TITLE PAGE

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Title:	PRINCIPAL: A Prospective Observational Study of Real World Treatment Patterns and Treatment Outcomes in Patients with Advanced or Metastatic Renal Cell Carcinoma Receiving Pazopanib

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2011N118677_01	2014-MAR-10	Amendment 01: To clarify inclusion criteria, revised sample size assumptions and enrolment period. Clarification of post progression efficacy data and updated recommended schedule of events.

Sponsor Signatory: **Signature:** **Date:**

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[redacted] 10th March 2014

SPONSOR INFORMATION PAGE

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INVESTIGATOR AGREEMENT PAGE

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Code of Federal Regulations
CR	Complete response
CT	Computed tomography
CYP	Cytochrome P
(e)CRF	(electronic) case report form
ECOG	Electronic data capture
EDC	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	EuroQoL
GCP	Good Clinical Practice
GPP	Good Pharmacovigilance Practices
GSK	GlaxoSmithKline
HIFα	Hypoxia-inducible factor alpha
HRQoL	Health related quality of life
ICH	International Committee on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IFN	Interferon
ISPE	International Society for Pharmacoepidemiology
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PFS	Progression-free survival
PR	Partial response
QD	Once daily
RAP	Research Analytic Plan
RCC	Renal cell carcinoma
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	Serious adverse event
SD	Stable disease
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau

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PROTOCOL SUMMARY

Rationale

Although the recently available targeted therapies have provided important improvements in disease prognosis for RCC, for some of these therapies adverse effects may affect tolerability and substantively impact patient quality of life. The availability of alternative treatments that offer similar (or improved) effectiveness with a more favourable safety and tolerability profile remains an unmet need for patients with advanced/metastatic RCC.

While the safety and efficacy of pazopanib has been evaluated in a pivotal randomized, double-blind, placebo-controlled, multinational trial [Sternberg, 2010] and other clinical studies, real-world data are needed to further evaluate the safety, tolerability and effectiveness of this selective tyrosine kinase inhibitor therapy. This is of particular importance for evaluating patient groups that were under-represented in the registration study, e.g., the elderly, patients with co-morbidities, as well as for determining patient compliance outside the normal parameters of a controlled trial.

The purpose of the PRINICIPAL study is to evaluate the real world effectiveness and safety of pazopanib in patients with advanced and/or metastatic RCC.

Objective(s)

The primary objectives of the PRINCIPAL study are:

1. To evaluate overall survival (OS), progression-free survival (PFS) and the overall response rate (ORR) in patients treated with pazopanib;
2. To characterise the relative dose intensity (RDI) and its observed effect on treatment outcomes;
3. To characterise the RCC patient population treated with pazopanib (e.g., by demographics, disease characteristics, previous RCC treatment history) in comparison to a selected clinical trial population;
4. To evaluate the change in health-related quality of life (HRQoL) relative to baseline in patients treated with pazopanib; and
5. To evaluate the frequency of serious adverse events (SAEs) and adverse events of special interest (AESIs) in patients treated with pazopanib.

The secondary objectives of the PRINCIPAL study are:

1. To evaluate clinical effectiveness, safety and RDI in those patients treated with pazopanib with comparable baseline characteristics to those included in the Phase III clinical trial VEG108844 (COMPARZ);
2. To evaluate clinical effectiveness, safety, RDI and HRQoL in relevant subgroups treated with pazopanib.

Study Design

This is a global, multi-centre, long-term, prospective, observational study to evaluate treatment patterns and clinical outcomes in patients with advanced or metastatic clear cell or predominantly clear cell RCC treated for the first time with pazopanib. The study is designed to enroll approximately 500-700 patients over the course of an enrollment period of approximately 30 months. To the extent possible, consecutive patients meeting inclusion/exclusion criteria will be enrolled.

There are no protocol–mandated visits or procedures associated with the study. Each patient is expected to participate for a maximum of 30 months or until premature discontinuation (i.e., due to death, withdrawal of consent, lost to follow-up or study termination). Follow-up information will be collected approximately every 3 months (a window of ± 4 weeks around the date of the suggested data collection will be allowed). It is anticipated that the frequency of patient assessment and imaging will differ according to local standard practice; therefore the quarterly data collection time points are intended to collect all assessments (with the date of assessment) since the previous visit date.

Study Assessments

As an observational study, no visits, scans or procedures at enrollment and during follow-up are required or recommended per protocol. It is expected that evaluations such as bone and brain scans will be performed as clinically indicated (e.g., presentation of bone pain).

The primary effectiveness measures of this study are:

- Overall survival (OS): defined as the time from first treatment with pazopanib until death due to any cause;
- Progression free survival (PFS): defined as the interval between the date of first treatment with pazopanib and the earliest date of disease progression (by tumour response assessed by imaging or by clinical deterioration, whichever comes first) or death due to any cause;
- Overall Response Rate (ORR): defined as the percentage of patients with documented response [complete response (CR) or partial response (PR)] at any time.

The primary safety events of interest in the study are serious adverse events (SAEs) and the following adverse events of special interest (AESI):

- Any adverse event that results in a pazopanib dose modification or discontinuation
- Any other reports of the following AEs, regardless of seriousness or severity:
    - Evidence of liver toxicity
    - New onset or worsened hypertension
    - Cardiac dysfunction
    - Thyroid dysfunction

In addition to these effectiveness and safety parameters, the relative dose intensity (RDI) of pazopanib and its relationship with treatment outcomes and health-related quality of life will be assessed.

1. INTRODUCTION

1.1. Background

Originating in the renal cortex, renal cell carcinomas (RCCs) account for 80-90% of all primary renal neoplasms [Ansari J, 2010]. Each year there are close to 200,000 new diagnoses of RCC worldwide. In both the US and the UK, the incidence of RCC increases with age, leveling off at around 70 years, and is more common in men than in women [Weikert, 2010]. In recent decades, the incidence of renal cancer has increased worldwide. It is estimated that in the US and most EU countries, the incidence of RCC is currently increasing by approximately 3% per year [Bratslavsky, 2010]. While increased incidence is partly due to better detection with improved diagnostic imaging, the increasing prevalence of RCC risk factors such as hypertension and obesity are also contributing factors [Sanford, 2010]. In terms of mortality, RCC deaths accounted for approximately 2% of cancer deaths in the US and the UK in 2008 [Kidney cancer statistics , 2010; Jemal, 2008].

For patients with clinically localized RCC, surgical resection is the mainstay treatment for curative intervention. For most patients with metastatic RCC (mRCC), treatment has traditionally involved cytokine therapy with interferon (IFN)-α or interleukin-2 (IL-2), due to the resistance of metastatic RCC to chemotherapy, radiotherapy and hormone therapy [Hutson 2011]. Cytokine therapy is less than ideal, however, with response rates between 10-20% and well-established toxicity [Clark, 2010].

In 2004, targeted therapies for metastatic RCC that have produced substantial gains in the management of metastatic RCC first became available. These advances in the treatment of RCC came from the recognition that RCC is a compilation of several histological subtypes caused by different genetic mutations that occur with varying incidences. Clear cell carcinoma, which accounts for approximately of 75% of RCC cases, is by far the most common histological subtype and the most widely studied. Other subtypes include papillary (12%), chromophobe (4%), oncocytoma (4%), collecting duct (<1%), and unclassified (3-5%) [Lang, 2010]. The pathogenesis of clear cell RCC often involves the mutation of the von Hippel-Lindau (VHL) protein, leading to high levels of hypoxia-inducible factor alpha (HIFα), which, in turn, leads to abnormal activation of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor alpha (TGFα).

