medications – Use with Caution

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

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

The Effects of Pazopanib on Other Drugs

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

- **Ergot derivatives**: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia).

- **Neuroleptics**: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death).

- **Antiarrhythmics**: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes).
• Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity).

• Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

The Effects of Other Drugs on Pazopanib

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

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction to 400 mg pazopanib should be considered when it must be co-administered with strong CYP3A4 inhibitors. **Strong CYP3A4 inhibitors include (but are not limited to):**

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

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
10.8.2. **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. Moreover, subjects should not have received any anti-cancer therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib. Subjects should not receive any other investigational drug within 15 days of the last dose of pazopanib and until post-treatment blood draws are completed.

11. **VISIT SCHEDULE AND ASSESSMENTS**

<table>
<thead>
<tr>
<th>Assessments/Procedures</th>
<th>Screening</th>
<th>On treatment</th>
<th>Discontinuation^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day -28 to 0</td>
<td>Day 1 (Pre-dose)</td>
<td>Week 2</td>
</tr>
<tr>
<td>Informed Consent Medical history</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Incl/Excl Criteria</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Vital Signs (BP, pulse rate &amp; body temperature)</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Physical Exam, ECOG PS</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Pregnancy test (if indicated)</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Electrocardiogram (ECG)</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>AE/Toxicity Assessment</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>RBC, Ht, Hb, WBC, PLT, differential</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>AST, ALT, total bilirubin, uric acid</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Serum electrolytes, creatinine, BUN</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Glucose, albumin, total protein, ALP, LDH</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Coagulation Tests (PT/PTT &amp; INR)</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Urinanalysis</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>HIV, HBV and HCV</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Thyroid Function Test (TSH, Free T3 and Free T4)</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>CT scan</td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>18FDG-PET scan</td>
<td></td>
<td></td>
<td>•</td>
</tr>
</tbody>
</table>
a: The visit of study termination should be performed within 14 days after treatment discontinuation.
b: To be followed for 28 days after the last drug administration, or until all drug related toxicities and ongoing SAEs have been resolved, whichever is later.
c: Not to be repeated if already done less than 1 month before.

12. SAFETY MEASUREMENTS

1.1 Definitions:

12.1.1. Adverse Events (AE) and Serious Adverse events (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in both this section of the protocol and in the AE/SAE section of the Clinical Record Form (CRF).

12.1.1.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:
• Significant or unexpected worsening or exacerbation of the condition/indication under study.
See Section “Lack of Efficacy”, for additional information.
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE do not include a/an:
• Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
• The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

12.1.1.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death
b) is life-threatening

NOTE: The term ‘life-threatening’ in the definition of ‘serious’ refers to an 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.

c) requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Version 2, 22 Jul 2010
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) is a congenital anomaly/birth defect

f) medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Disease-Related Events or Outcomes Not Qualifying as SAEs
An event which is part of the natural course of the disease under study (e.g., disease progression) does not need to be reported as a SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as a SAE. Any new primary cancer must be reported as a SAE.

Lack of Efficacy
“Lack of efficacy” per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

Clinical Laboratory Abnormalities and Other Abnormal Assessments
Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECG, X-ray, etc.) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, or SAE, as defined in the relevant sections. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.2. REPORTING OF SAEs TO GSK

SAEs will be reported promptly to GSK as described below, once the Investigator determines that the event meets the protocol definition of SAE.

From the time a patient consents to participate in the study until he or she has completed the study (including any follow-up period), all SAEs, including those ones assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), or related to a GSK concomitant medication, will be reported promptly to GSK.

Time Period, Frequency, and Method of Detecting AEs and SAEs

All AEs and SAEs, regardless of relationship to therapy, will be collected from the written informed consent to the last follow-up visit. SAEs brought to the attention of the investigator at any time after cessation of therapy and considered by the investigator to be related or possibly related to therapy must be reported if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

Subjects will be monitored at each scheduled assessment at the site, at any contact with the subject during the study, and at the withdrawal visit, for the occurrence of AEs/SAEs. The
investigator or designee will inquire about the occurrence of AEs/SAEs at every visit/contact during the study by asking the following standard questions:

- How are you feeling?
- Have you had any (other) medical problems since your last visit?
- Have you taken any new medications since your last visit/assessment?

**Recording of AEs and SAEs**

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE or SAE on the CRF. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Any AEs or SAEs occurring during the study must be documented in the subject's medical records and on the appropriate page of the CRF. Each AE or SAE is to be recorded individually.

**Assessment of Causality**

The investigator is obligated to assess the relationship between the study medical product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.

Causality should be assessed using the following categories: no (not related), or yes (reasonable possibility).

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The event having often been reported in literature for similar drugs as drug related (e.g. skin rashes, blood dyscrasia)
- The event being related by time to drug administration terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

The investigator will also consult the Investigational Brochure and/or Product Information in the determination of his/her assessment.

Version 2, 22 Jul 2010
There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE CRF to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE CRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will provide the assessment of causality as per instructions on the SAE form in the CRF.

**Time-frames for Submitting SAE Reports to GlaxoSmithKline**

Any SAEs which occur at any time during the study, whether or not related to the therapy, must be reported to GSK. Once an investigator becomes aware that a SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours by fax (+39 045 9218066) using the SAE form included in the CRF.

In rare circumstances and in the absence of facsimile equipment, notification by telephone/mail is acceptable. The contact for Clinical Safety & Pharmacovigilance of GSK S.p.A. are:

- +39 045 921 8222
- drugsurveillance-italy@gsk.com (shared e-mail box).

Concurrently a copy of the "SAE form" will be sent by mail to GSK. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE form in the CRF within the time frames outlined in the table below.

**Follow up information on SAEs must also be reported by the investigator within the same time frames (see the table below).**

<table>
<thead>
<tr>
<th>Type of SAE</th>
<th>Initial SAE Reports</th>
<th>Follow-up Information on a Previously Reported SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of SAE</td>
<td>Time Frame</td>
<td>Documents</td>
</tr>
<tr>
<td>All SAEs</td>
<td>24 hrs</td>
<td>&quot;SAE&quot; &quot; form in the CRF pages</td>
</tr>
</tbody>
</table>
If a non serious AE becomes serious, this and other relevant follow up information must also be reported to GSK according to the timeframe outlined in the above table. The SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. **If the investigator does not have all information regarding a SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received.**

It is not acceptable for the investigator to send photocopies of the subject’s medical records to GSK in lieu of completion of the appropriate AE or SAE CRF pages. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

**Follow-Up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK on the subject’s condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. If a subject dies during participation in the study or during a recognized follow-up period, GSK will be provided with a copy of any post-mortem findings, including histopathology.

*New or updated information will be recorded on the originally completed SAE form in the CRF, with all changes signed and dated by the investigator. The copy of the updated SAE form*
should be resent to GSK within the time frames outlined in “Timeframes for Submitting SAE Reports to GlaxoSmithKline”

12.3. Regulatory Reporting Requirements for SAEs

The Principal Investigator, or responsible person, will comply with the local regulatory requirements related to the reporting of SAEs to regulatory authorities (RA) and the Ethics Committee (EC).
In addition to report SAEs to the RA and EC, the investigator will promptly report all SAEs to GSK, according to the timeframe and procedure outlined in “Timeframes for Submitting SAE Reports to GlaxoSmithKline.

GSK has a legal responsibility to notify, both the local regulatory agency and other regulatory authorities, as appropriate, about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The Principal Investigator, or responsible person designated by the Sponsor, will notify GSK about the responsible person for Pharmacovigilance obligations and his/her contact details (e-mail, telephone, fax), to allow GSK to ask for clarifications/follow-up information, regarding SAEs notification.

12.3.1. Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period, as defined in “Time, period, frequency, and method of detecting AEs and SAEs. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the therapy, the investigator will promptly notify GSK.
12.3.2. SAEs Related to Study Participation

A SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly to GSK (see Section “Reporting of SAEs to GSK”).

12.3.3. PREGNANCY

Even if childbearing potential is usually an exclusion criteria, in the case that a pregnancy occurs, the investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form, provided by GlaxoSmithKline (GSK), and submit it to GSK within 2 weeks of learning of a subject’s pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and reported to GSK according to the timeframe outlined in Safety Measurements.

- A spontaneous abortion is always considered to be a SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy and which is considered reasonably related to the investigational product by the investigator, will be reported to GSK as described in Safety Measurements.

13. STATISTICAL CONSIDERATIONS

13.1. Statistical analyses

13.1.1. Primary study variable

The probability of response will be estimated by the corresponding relative frequency, together with the exact 95% confidence interval.
13.1.2. Secondary study variables

Descriptive statistics and frequency tabulation were used to summarize patient characteristics and toxicity profile. PFS time will be calculated as the interval between the date of enrollment and that of first disease progression or death regardless of the cause, with censoring at the date of last follow-up visit for patients alive and without progression. The PFS curve will be estimated by means of the Kaplan-Meier method.

13.1.3. Analysis populations

The population for primary efficacy analysis is the intent-to-treat (ITT) population, defined as all patients enrolled into the study; in addition, an analysis will be performed on the per-protocol (PP) population, including ITT patients who will receive at least one treatment dose; such patients should have at least one post-baseline tumor assessment and no major protocol violation. The safety population used for all safety analyses is the subset of patients from ITT population exposed to study medication.