Angiogenesis, the process of new blood vessel formation, plays an important role in the development of malignancy as well as the growth and progression of metastatic lesions. The molecular pathways involved in angiogenesis have been targeted for anti-tumor therapy which aim to either block the pathways that regulate HIFα levels, directly inhibit the function of VEGF, or interrupt signaling downstream from the VEGF receptor via tyrosine kinase inhibitors (TKIs). The TKIs inhibit VEGF and PDGF receptors on cancer cells, vascular endothelial cells, and pericytes, stopping the proliferation of tumour cells and the development of tumour blood vessels. One of the first oral TKIs made commercially available as a first line treatment for mRCC in 2006 was sunitinib (Sutent, Pfizer). Although sunitinib is considered an effective treatment, it is associated with a number of adverse events as a result of its toxicity (including hypertension, fatigue, diarrhoea, and hand-foot syndrome) [Schwandt, 2009], which can lead to substantial issues such as incomplete dosing or complete discontinuation.

VOTRIENT™ (pazopanib), a recently approved TKI, is a potent, selective, multi-targeted inhibitor of VEGF receptors (VEGFR) 1, 2, and 3; PDGF receptors α and ß; and stem cell factor receptor (c-Kit) [Sonpavde, 2007; Sonapavde, 2008]. It has been demonstrated to be a more selective kinase inhibitor than sunitinib with a higher binding affinity for VEGFR-2 in vitro [Karaman, 2008; Kumar, 2009]. In a pivotal Phase 3, randomized, double-blind trial [VEG105192], pazopanib when compared with placebo showed a statistically significant improvement in median progression-free survival (PFS) of approximately 8 months (10.8 versus 2.9 months [Independent Review Committee assessment, HR 0.36, 95% CI 0.24 to 0.55]) [Sternberg, 2010]. Pazopanib was associated with a significant improvement in objective response rate (ORR: complete response [CR] + partial response [PR]) compared with placebo (32% vs. 4%; $p<0.001$) as well as a clinically relevant reduction in risk of death. The most commonly reported adverse events in patients treated with pazopanib during the study were diarrhoea, hypertension, hair color changes, nausea, anorexia, vomiting and fatigue [for additional details, refer to local labeling for pazopanib].

Clinical data indicate that pazopanib is absorbed after oral administration and is generally well-tolerated at the 800 mg daily dosing regimen, its daily dosing regimen is an active monotherapy dose for patients with cancer (providing optimal biologic and clinical effects associated with VEGFR inhibition) and has encouraging efficacy in specific tumor settings such as RCC, sarcoma, non-small cell lung cancer, cervical and ovarian cancer. Additional supportive data specifically in RCC are available from a Phase 2 study [VEG102616] and the open-label extension study to the Phase 3 [VEG107769] [Hutson, 2010]. Consistent with the Phase 3 results, the response rate in VEG102616 was 34% in treatment-naive subjects and was 32% in VEG107769 (all subjects). Median PFS in these studies was similar to that reported in VEG105192. Qualitative and formal indirect evaluation of data from the pivotal clinical trials suggests that pazopanib has a favourable safety profile in comparison to other TKIs, predominantly in relation to haematological AEs, cardiotoxicity, and events that can affect patients' daily functioning and quality of life such as hand-foot syndrome, mucositis, stomatitis, and fatigue [NICE, 2010].

A head-to-head non-inferiority trial of pazopanib versus sunitinib in patients with locally advanced and/or metastatic RCC (COMPARZ, or "Comparing the efficacy, safety, and tolerability of pazopanib vs sunitinib") [VEG108844] has been reported. The VEG113078 Asian sub study was combined with VEG108844, this was made possible due to the similar study design and recruitment at the same sites. The primary endpoint is PFS; secondary endpoints include overall survival, duration of response, quality of life, medical resource utilisation and safety assessments. The study demonstrated non-inferiority of pazopanib for PFS in the intention to treat population and pazopanib statistically favoured quality of life in 11 of the 14 domains measured (Motzer, 2013).

In addition, there is a reported randomized, double-blind, cross-over study of pazopanib versus sunitinib [VEG113046], which is meant to assess how the tolerability and safety differences between each drug translate into patient preference (PISCES, or "Patient preference study of pazopanib versus sunitinib in advanced/metastatic RCC"). The PISCES patient preference study demonstrated that significantly more patients preferred pazopanib over sunitinib due to overall better HRQoL and less fatigue (Escudier, 2012).

Pazopanib was approved in the US in 2009 and conditionally approved in the EU in 2010 for treatment of advanced RCC, full approval was granted in 2013.

1.2. Study Rationale

Although the recently available targeted therapies have provided important improvements in disease prognosis, for some therapies adverse effects may limit tolerability and substantively impact patient quality of life. The availability of alternative treatments that offer similar (or improved) effectiveness with a more favourable safety and tolerability profile remains an unmet need for patients with advanced/metastatic RCC.

While the safety and efficacy of pazopanib has been evaluated in the pivotal randomized, double-blind, placebo-controlled, multinational trial and other clinical studies, real-world data are needed to further evaluate the safety, tolerability and effectiveness of this more selective TKI therapy. The purpose of the PRINICIPAL study is to evaluate the real world effectiveness and safety of pazopanib in patients with advanced and/or metastatic predominantly clear cell RCC.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary The primary objectives of the study are:	
1. To evaluate overall survival (OS), progression-free survival (PFS) and the overall response rate (ORR) in patients treated with pazopanib	PFS: defined as the interval between the date of first treatment with pazopanib and the earliest date of disease progression (by tumour response assessed by imaging or by clinical deterioration, whichever comes first) or death due to any cause OS: defined as the time from first treatment with pazopanib until death due to any cause ORR: defined as the percentage of patients with documented response (CR or PR) at any time during follow-up
2. To characterize the relative dose intensity (RDI) and its observed effect on treatment outcomes	Study population distribution of RDI
3. To characterise the RCC patient population treated with pazopanib (e.g., by demographics, disease characteristics, previous RCC treatment history) in comparison to a selected clinical trial population	Study population distribution of baseline characteristics
4. To evaluate the change in health-related quality of life (HRQoL) relative to baseline in patients treated with pazopanib	Change from baseline
5. To evaluate the frequency of serious adverse events (SAEs) and adverse events of special interest (AESIs) in patients treated with pazopanib	Any adverse event that results in a pazopanib dose modification or discontinuation Evidence of liver toxicity (e.g., increased ALT and/or AST, liver failure) New onset or worsened hypertension Cardiac dysfunction (e.g., decreased left ventricular function, congestive heart failure) Thyroid dysfunction
Secondary	
1.To evaluate clinical effectiveness, safety and RDI in those patients with comparable baseline characteristics to those included in the Phase III clinical trial [VEG108844 (COMPARZ)]	Same as primary effectiveness, safety and RDI objectives.
2. To evaluate clinical effectiveness, safety, RDI and HRQoL in relevant subgroups treated with pazopanib	Same as primary effectiveness, safety, HRQoL and RDI objectives.

3. STUDY DESIGN

This is a global, multi-centre, long-term, prospective, observational study to evaluate treatment patterns and clinical outcomes in patients with advanced or metastatic RCC treated for the first time with pazopanib. The study is designed to enroll approximately 500-700 patients in over the course of an enrollment period of approximately 30 months. Sites will be contacted and qualified by the estimated number of advanced or metastatic RCC patients available for enrollment annually. To the extent possible, consecutive patients meeting inclusion/exclusion criteria will be enrolled. Sites will be required to maintain a patient enrolment log of eligible patients at their treatment centres. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. The overall number of patients and sites may be adjusted during the study to meet enrollment goals, if needed. Eligible patients will be enrolled by medical oncologists and potentially by urologists experienced in the management of patients with RCC, if consistent with local practice.

There are no protocol–mandated visits or procedures associated with the study. Each patient is expected to participate for a maximum of 30 months or until premature discontinuation (i.e., due to death, withdrawal of consent, lost to follow-up or study termination). Patient completion is defined in Section 4. Follow-up information will be collected approximately every 3 months (a window of ± 4 weeks around the date of the suggested data collection will be allowed). If the patient is not seen for a regularly scheduled visit at that time, the site may contact the patient by telephone to solicit information regarding the events of interest and to limit loss to follow up. It is anticipated that frequency of patient assessment and imaging will differ according to local standard practice; therefore the quarterly data collection time points are intended to collect all assessments (with the date of assessment) since the previous visit date.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact patient safety.

3.1. Discussion of Design

Due to the need to have evaluable and comparable patients, the patient populations included in clinical trials are by design more restricted than those patients who will receive a therapy within a clinical setting. While clinical trials provide crucial information regarding the efficacy and safety of the drug, observational data can extend and augment what is known, including identifying optimal regimens and optimal therapies for special populations of patients (e.g., elderly patients, poor risk patients) who are unlikely to be adequately represented in clinical trials. In addition, real world data may help elucidate which patients might respond best to a particular therapy and may help in monitoring the benefits of a particular therapy throughout the treatment course.

4. PATIENT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Patient Selection Criteria

4.1.1. Number of Patients

Approximately 500-700 patients will be enrolled. See Section 9.1.1 for sample size assumptions.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information regarding pazopanib that may impact patient treatment is found in the local product labeling.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study. Therefore, adherence to the criteria as specified in the protocol is essential.

Patients eligible for enrolment in the study must meet all of the following criteria:

- Age ≥ 18 years at enrollment
- Documented diagnosis of advanced and/or metastatic clear cell or predominantly clear cell RCC
- Clinical decision made to initiate treatment with pazopanib prior to enrollment in the study, but within 30 days of enrollment. *Treatment with pazopanib can be started either prior to or after signed ICF as long as within 30 days of clinical decision made to initiate treatment with pazopanib.*
- Willing and able to provide written informed consent

4.1.3. Exclusion Criteria

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

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

- Patients currently participating in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol
- Previous exposure to an investigational or licensed multi-kinase inhibitor or an anti-VEGF angiogenesis inhibitor for advanced or metastatic disease (for guidance, refer to Appendix 1)
- Life expectancy < 12 weeks

4.2. Permanent Discontinuation from Study Treatment and Patient Completion Criteria

4.2.1. Permanent Discontinuation from Study Treatment

Patients will receive pazopanib at the discretion of the treating physician (e.g., until disease progression, death or unacceptable adverse event). The primary reason study treatment was permanently discontinued must be documented in the eCRF.

If the patient voluntarily discontinues from treatment due to toxicity, 'adverse event' should be recorded as the primary reason for permanent discontinuation in the eCRF.

All patients who permanently discontinue study treatment should be followed for progression, survival, health-related quality of life and efficacy of new therapies according to the protocol schedule, for up to 30 months post-enrollment.

4.2.2. Patient Completion

A patient will be considered to have completed the study if the patient dies during the study treatment or follow-up period or has been in follow-up for 30 months, whichever is sooner. Document the cause of death in the eCRF. A patient will be considered to have withdrawn from the study if the patient has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated.

5. STUDY TREATMENT

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the patient as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

5.1. Guidelines for Events of Special Interest and Dose Modifications

Guidance for dose modifications and interruptions for management of common toxicities associated with the study treatment is included in the product local labeling for pazopanib.

5.2. Relative Dose Intensity

All pazopanib dose changes, interruptions and discontinuations will be collected as part of this observational study.

Relative dose intensity (RDI) is a quantification of how closely an administered course of chemotherapy adheres to the intended regimen. Dose intensity can be increased or decreased through altering dose administered, time interval of administration, or both. For the purposes of this study, RDI will be calculated as the ratio of average daily dose of pazopanib to the recommended daily dose of pazopanib. During the pazopanib Phase III trial VEG108844; , the mean RDI was 0.835 (standard deviation 0.26).

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

As a long-term, observational study to evaluate treatment patterns and outcomes in patients treated in the post-marketing setting, no restrictions on concomitant treatments are associated with the study over and above those recommended in the regulatory authorisation. Investigators will be asked to record exposure to any concomitant treatments (within 6 weeks of initiating treatment with pazopanib and throughout follow-up) that are categorized as a CYP3A4 inhibitor or a CYP3A4 inducer.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the patient prior to any study-specific procedures or assessments. The web-based data collection, or Electronic Data Capture (EDC) system will comply with 21 CFR Part 11 regarding electronic records. All sites will be trained in the proper use of the EDC system as part of any site initiation visit or other activities prior to patient enrollment at the site. Once trained, physician and site personnel will be able to access their account with a username and password. The data collection is designed to minimise the burden on the participating physicians and patients, and maximise site and patient retention. Structured questionnaires, and the resultant electronic case report form (eCRF) for data entry, are designed to elicit the specific desired data points. During the baseline visit, the site will be instructed to obtain additional information regarding the patient, including secondary contact information for use in the event the site cannot reach the patient.

Refer to the Time and Events Table for the timing of data collection of assessments that may have been performed (Table 1). Details on effectiveness and safety assessments are presented in Section 7.3 and Section 7.4, respectively. Further details of study procedures and assessments can be found in the study procedures manual (SPM). Basic site and investigator level data will be collected in order to characterize the sites (e.g., practice type, practice size).

Procedures conducted as part of the patient's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent should be utilized for determining eligibility and baseline purposes.

Table 1 Table of Recommended Assessments [Time and Events]

	Baseline	Every 3 months (± 4 weeks)	Early discontinuation from the Study
Inclusion/exclusion	X		
Demography	X		
Patient height & weight	X		
RCC disease history	X		
RCC treatment history	X		
MSKCC risk category, if recorded	X		
Medical history/concomitant conditions	X	X	X
Performance status (ECOG and Karnofsky score), if recorded	X	X[d]	
Pazopanib exposure	X[a]	X	X
Exposure to select concomitant medications	X	X[d]	X[d]
Select laboratory testing (if performed)	X	X[d]	X[d]
Evidence of radiographic and or clinical progression		X[d]	X[d]
Additional / subsequent treatments for RCC		X[d]	X[d]
HRQoL [EQ-5D, FKSI-19 and FACIT Fatigue scale][b]	X	X[d]	X[d]
Adverse events (SAEs and AESIs)[c]	X----------> X[e]		
Reason for discontinuation (if applicable)			X[d]

a. Only for patients who have received their first dose within 30 days of enrollment
b. Applicable only to sites where HRQoL questionnaires may be administered
c. Refer to Section 7.4 regarding details of the timing and nature of events to be reported.
d. Post progression data following pazopanib treatment to be collected
e. Adverse Events that occur while on pazopanib therapy or are related to pazopanib must be reported. Adverse Events that occur on subsequent RCC therapy are not required to be reported in the eCRF

7.1. Baseline Assessments

7.1.1. Baseline Data

Baseline data collection will include:

- Demographics (date of birth, sex, race/ethnicity)
- Weight, Height (calculated BMI)
- Medical history (including cardiovascular, hepatic, endocrine, secondary malignancies, renal including presence of hereditary RCC syndromes)

- RCC history, including:
    - Date of initial RCC diagnosis
    - Date of diagnosis with advanced/metastatic RCC
    - Site of metastases (lung, bone, liver, adrenal glands, CNS, lymph nodes, other)
        - Number of metastatic sites
        - Existence of measurable lesions (yes/no)
        - Whether disease status evaluation conducted as part of routine care was consistent with RECIST methods (yes/no)
    - Metastasis confirmed by imaging (type, date) and by biopsy (yes/no, date)
    - Other histopathology: sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system
- RCC treatment history
    - Surgical history (simple, radical or partial nephrectomy; arterial embolization; metastatic lesion resection), dates, status post-surgery
    - Radiation therapy, stereotactic radiotherapy
    - Radiofrequency or cryo-ablation
    - Previous lines of systemic therapy, including immunotherapy (e.g., interferon α, IL-2)
- Performance status (ECOG and Karnofsky scales, included in Appendix 3) at enrollment, if recorded
- MSKCC and/or modified Heng risk category at enrollment (favourable/good, intermediate or poor), if recorded (for description, refer to Appendix 3)
- Initial pazopanib prescription
- Pazopanib start date
- Any changes to pazopanib dose or regimen since starting, with dates and dose changes, duration of interruption (if applicable)
- Selected concomitant medications (CYP3A4 inhibitors and inducers)
- Relevant laboratory testing (e.g., haemoglobin, platelet count, LDH, AST, ALT)
- HRQoL [EQ-5D, FKSI-19 and FACIT Fatigue scale, refer to Section 7.5], where applicable
- Occurrence of any SAEs/AESIs since starting pazopanib

7.2. Follow-up Assessments

Follow-up data collection will include:

- Visit date
- ECOG and Karnofsky scales (if recorded)/Survival status
- Date and cause of death, if applicable
- New onset co-morbidities and updated medical history
- Tumor response status
- Evidence of radiographic and or clinical progression in the opinion of the physician
    - Date of physician-identified disease progression
    - Documented signs of clinical or radiographic progression
        - Tumour response based on imaging results performed as part of standard of care
        - Clinical deterioration [symptomatic deterioration, need for palliative therapies, need for medical intervention (e.g., ER, hospitalization, surgery]
- Whether disease status evaluation as part of routine care was consistent with RECIST methods (yes/no)
- Updated pazopanib exposure
- If dose changes/discontinuations, change type, date (or duration) of change and reason for change
- Additional treatment strategies for RCC
- HRQoL [EQ-5D, FKSI-19 and FACIT Fatigue scale, refer to Section 7.5], where applicable
- Selected concomitant medications (CYP3A4 inhibitors and inducers)
- Relevant laboratory testing
- Occurrence of any SAEs/AESIs since last visit

7.3. Effectiveness

7.3.1. Effectiveness Endpoints

The primary effectiveness endpoints of this study are:

- Overall survival (OS): defined as the time from first treatment with pazopanib until death due to any cause;
- Progression free survival (PFS): defined as the interval between the date of first treatment with pazopanib and the earliest date of disease progression (by tumour

response assessed by imaging or by clinical deterioration, whichever comes first) or death due to any cause;

- Overall Response Rate (ORR): defined as the percentage of patients with documented response [complete response (CR) or partial response (PR)] at any time.

7.3.2. Effectiveness Assessment

See the Time and Events Table (Section 7) for the recommended schedule of assessments. Assessments are based on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of ± 4 weeks is permitted to allow for flexible scheduling and data entry.

As an observational study, no scans or procedures at enrollment and during follow-up are required or recommended per protocol. It is expected that evaluations such as bone and brain scans will be performed as clinically indicated (e.g., presentation of bone pain).

7.3.2.1. Follow-up Assessments for Patients Permanently Discontinued from Study Treatment

Refer to Section 4.2.1 Permanent Discontinuation from Study Treatment for follow-up assessment of patients who are to be followed up for disease progression, subsequent RCC treatment efficacy, health-related quality of life and/or survival after permanently discontinuation from pazopanib.

7.3.2.2. Assessment of Patient Completion

If the last radiographic assessment was more than 3 months prior to withdrawal from study and progressive disease has not been documented, if possible a disease assessment should be obtained recorded at the time of withdrawal from study.

7.3.3. Guidelines for Evaluation of Disease

For the purposes of categorizing patients at enrollment in regards to the presence of measurable lesions, general guidance consistent with RECIST 1.1 is provided in Appendix 2.

7.3.4. Response Criteria

Since PRINCIPAL is not a clinical trial but an analysis of real world treatment population, no specific criteria for the evaluation of response (e.g., RECIST) is specified. Participating physicians are asked to assess tumour responses according to local processes and their own medical judgment. Because timing of assessments may be further apart than is seen in a typical RCT, any calculation of time to progression will be evaluated with appropriate caution and sensitivity analyses will be performed where feasible and relevant.

For the purposes of categorizing response in patients with measurable lesions, general guidance consistent with RECIST 1.1 is provided in Appendix 2.

7.4. Safety

7.4.1. Safety Endpoints

In addition to SAEs, the following adverse events of special interest (AESI) will be solicited:

- Any AE that results in a pazopanib dose modification or discontinuation
- Any other reports of the following AEs, regardless of their seriousness or severity:
    - Evidence of liver toxicity
    - New onset or worsened hypertension
    - Cardiac dysfunction
    - Thyroid dysfunction

7.4.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 7.3.

7.4.2.1. Definition of an AE

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

Note: 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, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment 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 study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of effectiveness" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical

sequelae resulting from "lack of effectiveness" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- 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 patient's condition.

7.4.2.2. 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 patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the patient 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.

   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, or

   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. 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 patient 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.

7.4.2.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as an SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

7.4.2.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Discontinuation CRF form. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the patient, 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 an SAE.

7.4.2.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

SAEs and AESIs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of pazopanib regardless of initiation of a new cancer therapy or transfer to hospice.

In addition, any SAE assessed **as related** to pazopanib or a GSK concomitant medication must be recorded from the time a patient consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.4.2.6.

After discontinuation of study treatment, to the extent feasible, the investigator should monitor all AESIs/SAEs that are ongoing until resolution or stabilization of the event or until the patient is lost to follow-up.

7.4.2.6. Prompt Reporting of SAEs and Other Events to GSK

SAEs and pregnancies must be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE CRF	24 hours	Updated SAE CRF
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form

Methods for detecting, recording, evaluating, and following up on AEs and SAEs are provided in the SPM.

7.4.2.7. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will notify the IRB/IEC, if appropriate according to local requirements.

7.4.3. Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a pregnancy form. To ensure patient safety, each pregnancy must be reported to GSK within 2 weeks

of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study patients who become pregnant while the patient is enrolled in the study. Pregnancy information must be reported to GSK as described above.

7.4.4. Laboratory Assessments

Table 2 Laboratory Assessments (if performed)

Hematology	Standard Chemistry	Other
Hemoglobin*	Sodium	C-reactive protein (CRP)
Hematocrit	Potassium	Thyroid-stimulating hormone (TSH) or thyrotropin
Platelet count*	Calcium*	
Absolute neutrophil count*	Phosphate	
	Blood urea nitrogen or urea	
	Creatinine	
	Lactate dehydrogenase (LDH)*	
	Aspartate aminotransferase (AST)	
	Alanine aminotransferase (ALT)	
	Total bilirubin	
	Total protein	
	Albumin	

*These values, particularly at baseline, are critical for evaluation of patient risk category at enrollment

7.5. Health Outcomes

7.5.1. Health Outcomes Endpoints

Health-related quality of life (HRQoL) will be assessed using the EQ-5D (3L) Index and VAS, the FKSI-19 and the FACIT Fatigue scale. These assessments will be restricted to sites where the administration of HRQoL questionnaires is permitted and has received local ethical and/or regulatory approval.

7.5.2. Health Outcomes Assessments

The Euro Qol (EQ-5D 3L) questionnaire is a generic preference-based QoL measure comprised of a 5-item health status measure and a visual analogue scale (VAS) [Kind, 1996; Rabin, 2001] and used to generate two scores. The EQ-5D utility score is based on

answers to 5 questions that evaluate mobility, self-care, usual activities, pain, discomfort, and anxiety and/or depression. Answers range from 1 to 3, depending on whether the patients perceives no problems (= 1), some problems (= 2), or significant problems (= 3) in that aspect of their health. The EQ-5D VAS generates a single health status index in which patients are asked to rate their current health by drawing a line from a box marked, "Your health state today" to the appropriate point on a 20-cm visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state). Patients will complete the EQ-5D at baseline and approximately every 3 months thereafter.

The Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 (FKSI-19) measures disease and treatment-related symptoms specifically in renal cancer patients. FKSI-19 uses five point Likert scale ranging from 'not at all' (0) to 'very much' (4). It includes patients self-reports on experience of symptoms in the past seven days such as lack of energy, pain, bone-pain, shortness of breath, fatigue and blood in urine [Cella, 2006]. Patients will complete the FKSI-19 at baseline and approximately every 3 months thereafter.

The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale is a short, 13-item validated instruments that measures a patient's level of fatigue during the usual activities over the past 7 days, based on a four point Likert scale ranging from 'not at all fatigued' (4) to 'very much fatigued' (0) [Webster, 2003]. Patients will complete the FACIT Fatigue scale at baseline and approximately every 3 months thereafter.

8. DATA MANAGEMENT

Patient data will be collected using defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

All data will be collected and entered by the participating sites directly into the EDC system. All sites will be fully trained for using the on-line data capture system, including eCRF completion guidelines and help files. Sites will have the ability to add a new record, to search for and modify existing records, to search for patients for whom follow-up is due, to identify records with outstanding queries and to identify records that require signatures. Throughout participation in the study, individual physicians will have access to their own patients' data and select reports via the EDC system. The study database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Committee on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained. Data quality will be confirmed through a series of programmed data quality checks that automatically detect out-of-range or anomalous data, as detailed in the study data monitoring plan. A clinical monitoring plan, including for-cause monitoring, that is appropriate for the study design will also be developed and implemented.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing

errors and inconsistencies in the data. Adverse events terms will be coded using MedDRA eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, patient initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Study Design Considerations

9.1.1. Sample Size Assumptions

Due to the descriptive nature of the study, no formal sample size estimation was conducted. The targeted sample size of 500-700 was based on the expected precision around the estimates for the outcomes of interest, and the feasibility of enrolling the desired population during the enrolment period (30 months). Since consecutive enrollment of eligible patients is sought, it is unknown what the distribution of patient baseline characteristics will be and the sample size does not take into consideration subgroup size (e.g., the number of elderly patients enrolled). No formal hypothesis or statistical significance testing is planned. This approach follows the *Guidelines for Good Pharmacoepidemiology Practices*, Section D, point 10.

Recent clinical trial data were reviewed in order to identify applicable rates to apply to sample size estimations, to determine the number of patients needed.

Progression-Free Survival

In VEG108844, the PFS rate at 12 months (estimated from the Kaplan-Meier estimate) was approximately 40% [Motzer,2013]. Taking this as a baseline proportion, the sample sizes (N) required for different levels of precision are shown in Table 3. These are calculated using the normal approximation to the binomial proportion distribution.

Table 3 Sample size estimates for PFS (at 12 months post-enrollment)

Precision (half-width)	10%	5%	4%	3%
Estimated 95% CI	(30%, 50%)	(35%, 45%)	(36%, 44%)	(37%, 43%)
N	93	369	577	1025

A sample size of 700 patients will provide for a precision of less than 4% for PFS at 12 months. Similarly, a sample size of 500 patients will provide a precision of less than 5% for PFS at 12 months. These estimates assume that <25% of patients will be lost to follow-up before disease progression or death.

Overall Response Rate (ORR)

In the phase III study of pazopanib VEG108844, the overall response rate (ORR) observed in the pazopanib arm was 31% [Motzer,2013] . Using this as a baseline proportion, the sample sizes (N) required for several different levels of precision are shown in Table 4.. These are calculated using the normal approximation to the binomial proportion distribution.

Table 4 Sample size estimates for ORR (at 12 months post-enrollment)

Precision (half-width)	10%	5%	4%	3%
Estimated 95% CI	(21%, 41%)	(26%, 36%)	(27%, 35%)	(28%, 34%)
N	83	329	514	913

A sample size of 700 patients will provide for a precision of less than 4% for ORR and a sample size of 500 patients will provide a precision of less than 5% for ORR.

Overall Survival (OS)

In VEG108844, the OS rate at 12 months (estimated from the Kaplan-Meier estimate) was approximately 79% [Motzer,2013]. Taking this as a baseline proportion, the sample sizes (N) required for different levels of precision are shown in Table 5. These are calculated using the normal approximation to the binomial proportion distribution.

Table 5 Sample size estimates for OS (at 12 months post-enrollment)

Precision (half-width)	10%	5%	4%	3%
Estimated 95% CI	(69%, 89%)	(74%, 84%)	(75%, 83%)	(76%, 82%)
N	64	255	399	709

A sample size of 500-700 patients will provide a precision of less than 4% for OS at 12 months.

9.1.2. Sample Size Re-estimation

No formal sample size re-estimation is planned. The time required for the expected number of enrolled patients to have an event will depend on the rate of patient accrual and premature loss to follow-up and the median survival and progression free survival. The number of patients to be recruited may be revised if necessary to achieve the number of events necessary to perform the desired analyses.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

All patients who receive at least one dose of study treatment will be evaluable for both effectiveness and safety and will comprise the All Treated Patients (AT) population.

The Measurable Disease (MD) population will comprise all patients who had measurable disease at baseline. This population will be the primary population for the analysis of Overall Response Rate.

9.2.2. Treatment Comparisons

9.2.2.1. Primary Comparisons of Interest

As this is a single arm study, there are no treatment comparisons. Effectiveness (OS and PFS), safety and health outcome endpoints will be summarized utilizing the AT population. Evaluation of overall response rates will be restricted to those patients with measurable disease at baseline (i.e., the MD population).

9.2.3. Interim Analysis

Interim analyses may be conducted and will be fully described in the RAP.

9.2.4. Key Elements of Analysis Plan

The demographic and clinical profile of the study population will be described using baseline data. Continuous variables (e.g., age) will be reported as means, medians, ranges and standard deviations, as appropriate. Categorical variables (e.g., gender, race/ethnicity) will be summarized as number and percentage (%) of the total study population. Statistical analyses will be fully described in the written statistical analysis plan RAP. Evaluations and interpretations will be based on point estimates and 95% confidence intervals (CI) as evaluation of the statistical precision around the point estimate, where relevant. Effectiveness and safety analyses will be stratified by patient risk category, performance status (ECOG) and age (< 65 and ≥ 65 years) at enrollment, where relevant. Analyses may be additionally stratified by prior treatment, history of nephrectomy, histologic subtype and other characteristics as appropriate and as the distribution of characteristics allow. No formal hypothesis or statistical significance testing is planned. This approach follows the *Guidelines for Good Pharmacoepidemiology Practices*, Section D, point 10.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis. All data up to the time of study completion/withdrawal from

study will be included in the analysis, regardless of duration of treatment. There will be no imputation for missing data.

For the analysis of overall survival, the last date of known contact will be used for those patients who have not died at the time of analysis; such patients will be considered censored.

Progression will be determined by tumour response assessed by imaging or by clinical deterioration, whichever comes first, and regardless of whether treatment was discontinued or modified. For the analysis of PFS, if the patient received subsequent anti-cancer therapy prior to the date of documented progression or death, progression free-survival will be censored at the last adequate assessment (e.g., assessment where visit level response is complete response, partial response or stable disease) prior to the initiation of therapy. Otherwise, if the patient does not have a documented date of progression or death, progression-free survival will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

Details on the determination of tumour response are given in Appendix 2. Additional details on effectiveness analyses are provided in Section 9.2.4.1. Similarly additional details on safety analyses are provided in Section 9.2.4.1.

9.2.4.1. Effectiveness Analyses

9.2.4.1.1. Primary Analysis

The primary analysis will evaluate the [population on OS and PFS based on the investigator's assessment, as defined in Section 7.3. Censoring rules will be outlined in detail in the RAP. PFS and OS duration will be summarised using Kaplan-Meier methods. Rates of PFS and OS at 12 months will be summarised. AT will be the primary population.

The overall response rate (ORR) will be based on the investigator assessment of overall response in the MD population. Patients with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage. Separate summaries of the number and percentage of patients with only non-measurable disease who achieve a best response of CR or SD will be provided. Exact methods for calculated confidence intervals will be utilized.

Several sensitivity analyses will be conducted in order to confirm the results of the primary analysis. Some key sensitivity analyses are provided below. Additional sensitivity analyses will be defined in the RAP.

1. The first sensitivity analysis, limited to the MD population, will be based on investigators' assessment of progression together with clinical evidence of symptomatic deterioration determined by investigator. This analysis will take into account the fact that some patients may have progression based on clinical evidence of symptomatic deterioration prior to documentation of progression via CT/MRI.
2. The second sensitivity analysis will be based on the patients in the MD population for whom follow-up was conducted consistent with RECIST 1.1.

3. The third sensitivity analysis will take into account the extended lost-to-follow up. If a progression event occurs after an extended lost-to-follow-up time the primary analysis will censor those patients at the date of their last visit with an adequate assessment even if subsequent information is available regarding tumour measurements or date of death. The extended lost-to-follow-up will be defined in the RAP.
4. The fourth sensitivity analysis will assign the start date of the new anti-cancer therapy as the progression date for patients who start a new anti-cancer therapy without documented disease progression in the primary analysis.
5. The fifth sensitivity analysis will utilize alternative methods for handling patients with unknown or missing response in evaluation of ORR (methods will be defined in the RAP).

9.2.4.1.2. Secondary Analyses

Secondary effectiveness endpoints are listed in Section 2 and Section 7.2.

If sample size permits, subgroup analyses by patient risk category at enrollment, patient age, prior treatment status and performance status at enrollment will be performed, as follows:

- Elderly patients (< 65 years and ≥ 65 years)
- ECOG status at enrollment (< 2 and ≥ 2)
- Risk categorization (by MSKCC, Motzer 1999) (poor, intermediate, favourable/good)
- Risk categorization (according to Heng criteria; Heng 2009) (poor, intermediate, favourable/good)
- Treatment naïve patients vs. cytokine pre-treated patients (first line vs. second line)

Further details will be provided in the RAP. Additional subgroups may be pre-specified in the RAP, if appropriate based on new information on the disease or medication under study.

Sufficient baseline information will be captured in order to programmatically characterize patients based on the baseline data from the COMPARZ(VEG108844) study. If sample size permits, the primary effectiveness, safety and RDI will be evaluated within this population of patients, and the clinical trial eligible population within the study will be compared to the non-clinical trial eligible population within the study. Further details will be provided in the RAP.

If sample size permits, exploratory analyses of duration of response and time to response will be summarized descriptively for the MD population using Kaplan-Meier medians and quartiles. Only the subset of patients who show a confirmed complete or partial tumor response will be included. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP.

In addition, an analysis of the time to scheduled assessments will also be performed to evaluate consistency across sites and the differences between clinical trial and real world assessments. Details will be provided in the RAP.

9.2.4.2. Safety Analyses

Safety endpoints are described in Section 2 and Section 7.3.

The AT population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

9.2.4.2.1. Extent of Exposure

The number of patients administered study treatment will be summarized according to the duration of therapy. Average daily dose and duration of treatment (with and without interruptions) and RDI will be summarized. The number and proportion of patients treated with various initial and subsequent dose regimens and changes in treatment patterns over time will be summarized. Discontinuations, and primary reasons for treatment and/or study discontinuation, will also be described.

9.2.4.2.2. Adverse Events

Adverse events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4.0).

Events will be summarized by frequency and proportion of total patients, by system organ class and preferred term. Separate summaries will be given for all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation of study treatment.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of special interest will be summarized separately:

- Any adverse event that results in a pazopanib dose modification or discontinuation
- Any other reports of the following AEs:
    - Evidence of liver toxicity (e.g., increased ALT and/or AST, liver failure)
    - New onset or worsened hypertension
    - Cardiac dysfunction
    - Thyroid dysfunction
    - The incidence of deaths and the primary cause of death will be summarized.

9.2.4.2.3. Clinical Laboratory Evaluations

Laboratory testing performed locally as part of routine practice and reported in the CRF will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Further details will be provided in the RAP.

9.2.4.3. Relative Dose Intensity

Relative dose intensity will be summarized as proportion of patients with reduced RDI and by median (range), and its relationship with treatment outcomes will be evaluated using appropriate regression methods. Multiple logistic regression will also be applied to identify factors potentially influencing RDI. These analyses will be repeated for the subgroups, where relevant.

9.2.4.4. Health Outcomes Analyses

Health-related quality of life (HRQoL) will be assessed using the EQ-5D (3L) Index and VAS, the FKSI-19 and the FACIT Fatigue scale.

The EQ-5D questionnaire will be completed at baseline and approximately every three months until study discontinuation/completion. Frequency of assessments will depend on the particular study. Two scores will be estimated – the utility score calculated from the 5 domains using a scoring algorithm and the VAS score based on the 0-100 feeling thermometer. Changes from baseline will be summarised and at specified timepoints of interest. The calculation of scores and methods to deal with missing data will be handled according to the questionnaire's standard scoring guidelines.

The FKSI-19 and FACIT Fatigue scale will be completed at baseline, and approximately every three months until study discontinuation/completion. Changes from baseline will be summarised and at specified timepoints of interest will be analysed. The calculation of scores and methods to deal with missing data will be handled according to the questionnaire's standard scoring guidelines. Full details of all the health outcomes analyses will be provided in the RAP.

10. STUDY CONDUCT CONSIDERATIONS

10.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of patients begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

This non-interventional study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE). Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP) (as they apply to observational research), all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments

- Patient informed consent
- Investigator reporting requirements

GSK will provide full details of the above procedures, either verbally, in writing, or both. Written informed consent must be obtained from each patient prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

Data quality will be confirmed through a series of programmed data quality checks that automatically detect out-of-range or anomalous data, as detailed in the study data monitoring plan. Full details will be provided in the clinical monitoring plan, including for-cause monitoring that is appropriate for the study design. The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements and all applicable regulatory requirements

10.4. Quality Assurance

To ensure compliance with all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

10.5. Study and Site Closure

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe

noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

GSK may close sites which fail to recruit within a predefined timeframe, as defined within the Study Procedures Manual.

10.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate.

The results summary will be posted to the Clinical Study Register no later than 12 months after the last patient's last visit (LPLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LPLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

10.8. Steering Committee

A scientific steering committee consisting of global experts specializing in oncology, as well as appropriate representatives from the sponsor project team will be chartered to provide input on the scientific operations of the study as well as review of the interim and final data analyses and reports.

10.9. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be not be utilized in this study.

10.10. Independent Review Committee

An Independent Review Committee (IRC) will be not be utilized in this study.

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12. APPENDICES

12.1. Appendix 1 List of Previous Exposures Requiring Exclusion

The following guidance is in reference to the exclusion criterion: "Previous exposure to an investigational or licensed multi-kinase inhibitor or an anti-VEGF angiogenesis inhibitor for advanced or metastatic disease".

Patients that have exposure to any of the following treatments (for any indication) prior to enrollment are to be excluded:

Investigational or licensed multi-kinase inhibitors	**Investigational or licensed anti-VEGF angiogenesis inhibitors**
sunitinib (Sutent) sorafenib (Nexavar) axitinib (Inlyta) everolimus (Afinitor) temsirolimus (Toricel) Any investigational or subsequently licensed multi-kinase inhibitor (e.g., tivosanib, dovitinib)	Bevacizumab (Avastin) Any other investigational or subsequently licensed anti-VEGF angiogenesis inhibitor

It should be noted that additional treatments may meet this criteria and be added to the list over the course of the study.

12.2. Appendix 2 Evaluation of Response

The following information is provided for reference only and based on the RECIST (version 1.1 guidelines [Eisenhauer, 2009]); no specific definitions or assessment procedures are mandated or recommended by the study. Disease status and progression are to be assessed according to routine clinical practice at each individual site.

1. Measurable and Non-Measurable Lesions

Measurable lesion:

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm calliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis is measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease:

The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations are not utilized as the only measurable lesion.

Non-Measurable only disease:

The presence of only non-measurable lesions.

2. Objective evaluation of lesions

According to the RECIST methods, when more than one measurable lesion is present, up to five "target" lesions representative of all involved organs may be identified to facilitate

consistent tumour response evaluation. Definitions for assessment of response for target lesion(s) consistent with RECIST ***are provided for reference only***:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are <u>not</u> assessed, sum of the diameters <u>cannot</u> be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

3. Evaluation of non-target lesions.

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently.
- Sites of non-target lesions, which are not assessed at a particular timepoint, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

4. New lesions

New malignancies denoting disease progression should be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions. For any equivocal new lesions, if at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

5. Evaluation of overall response

Table 6 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for patients with measurable disease at baseline.

Table 6 Evaluation of Overall Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Table 7 presents the overall response at an individual time point for all possible combinations of tumour responses in non-target lesions with or without the appearance of new lesions for patients with non-measurable only disease at baseline.

Table 7 Evaluation of Overall Response for Patients with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response, PD=progressive disease, and NE=Not Evaluable

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, the residual lesion may be investigated (fine needle aspirate/biopsy) to confirm the CR.

6. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 56 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Patients lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

12.3. Appendix 3 Performance Status scales and prognostic risk categories

A. The **ECOG Performance Status** instrument is a widely accepted and used method based on a 5-point scale for assessing the functional status of patients with cancer and their ability to maintain self-care [Oken, 1982; Buccheri, 1996].

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

B. The **Karnofsky Performance Scale** is an additional tool intended to assist clinicians and caretakers in gauging a patient's functional status and ability to carry out activities of daily living.

Percent (%)	Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly

C. The **Memorial Sloan Kettering Cancer Center (MSKCC) and Heng risk model systems** stratify patients with metastatic renal cell carcinoma into poor-, intermediate-, and favorable-risk categories based on the number of adverse clinical and laboratory parameters present.

MSKCC [Motzer, 1999]	**Heng [Heng, 2009]**
Karnofsky performance status < 80%	Karnofsky performance status < 80%
Time from diagnosis (with advanced or metastatic RCC) to treatment with pazopanib less than 12 months	Time from diagnosis (with advanced or metastatic RCC) to treatment with pazopanib less than 12 months
Corrected serum calcium (based on serum albumin) greater than 10.0 mg/dl	Corrected serum calcium (based on serum albumin) greater than 10.0 mg/dl
Hemoglobin less than the lower limit of normal	Hemoglobin less than the lower limit of normal
Serum lactate dehydrogenase (LDH) more than 1.5 times the upper limit of normal	*[LDH not included]*
[Neutrophil count not included]	Absolute neutrophil count greater than the upper limit of normal
[Platelet count not included]	Platelet count greater than the upper limit of normal

For both risk criteria model, the following scoring is applied:

Risk group	**Criterion**
Favourable	No poor prognostic factors at enrollment
Intermediate	One or two poor prognostic factors at enrollment
Poor	More than two poor prognostic factors at enrollment

12.4. Appendix 4: Summary of Changes from the Previous Version of the Protocol

Protocol Amendment No. 1

A tabular summary of the changes in this amendment (No. 1) relative to the currently approved study protocol (effective 02 March 2012) is provided below.

No	Change	Sections Affected
1	Author changes.	Cover page
2	Sponsor Signatory Change.	Sponsor Signatory
3	Primary medical monitor change.	Sponsor Information page
4	Amended Text Replaced reference to VEG105192 with VEG108844. Reason for change To correlate against more recently reported study data.	Protocol Summary Objective(s)
5	Amended Text 700-1000 patients replaced with 500-700 patients 18 months replaced with 30 months. Reason for change To reflect sample size assumptions and the projected enrolment period.	Study Design
6	Original Text A head-to-head non-inferiority trial of pazopanib versus sunitinib in patients with locally advanced and/or metastatic RCC (COMPARZ, or "Comparing the efficacy, safety, and tolerability of pazopanib vs sunitinib") [VEG108844] is ongoing. The primary endpoint is PFS; secondary endpoints include overall survival, duration of response, quality of life, medical resource utilisation and safety assessments. In addition, there is an ongoing randomized, double-blind, cross-over study of pazopanib versus sunitinib [VEG113046], which is meant to assess how the tolerability and safety differences between each drug translate into patient preference (PISCES, or "Patient preference study of pazopanib versus sunitinib in advanced/metastatic RCC"). Pazopanib was approved in the US in 2009 and conditionally approved in the EU in 2010 for treatment of advanced RCC. Amended Text A head-to-head non-inferiority trial of pazopanib versus sunitinib in patients with locally advanced and/or metastatic RCC (COMPARZ, or "Comparing the efficacy, safety, and tolerability of pazopanib vs sunitinib") [VEG108844] has been reported. The VEG113078 Asian sub study was combined with VEG108844, this was made possible due to the similar study design and recruitment at the same sites. The primary endpoint is PFS; secondary endpoints include overall survival, duration of response, quality of life, medical resource utilisation and safety assessments. The study	Background

No	Change	Sections Affected
	demonstrated non-inferiority of pazopanib for PFS in the intention to treat population and pazopanib statistically favoured quality of life in 11 of the 14 domains measured (Motzer, 2013). In addition, there is a reported randomized, double-blind, cross-over study of pazopanib versus sunitinib [VEG113046], which is meant to assess how the tolerability and safety differences between each drug translate into patient preference (PISCES, or "Patient preference study of pazopanib versus sunitinib in advanced/metastatic RCC"). The PISCES patient preference study demonstrated that significantly more patients preferred pazopanib over sunitinib due to overall better HRQoL and less fatigue (Escudier, 2012). Pazopanib was approved in the US in 2009 and conditionally approved in the EU in 2010 for treatment of advanced RCC, full approval was granted in 2013. Reason for change To clarify VEG108844 combined the VEG113078 Asian sub study and VEG108844 and VEG113046 are now reported. To clarify approval status for advanced RCC.	
7	Amended Text Replaced reference to VEG105192 with VEG108844. Reason for change To correlate against more recently reported study data.	Section 2. Objectives and Endpoints
8	Amended Text 700-1000 patients replaced with 500-700 patients 18 months replaced with 30 months. Reason for change To reflect updated sample size assumptions and the projected enrolment period.	Section 3. Study Design
9	Amended Text 700-1000 patients replaced with 500-700 patients. Reason for change To reflect updated sample size assumptions.	Section 4.1.1 Number of Patients
10	Amended Text 700-1000 patients replaced with 500-700 patients. Reason for change To reflect sample size assumptions.	4.1.1 Number of Patients
11	Added Text *Treatment with pazopanib can be started either prior to or after signed ICF as long as within 30 days of clinical decision made to initiate treatment with pazopanib.* Reason for change To clarify inclusion criteria bullet 3.	4.1.2. Inclusion Criteria

No	Change	Sections Affected
12	Original Text All patients who permanently discontinue study treatment should be followed for progression, survival and new therapies according to the protocol schedule, for up to 30 months post-enrollment. Amended Text All patients who permanently discontinue study treatment should be followed for progression, survival, health-related quality of life and efficacy of new therapies according to the protocol schedule, for up to 30 months post-enrollment. Reason for change To clarify capture of pazopanib post progression data such as quality of life data and efficacy data on other RCC therapies.	
13	Amended Text Replaced VEG105192 with VEG108844 RDI and standard deviation. Reason for change To reflect the more recently reported study data.	Section 5.2 Relative Dose Intensity
14	Original Text Refer to the Time and Events Table for the timing of all assessments (Table 1). Amended Text Refer to the Time and Events Table for the timing of the data collection time points for assessments that may have been performed (Table 1). Reason for change To clarify data collection per the recommended time and events table, based on assessments that may have been performed.	Section 7, Study assessments and procedures
15	Amended Text Recommended Schedule of Events updated. Reason for change To clarify early discontinuation header and clarify the pazopanib post progression data required to be captured.	Section 7, Table 1
16	Deleted text Removed text 'current weight (kg)'. Reason for change To correlate with Table 1 recommended schedule of assessments.	Section 7.2 Follow-up assessments
17	Added Text Subsequent RCC treatment efficacy, quality of life. Reason for change To clarify capture of pazopanib post progression data such as	Section 7.3.2.1 Follow-up Assessments for Patients Permanently Discontinued from Study Treatment

<table>
<tr><th>No</th><th>Change</th><th>Sections Affected</th></tr>
<tr><td></td><td>health-related quality of life data and efficacy data on other RCC therapies.</td><td></td></tr>
<tr><td>18</td><td>Amended Text
The targeted sample size of 500-700 was based on the expected precision around the estimates for the outcomes of interest, and the feasibility of enrolling the desired population during the enrolment period (30 months).

Reason for change
To reflect current sample size assumptions and enrolment period.</td><td>Section 9 Data Analysis and Statistical Considerations

9.1.1 Sample Size Assumptions</td></tr>
<tr><td></td><td>Amended Text and Tables

In VEG108844;, the PFS rate at 12 months (estimated from the Kaplan-Meier estimate) was approximately 40% [Motzer, 2013].
Table 3 Sample size estimates for PFS (at 12 months post-enrollment)
<table>
<tr><td>Precision (half-width)</td><td>10%</td><td>5%</td><td>4%</td><td>3%</td></tr>
<tr><td>Estimated 95% CI</td><td>(30%, 50%)</td><td>(35%, 45%)</td><td>(36%, 44%)</td><td>(37%, 43%)</td></tr>
<tr><td>N</td><td>93</td><td>369</td><td>577</td><td>1025</td></tr>
</table>
In the phase III study of pazopanib VEG108844, the overall response rate (ORR) observed in the pazopanib arm was 31% [Motzer,2013]

Table 4 Sample size estimates for ORR (at 12 months post-enrollment)
<table>
<tr><td>Precision (half-width)</td><td>10%</td><td>5%</td><td>4%</td><td>3%</td></tr>
<tr><td>Estimated 95% CI</td><td>(21%, 41%)</td><td>(26%, 36%)</td><td>(27%, 35%)</td><td>(28%, 34%)</td></tr>
<tr><td>N</td><td>83</td><td>329</td><td>514</td><td>913</td></tr>
</table>
A sample size of 700 patients will provide for a precision of less than 4% for ORR and a sample size of 500 patients will provide a precision of less than 5% for ORR.
Added Text
In VEG108844, the OS rate at 12 months (estimated from the</td><td>Progression-Free Survival

Overall Response Rate</td></tr>
</table>

No	Change	Sections Affected
	Kaplan-Meier estimate) was approximately 79% [Motzer,2013]. Taking this as a baseline proportion, the sample sizes (N) required for different levels of precision are shown in Table 5. These are calculated using the normal approximation to the binomial proportion distribution. **Table 5 Sample size estimates for OS (at 12 months post-enrollment)** **Precision (half-width)** | 10% | 5% | 4% | 3% **Estimated 95% CI** | (69%, 89%) | (74%, 84%) | (75%, 83%) | (76%, 82%) **N** | 64 | 255 | 399 | 709 A sample size of 500-700 patients will provide a precision of less than 4% for OS at 12 months. Deleted Text **Relative Dose Intensity (RDI)** Relative dose intensity (RDI) will be evaluated using a one sample t-test to compare the RDI against an estimate obtained from the Phase III registration study for pazopanib [VEG105192] using a minimal acceptable value (the average RDI obtained from the VEG105192 minus a margin of inferiority of 0.1). The sample size is determined by the formula: N= (Z1- α/2 +Z1-β)^2 * σ ^2 / δ ^2 Where σ is the estimated standard deviation for the RDI distribution and δ is the difference to be detected. An α (type I error) of 0.05 and β (type II error) of 0.10 is assumed (for 90% power). If the mean RDI in this observational study is assumed to be the same as in VEG105192, δ would be equivalent to the inferiority margin. However, the expected RDI in the real world setting should conceivably be slightly smaller than the RDI in the clinical trial setting, therefore for the purposes of sample size estimation a 0.05 decrement was used (i.e., δ = inferiority margin – 0.05). A reasonable assumption for the standard deviation would be 0.25. The standard deviation calculated from VEG105192 was 0.185, and a larger standard deviation might be expected for an observational study. Table 4 gives the number of patients required to obtain the specified precision, assuming a standard deviation (SD) of 0.25 and a more conservative value of 0.4. Within the table, the precision is related to the SD by the formula: precision = Z[1 – alpha/2] * SD/sqrt(N) **Table 4 Sample size estimates for RDI**	Overall Survival Relative Dose Intensity

No	Change	Sections Affected

Precision (half-width)	0.1	0.1	0.05	0.05	0.03	0.03
Estimated 95% C.I.	(0.775, 0.975)		(0.825, 0.925)		(0.845, 0.905)	
Std. Dev.	0.25	0.4	0.25	0.4	0.25	0.4
N	25	62	97	246	267	683

Based on the results from the sample size estimations, it can be seen that a total of 700 is sufficient to generate a power of 90% even in pessimistic assumptions (small margin of inferiority, large standard deviation for RDI and average RDI for real-world setting somewhat lower than in VEG105192).
Secondary analyses will be carried out on the subgroup of patients who would have been eligible for VEG105192 ("clinical trial eligible" subgroup). Assuming that 60 or 70% of patients in the observational study (i.e., between 420 and 490 of the enrolled patients) will be considered clinical trial eligible, the precision for RDI will be as follows for
different values of the standard deviation is shown in Table 5.

Table 5 Sample size estimates for RDI (clinical trial eligible)

N	420	420	420	490	490	490
Std. Dev.	0.25	0.30	0.40	0.25	0.30	0.40
Precision (half-width)	0.024	0.029	0.038	0.022	0.027	0.035

Reason for change
To reflect data in the more recently reported VEG108844 study and to reflect current sample size assumptions and enrolment period.

OSS replaced with ORR to correct typographical error.

Added overall survival (OS) to include variability and precision rates for 500-700 patients for OS.

Removed section for the Relative Dose Intensity with the intention to be a descriptive summary and have no requirement for a formal statistical test to be performed. This should avoid potential bias in patient selection and reduce the validity of analysis (i.e. patients who are not eligible for other clinical studies).
In addition comparison of RDI between two studies is unlikely to determine interpretable results based on variability of pazopanib absorption.

19	Original Text	Section 9.2.4 Key

No	Change	Sections Affected
	As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be information, data from all participating centers will be pooled prior to analysis. All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment. There will be no imputation for missing data. Amended Text As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis. All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment. There will be no imputation for missing data. Reason for change Clarification of typographical error, replaced information with informative.	Elements of Analysis Plan
20	Original Text Sufficient baseline information will be captured in order to programmatically characterize patients based on the inclusion/exclusion criteria from the pivotal Phase III clinical trial (VEG105192). Amended Text Sufficient baseline information will be captured in order to programmatically characterize patients based on the baseline data from the COMPARZ(VEG108844) study. Reason for change Patients will be characterised from available data captured in this study and based on baseline information from the COMPARZ (VEG108844) study.	Section 9.2.4.1.2 Secondary Analyses
21	Added references Escudier BJ, Porta C, Bono P et al. Patient preference between pazopanib (Paz) and sunitinib (Sun): Results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma (mRCC)—PISCES study, NCT 01064310. Journal of Clinical Onology 2012;30 suppl 15:CRA4502. Motzer RJ, Hutson TE, Cella D, , *et al.* Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. N Engl J Med 2013;369:722-31.	Section 11 References