13.1.4. Sample size

The study is planned according to the optimal two-stage Simon design having overall response as the primary efficacy end-point, with a maximum overall accrual of 41 patients. The first stage is designed for 21 patients; with one or no responses, the trial will be terminated and the experimental treatment will be considered inactive. With 2 or more responses in the first stage, the trial will continue and accrue 20 additional patients. The treatment will be considered active if ≥ 5 patients will respond. Type I and type II error rates were set at the 5% and 10% level, respectively, assuming response rates of 5% and 20% under the null and alternative hypotheses, respectively.
14. REFERENCES


25. Li B, Ogasawara RH, Wei W, et al. KDR (VEGF Receptor 2) is the major mediator for the hypotensive effect of VEGF. Hypertension 2002;39:1095-100.


Appendix A: Eastern Cooperative Oncology Group Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Appendix B: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION
1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association 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 only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality. 7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

**B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. 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 on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, 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. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.1

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.2

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

1 Note of clarification on paragraph 29 of the WMA Declaration of Helsinki
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

2 Note of clarification on paragraph 30 of the WMA Declaration of Helsinki
The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.
APPENDIX C: Eligibility form

<table>
<thead>
<tr>
<th>INSTITUTION</th>
<th>Fondazione INT Milano Fax n°: 02 2390 2708</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT. INITIALS</td>
<td>DATE OF BIRTH (dd/mm/yyyy): _ _ / _ _ / _ _</td>
</tr>
</tbody>
</table>

**ELIGIBILITY CRITERIA**

**Inclusion (if answer to any inclusion criteria is “NO” the subject is NOT to be entered in this study)**

1. Signed Informed Consent Form, please specify date [____] / [____] / [____]

2. Age ≥ 18 years

3. Histologically confirmed diagnosis of transitional cell tumor of the bladder or the urothelium

4. Metastatic disease

5. ECOG performance status of 0 or 1

6. Life expectancy of at least 12 weeks

7. Measurable disease, defined as ≥ 1 unidimensionally measurable lesion ≥ 2 cm by conventional techniques or ≥ 1 cm by spiral CT scan

8. Failed at least 1 cisplatin-based conventional chemotherapy regimen for metastatic disease (neoadjuvant/adjuvant therapy excluded), considered incurable and would be treated with 2nd line or subsequent line salvage regimens with palliative intent

9. ANC ≥ 1000/µL, PLT count ≥7500/µL, Hb ≥ 9 g/dL

10. Total bilirubin ≤ 1.5 x ULN

11. AST/ALT ≤ 2.5 x UNL

12. Alkaline phosphatase ≤ 4 x ULN

13. Serum creatinine ≤ 1.5 mg/dL or measured creatinine clearance ≥ 50mL/min

14. PT-INR/PTT < 1.5 x ULN [Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.]

15. Negative serum pregnancy test within 2 weeks prior to the first dose of study treatment

16. Use of an effective means of contraception for woman of childbearing potential and men with partners of childbearing potential

17. Willingness and capability to comply with the requirements of the study

Do you confirm that the patient fulfills every inclusion criteria?

**YES** | **NO**  
--- | ---  
If no, please comment below, specifying the section not fulfilled by the patient and the case will be discussed with Italfarmaco/its designee

**Exclusion (if answer to any exclusion criteria is “YES” the subject is NOT to be entered in this study)**

1. Pregnancy or lactation

2. A marked baseline prolongation of QT/QTC (QTC interval > 450 msec)

3. History of any one or more of the following cardiovascular conditions within the past 6 months: cardiac angiplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted), symptomatic peripheral vascular disease, NYHA class III or IV congestive heart failure

4. Poorly-controlled hypertension

5. History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months

6. Positive blood test for HIV, HBV and HCV

7. Symptomatic metastatic brain or meningeal tumors

8. Active clinically serious infections (> grade 2 NCI-CTC version 4.0)

9. Evidence or history of bleeding diathesis
10. Hemoptysis within 6 weeks of first dose of study drug
11. Known endobronchial lesions or involvement of large pulmonary vessels by tumor
12. Seizure disorder requiring medication
13. Renal dialysis
14. Clinically significant gastrointestinal abnormalities that may increase the risk of GI bleeding or may affect the absorption of investigational study drug
15. Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study EXCEPT cervical carcinoma in situ, treated basal cell carcinoma or any cancer curatively treated > 5 years prior to study entry
16. Substance abuse, medical, psychological or social conditions that may interfere with the patient’s participation in the study or evaluation of the study results
17. Unable to swallow oral medications
18. 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 OR chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib
19. Prior exposure to study drug
20. Any ongoing toxicity from prior anticancer therapy that is > Grade 1 and/or that is progressing in severity
21. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug
22. History of other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications

Do you confirm that the patient does not fulfil any exclusion criteria? [YES] [NO] If no, please comment below, specifying the section not fulfilled by the patient and the case will be discussed with Italfarmco/its designee

PLANNED TREATMENT START DATE: __ / __ / ___ REQUEST OF REGISTRATION DATE: __ / __ / ___

INVESTIGATOR’S NAME AND SIGNATURE: