**Title:** An open label, multi-centre, non-interventional post-marketing surveillance (PMS) to monitor the safety and effectiveness of Votrient administered in Korean patients according to the prescribing information

**Abbreviated title:** Votrient PMS

**Identifier:115578**

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**Effective Date:**
Protocol Version 2, 06 Jan 2013

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

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the PMS in compliance with the protocol.
- I acknowledge that I am responsible for overall PMS conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the PMS are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:_____

Investigator Signature Date

# 1. INTRODUCTION

## 1.1. Background

Kidney cancers account for about 86% of cancers of the kidney/renal pelvis [Chow, 1999], the incidence of renal cell carcinoma (RCC) has been increasing steadily in nearly all regions of the world [Murai, 2004]. Advanced RCC (Stage IV) is generally resistant to chemotherapy and hormonal therapy, with responses usually not exceeding 10% for any cytotoxic regimen that has been studied in adequate numbers of subjects [Motzer, 2000]. RCC has been considered an immunosensitive tumor and over the past several decades immune-based therapies with interleukin-2 (IL-2) and interferon α (IFNα), have been extensively investigated in subjects with advanced RCC. Collectively, the objective response rate seen with IFNα treatment is approximately 10-15%; and the responses are rarely complete or durable [McDermott, 2004]. The overall survival seen with high-dose IL-2 is similar to that of IFNα [McDermott, 2005].

Clear cell RCC, which constitutes approximately 75 - 80% of RCC, has been found to be associated with a high incidence of biallelic inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene [Kim, 2004]. VHL plays a key role in regulating the angiogenic pathways that are mediated by the hypoxia-inducible factor-1α (HIF-1α). HIF-1α is usually activated under hypoxic conditions within a tumor which leads to transcription of various down-stream angiogenic growth factors and cytokines, most notably, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-α (TGFα) and erythropoietin. These trigger various signal transduction pathways resulting in initiation and augmentation of tumor angiogenesis. [Geoarge, 2003]

Angiogenesis is critical for the growth and survival of human tumours. [Karamysheva, 2008] The process is controlled by a balance between pro-angiogenic factors (e.g. VEGF, PDGF and FGF) and anti-angiogenic factors (e.g. angiostatin, endostatin and thrombopondin) [Distler et al, 2003] VEGF is the most potent pro-angiogenic factor, and is overexpressed in virtually all solid tumours. [Ferrara et al, 1997]

Pazopanib (Votrient) is a potent multi-target receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3, platelet-derived growth factor receptors (PDGFR) –α and -β, and stem cell factor receptor (c-kit). [kumar, 2007] VEGFR regulates angiogenesis [Kerbel, 2008] and PDGFR regulates angiogenesis and proliferation of some tumour cells [Yu et al, 2003, Homsi et al, 2007]. And c-Kit regulates cellular proliferation, survival and metastasis. [Demetri, 2001] Pazopanib targets these key molecules involved in tumour angiogenesis. [Sonpavde et al, 2008] Pazopnib is a more selevtive multikinase inhibitor compared with sunitinib. [Kumar et al, 2009] Besides VEGFR, PDGFR and c-Kit, sunitinib inhibits 49 additional kinases. By contrast, pazopanib inhibit seven additional kinases. And pazopanib has a greater affinity to VEGFR-2 then sunitinib. [Kumar et al, 2009, Karamen et al, 2008]

Clinical efficacy and safety of pazopanib in treating advanced RCC patients have been established in a randomized double-blind placebo-controlled Phase III study that enrolled 435 treatment-naïve or cytokine-pretreated subjects. PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P< 0 .0001), the treatment-naive subpopulation (median PFS 11.1 v 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P < 0.0001), and the cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2months; HR, 0.54; 95% CI, 0.35 to 0.84; P < 0.001). The objective response rate was 30% with pazopanib. [Sternberg et al, 2010]

Soft Tissue Sarcoma (STS) is a rare group of heterogeneous mesenchymal cancers originating from connective tissue. The annual incidence of STS is around 2-3/100,000. Overall, STS account for approximately 1% of all malignancies, while they give rise to 2% of the total cancer-related mortality. The 5-year survival in Europe for adult STS (excluding visceral STS) averages 60%, with substantial geographic variations. [Storm et al, 1998] The median survival time in patients with metastatic STS is usually < 12 months.

Surgery is usually the first line of management for localized disease. Standard treatment is generally a wide surgical excision or even more radical surgery of the primary tumor combined with adjuvant radiotherapy in selected cases. The addition of post-operative radiotherapy appears to reduce the rate of local recurrence. [Leibel et al, 1982] However, even optimal local treatment does not prevent the occurrence of distant metastases in many patients, especially those with high-grade tumors. Although the effect of adjuvant chemotherapy has been studied by several groups, the results do not allow to draw any final conclusions. An international meta-analysis indicated an effect of adjuvant systemic treatment on progression free survival but did not show a significant effect on overall survival. [Sarcoma Meta-analysis Collaboration, 1997] STS metastasizes primarily to the lungs but also to bone, liver and other organs, depending on the subtype. Chemotherapy is widely used in the treatment of irresectable advanced disease, basically with a palliative intent, as most initially chemotherapy-sensitive patients will ultimately relapse and present at that point with chemotherapy-resistant disease.

Clinical efficacy and safety of pazopanib in soft tissue sarcoma patients have been established in a randomized double-blind placebo-controlled Phase III study that enrolled 369 randomized pts (246 pazopanib, 123 placebo). The progression-free survival (PFS) per independent review is significantly prolonged with pazopanib (median: 20 vs 7 weeks; HR=0.31, 95% CI 0.24-0.40 ; P<0.0001). The interim analysis for overall survival shows a statistically non-significant improvement of pazopanib vs placebo (median: 11.9 vs 10.4 months, HR=0.83, 95% CI 0.62-1.09). Main on-therapy grade 3-4 toxicities in the pazopanib vs placebo arm respectively: fatigue (13%, 6%), hypertension (7%, nil), anorexia (6%, nil), and diarrhea (5%, 1%). Similarly, thromboembolic events (grade 3-5 ) (3%, 2%), LVEF drop of >15% (8%, 3%). [Van et al, 2011]

Despite the rigorous requirements of the drug approval process, the full range of a drug's risks cannot be evaluated until that drug is marketed and used in the real world of clinical practice. In premarketing studies, only small numbers of carefully screened and otherwise healthy subjects who are treated for only short periods and monitored only for short-term outcomes. These kind of limitations in premarketing studies make it necessary to conduct postmarketing studies to explore both the effectiveness and the risks of medications as they are used in more realistic settings. Korean regulatory authority has requested the marketing authorization holder to conduct regulatory-mandated post-marketing surveillance (PMS) for collecting safety and effectiveness data of product in Korean patients since 1995. Therefore, this Votrient PMS is to meet Korean regulatory requirements.

## 2. OBJECTIVES

### 2.1. Primary objective

- The primary objective of this PMS is to monitor the incidence of adverse events administered Votrient in Korean patients.

### 2.2. Secondary objective

The secondary objectives are to identify as follow in cancer patients administrated Votrient .

- Unexpected adverse drug reaction (ADR) and serious adverse events(SAE)
- Effectiveness

## 3. PMS DESIGN OVERVIEW

- Non-interventional, open-label, single group, multicenteric post-marketing surveillance in Korea.
- Indication:

1. Advanced renal cell carcinoma

2. Advanced soft tissue sarcoma who have received prior chemotherapy
: Adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated.

- Subjects treated and/or will be treated with Votrient according to the prescribing information will be enrolled.
- Control: None
- Data collection: Standardized electronic Case Report Form (e-CRF)

## 4. POPULATION

### 4.1. Number of subjects

3000 subjects will be enrolled according to the Korean PMS regulation.

### 4.2. Eligibility criteria

The investigators enroll advanced renal cell carcinoma or Soft Tissue Sarcoma (STS) patients administrated Votrient at the site.

All subjects must satisfy the following criteria at PMS entry according to KFDA PMS regulation:

- Subject who received Votrient as described the prescribing information
- Subject who don't have contraindication according to the prescribing information
- Subject is willing and able to provide written informed consent

## 5. ASSESSMENT OF PMS

### 5.1. Outline of PMS procedures

**Table 1 Overview of PMS procedures**

| Visit | BASELINE | DURING TREATMENT[1] | LAST OBSERVATION[2] |
|---|---|---|---|
| Check eligibility criteria | X | | |
| Cancer information | X | | |
| Demography | X | | |
| Medical history | X | | |
| Concomitant medication | X | X | X |
| Prescription | X | X | |
| Adverse events occurrence | | X | X |
| Laboratory Test Results(optional) | X | X | X |
| Tumor assessments(optional) | X | X | X |
| Survival | | | X |

1. The every-4week assessment of AE and tumor will be recommended. Disease assessment will be done by the study site's institutional standard.

2. Last observation is recommended to be conducted at 12 months after baseline excluding progression, death, drop-out (e.g. due to unacceptable AE/SAEs) or follow-up loss.

## 5.2. Detailed description of PMS stages/visits

### 5.2.1. Baseline

- Eligibility criteria
- Cancer information
  - ✓ Diagnosis, stage
  - ✓ Metastatic lesion
  - ✓ Histopathology
  - ✓ Nephrectomy history
  - ✓ Previous cancer treatment
- Demography
  - ✓ Age
  - ✓ Gender
  - ✓ Pregnancy
  - ✓ Height and weight
- Medical history
  - ✓ Allergy history
  - ✓ Renal impairment
  - ✓ Hepatic impairment
  - ✓ Cardiovascular disease
  - ✓ Concomitant disease
- Concomitant medication
- Laboratory test result
- Tumor evaluation
- Prescription of Votrient

### 5.2.2. Treatment

- Safety Assessment
- Concomitant medication
- Laboratory test result
- Prescription of Votrient

- Tumor evaluation

5.2.3. Last observation

- Safety Assessment
- Concomitant medication
- Laboratory test result
- Tumor evaluation
- Disease progression
- Survival

## 5.3. Safety Assessment

This is the primary endpoint of Votrient PMS. All subjects who receive at least one dose of the drug and at least once safety assessment will be safety population.

The collecting information includes, (Refer to Section 9)

- Adverse Event Term
- Onset Date
- Outcome of Adverse Event
- Intensity(refer to NCI CTCAE-V4)
- Assessment of Causality of AE
- Action taken for AE

## 5.4. Effectiveness Assessment

Effectiveness of Votrient is secondary end point of Votient PMS

- Overall response rate by RECIST 1.1 : (CR+PR)/evaluable for response

  - As a appendix 2, tumour evaluation can be done using RECIST 1.1 criteria

- Progression free survival (PFS)

# 6. PRODUCT(S) AND ADMINISTRATION

## 6.1. Investigational product

The medicine is not provided to the subjects by GSK. The patients will purchase the commercially available Votrient with the prescription in routine medical practice.

### 6.2. Dosage and administration

Votrient will be administerd as described on the prescribing information. The treatment of patient does not be affected by this PMS.

## 7. CONCOMITTANT MEDICINE

This PMS is non-interventional , therefore all concomitant medications according to local practice are allowed during the PMS and the information of drug-drug interaction may be referred to.

## 8. SUBJECT COMPLETION AND WITHDRAWAL

### 8.1. Subject completion

All subjects who receive at least one dose of the drug and at least once safety assessment will be safety population. Last observation is recommended to be conducted at 12 months after baseline in order to evaluate safety and effectiveness. If the subject do not return to follow-up visit, all data collected until the date of last contact of the subject will be used for the analysis.

### 8.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event. Withdrawals will not be replaced.

A subject is considered a 'withdrawal' from the PMS when no PMS procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

## 9. ADVERSE EVENTS(AE) AND SERIOUS ADVERSE EVENS (SAE)

During PMS, when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in this section of the protocol Definition of an AE

### 9.1. Definition of a AE

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

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

Examples of an AE **include**:

• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
• New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the PMS
• Signs, symptoms, or the clinical sequelae of a suspected interaction

•Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)
• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Examples of an AE **do not include** a/an:

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

### 9.2. Definition of a SAE

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

a) Results in death.

b) is life-threatening.

*NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*

c) requires hospitalization or prolongation of existing hospitalization.

*NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the doctor'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.

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

### 9.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, and urinalysis) or other abnormal assessments (e.g. vital signs, etc.) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE.(Refer to Section 9.1 and 9.2) Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the PMS or are present at baseline and significantly worsen following the start of the PMS will be reported as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the PMS and do not worsen, will not be reported as AEs or SAEs.

### 9.4. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF.

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

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

From the time a subject agree to his or her participaing in this PMS until one month after he or she has completed Votrient treatment (including any follow-up period), AE/SAE will be reported promptly to GSK.

Any signs and symptoms present at the time the first dose is administered will be documented as baseline signs and symptoms. Any medical occurrences which present after administration of the medication and on or before the final follow up visit must be reported as Adverse Events. All AEs must be recorded irrespective of whether they are considered drug related. At each visit/assessment in the period defined above, AEs/SAEs will be evaluated by the investigator and recorded. Any AEs/SAEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented. If an AE changes in intensity then the maximum intensity should be captured in the CRF.

### 9.5. Evaluating AEs and SAEs

#### 9.5.1. Assessment of Intensity

The investigator will make an assessment of intensity of each AE and SAE reported during PMS. The intensity of AEs and SAEs will be graded on a scale of 1 to 5 according the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 and are available at http://ctep.nci.gov/reporting/ctc.html. (appendix 1)

**9.5.2. Assessment of Causality**

Every effort should be made by the investigator to explain each adverse event and assess its relationship, if any, to study drug treatment. The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

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

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received and forwarded to GSK. The investigator will always provide an assessment of causality at the time of the initial report. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE Report Form
The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.
As per KFDA requirements, causality will be assessed as:

1. Certain:
   - The relationship of the administration and use of the drug is reasonable and it is not able to be explained by other medication, chemical substances or concomitant disease, it shows clinically reasonable response on withdrawal of the drug, the decisive case in the pharmacological or phenomenological aspect on re-challenge of the drugs if needed.

2. Probable/Likely:
   - The temporal sequence of the administration and use of the drug is appropriate and it does not seem that it is accompanied by other medications, chemical substances or concomitant disease, in the case that shows clinically appropriate response on withdrawal of the drug (no information for re-challenge).

3. Possible:
   - The temporal sequence of the administration and use of the drug is appropriate but it is also able to be explained by other medications, chemical substances or concomitant disease, and information related to withdrawal of the drug is insufficient or vague.

4. Unlikely:

   - It is a transitory case which may not have causality with the administration and use of the drug, it is also able to be explained reasonably by other medications, chemical substances or latent disease.

5. Conditional/Unclassified:

   - In the case that more information is needed for a proper evaluation or additional information is under review.

6. Unassessible/Unclassifiable:

   - In the case that could not be judged due to insufficient or conflicting information and no way to complement or validate.

### 9.6. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and that are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology (may not be required for studies where death is an endpoint).

New or updated information will be recorded in the originally completed SAE data collection tool. The investigator will submit the updated SAE data to GSK within the designated reporting time frames.

### 9.7. Prompt Reporting of SAEs to GSK

#### 9.7.1. Timeframe of SAE reporting

SAEs will be promptly reported to GSK as described in the following table once the investigator determined that the event meets the protocol definition of an SAE.

| | Initial SAE Reports | | Follow-up Information on a Previously Reported SAE | |
|---|---|---|---|---|
| Type of SAE | Time Frame | Documents | Time Frame | Documents |
| All SAEs | 24 hrs | "SAE" CRF pages | 24 hrs | Updated "SAE" CRF pages |

### 9.7.2. Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours or as outlined in the protocol in the section titled, "Prompt Reporting of Serious Adverse Events and Other Events to GSK". The SAE form will always be completed as thoroughly as possible with all available details of the event, and submitted to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate form. The SAE form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in the section of this document titled, "9.5.2 Assessment of Causality".

The primary mechanism for reporting SAEs to GSK will be the electronic data collection tool, the InForm system. If the electronic system is unavailable for greater than 24 hours, the site will use the SAE form and fax it to GSK. GSK will provide a separate list of contact details for reporting SAEs, including fax numbers and telephone numbers

## 9.8. 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 subjects 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.

## 9.9. AE/SAE after end of surveillance

AE/SAE is defined as any event that occurs outside of the AE/SAE detection period as defined in the protocol.(Refer to Section 9.4)

Investigators are not obligated to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the surveillance, and considers the event reasonably related to the drug, the investigator will promptly notify GSK.

# 10. REPORTING OF PREGNANCY

Any subject in person or his or her partner who becomes pregnant should be advised to discontinue Votrient. The investigator will collect pregnancy information on any subject in person or his or her partner who becomes pregnant while participating in this PMS. The investigators will record pregnancy information on the Pregnancy Report Form and submit it to GSK within 24 hours of learning of a subject's pregnancy. The subject will be instructed to investigator of inform pregnancy if investigator get this information this will be forwarded to GSK. While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE.

Follow the subject to determine the outcome of the pregnancy and forward the outcome information to GSK no later than 6 to 8 weeks following the estimated delivery date.

# 11. DATA ANALYSIS AND STISTICAL CONSIDERATION

## 11.1. Primary endpoint

- Occurrence of adverse events after Votrient administration by indication

## 11.2. Secondary endpoints

- Occurrence of unexpected or serious adverse event after Votrient administration by indication
- Effectiveness of Votrient by indication
  - Overall response rate by RECIST 1.1 : (CR+PR)/evaluable for response
    - As a appendix 2, tumour evaluation can be done using RECIST 1.1 criteria
  - Progression free survival (PFS)

## 11.3. Planned interim analysis

The interim analysis is performed annually per KFDA requirements. The interim PMS report is submitted to KFDA. (Interim Analysis could be done at the time after 6-month if it's needed)

## 11.4. Estimated sample size

The number of subjects to be included in this PMS was determined to be 3000 subjects as per Korean regulatory authority requirements.

## 11.5. Analysis population

Two populations will be considered in the analysis:

- Safety population

All subjects who receive at least one dose of the drug and at least once safety assessment will be safety population. This is the primary population for the analyses of the safety data.

- Effectiveness population

All subjects who complete all procedure according to this protocol will be efficacy population. This is the primary population for the analyses for the effectiveness data.

Both analysis will be conducted based on each indications.

## 11.6. Final analyses

### 11.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, gender, etc.) will be tabulated.

### 11.6.2. Analysis of safety

The percentage of subjects reporting each individual adverse event after administration of Votrient will be tabulated with 95% confidence interval. Cases with serious adverse events and/or unexpected adverse events will be described in detail. The distribution of adverse events by frequency, severity, outcome, investigator's causal assessment will be tabulated.

The percentage of subjects reporting adverse event by age, gender, past medical history, concomitant medication, the elderly, allergy, and diagnosis will be calculated.

The percentage of subjects reporting adverse events among special care population such as the elderly, hepatic impairment subjects, renal impairment subjects or cardiovascular disease subjects will be tabulated respectively.

### 11.6.3. Analysis of effectiveness

The percentage of subjects after administration of Votrient will be tabulated.

The percentage of subjects after administration of Votrient by age, gender, past medical history, concomitant medication, the elderly, allergy, diagnosis and indication will be calculated.

- These endpoints below by indication will be calculated **Overall Response Rate**
  This is defined as the percentage of subjects achieving either a complete (CR) or partial (PR) tumor response. The response rate will be calculated from the evaluation by treating physicians of best response which records of PR and CR only. Subjects with unknown or missing response will be treated as not evaluable; i.e. they will be included in the denominator when calculating the percentage. Response rates will be compared between treatment arms using stratified Fisher's exact tests. Approximate 95% confidence limits for the difference in response rates will be calculated. Exact 95% confidence limits for the tumor response rates in each arm will also be calculated

- **Progression-free survival**
  This is defined as the time from initiation of medication until the earliest date of disease progression or death due to any cause, if sooner. Date of disease progression will be based on data that is captured on the case report form. At the time of analysis, for subjects who have not progressed or died, progression-free survival will be censored at the date of discontinuation of medication.

## 12. ADMINISTRATIVE MATTERS

### 12.1. Disclosure of PMS

The information of this PMS will be posted on *ClinicalTrial.gov*.

### 12.2. Quality Control

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the PMS to review with the site staff the protocol, PMS 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.

GSK will monitor the study to ensure that the:

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

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

## 12.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit of the site records, and the 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.

## 12.4. Study and Site Closure

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

GSK reserves the right to temporarily suspend or terminate the PMS at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. 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 PMS is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the PMS. 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.

## 12.5. Records Retention

Following closure of the PMS, the investigator or head of the medical institution (where applicable) must maintain all site PMS 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.

### 12.6. Provision of Study Results and Information to Investigators

After the PMS completed and analyzed, 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.

If this surveillance evaluate effectiveness of drug GSK will ensure public disclosure of the clinical trial research results via the GSK Clinical Trials Register according to the GSK SOP and provide the investigator with the full summary of the PMS results. In addition, the manuscript would be submitted within 18 months upon completion of data analysis.The investigator is encouraged to share the summary results with the study subjects, as appropriate.

### 12.7. Personal Information and Data Protection

Records of personally identifiable information will be not included in the study results and managed by a serial number so they will not be included on publication and disclosure of study results. Investigators take responsibility for protecting from personal and medical information leaking.

## 13. STUDY PUBLICATION

### 13.1. Ownership

All data generated during this PMS and provided to GSK are the property of GSK.

### 13.2. Confidentiality

The investigators and other study personnel will keep any information provided by GSK confidential. The information includes this protocol, all data and records generated in the course of conducting this PMS. The investigators and other study personnel will not use the information, data, or records for any purpose other than conducting the PMS. These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator of site personnel;
- Information that is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study;
- Information that is necessary to disclose in order to provide appropriate medical care to a patient; or
- Study results that may be published, as described in the next paragraph.

### 13.3. Publication

For any multi-centre study, data from any individual centre must not be published or presented until the complete multi-centre study has been published or presented in full. Any subsequent publications should refer to the published multi-centre findings.

Prior to submitting for publication, presenting, using for instructional purposes or otherwise disclosing the results of the study, the investigator shall allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed publication or disclosure prior to its submission for publication or other disclosure. Publications or

disclosures of PMS results shall not include other confidential information of GSK's. If the proposed publication/disclosure risks GSK's patent any invention related to the PMS, the publication or disclosure will be modified or delayed a sufficient time to allow GSK to seek patient protection of the invention. This statement does not give GSK any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of GSK's confidential information.

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**Appendix 1. The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE)**


CTCAE v4

**Appendix 2. Response Evaluation Criteria In Solid Tumors (RECIST) criteria 1.1**

RECIST1.1.pdf

**Appendix 3: Supportive Care Guidelines for Diarrhea, Nausea, and Vomiting**

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

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

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

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

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

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

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

**Management Guidelines**

**Uncomplicated diarrhea of CTCAE Grade 1 or 2:**

- Hydration: have subject drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
- If Grade 2 diarrhea, consider dose reduction of investigational products.
- Dietary modifications: have subject stop all lactose-containing products and eat frequent, small meals
- Pharmacologic intervention using loperamide:
  - Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.

- Continuation of loperamide is suggested until diarrhea-free for 12 hours.
- If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes.
- If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

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

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

**Alternative Pharmacologic Intervention for Uncomplicated and Complicated Diarrhea**

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

### 1.1 Nausea and Vomiting

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

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

If a subject vomits after taking study medication, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking pazopanib at the next

scheduled dose on the following day. If vomiting persists, then the subject should contact their physician.

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

**Reference:**

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

**Appendix 4:Amendment to the Protocol**

Rationale/background for changes.

Major change was made for reflect the changes in prescribing information.

Other minor changes were made for clarity, as a correction, new information or based on new local regulations requirements.

| Version Number | version 1.0 | version 2.0 | Rationale for changes |
|---|---|---|---|
| Effective date | Apr 2011 | Jan 2012 | |
| Contributing Authors: | [redacted] PMS Associate, GSK Korea<br>[redacted] Oncology Medical Advisor, GSK Korea<br>[redacted] Oncology Medical Director, GSK Korea | [redacted] PMS Associate, GSK Korea<br>[redacted] PMS team Manager, GSK Korea<br>[redacted] Oncology Medical Advisor, GSK Korea<br>[redacted] Oncology Medical Director, GSK Korea<br>[redacted] Director of Medical & Reguratory, GSK Korea | Reflect a change in the approval page for contributing authors. |
| Sponsor Signatory | [redacted] MD PhD<br>Oncology Medical Director, China and Asia<br>R&D China and Global Oncology<br>GlaxoSmithKline | [redacted]<br>Oncology Medical Director, MEA and<br>acting Oncology Medical Director, Asia Pacific | Reflect a change in the approval page for internal protocol signoff. |
| PMS Contact Person | • [redacted] PMS associate<br>• Tel: [redacted]<br>• Fax: [redacted]<br>• E-mail: [redacted] | • [redacted] PMS associate<br>• Tel: [redacted]<br>• Fax: [redacted]<br>• E-mail: [redacted] | Reflect a change in the sponsor information page |

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|---|---|---|---|
| 1.1 background | NA | Soft Tissue Sarcoma (STS) is a rare group of heterogeneous mesenchymal cancers originating from connective tissue. The annual incidence of STS is around 2-3/100,000. Overall, STS account for approximately 1% of a l malignancies, while they give rise to 2% of the total cancer-related mortality. The 5-year survival in Europe for adult STS (excluding visceral STS) averages 60%, with substantial geographic variations. [Storm et al, 1998] The median survival time in patients with metastatic STS is usually < 12 months.<br><br>Surgery is usually the first line of management for localized disease. Standard treatment is generally a wide surgical excision or even more radical surgery of the primary tumor combined with adjuvant radiotherapy in selected cases. The addition of post-operative radiotherapy appears to reduce the rate of local recurrence. [Leibel et al, 1982] However, even optimal local treatment does not prevent the occurrence of distant metastases in many patients, especially those with high-grade tumors. Although the effect of adjuvant chemotherapy has been studied by several groups, the results do not allow to draw any final conclusions. An international meta-analysis indicated an effect of adjuvant systemic treatment on progression free survival but did not show a significant effect on overall survival. [Sarcoma Meta-analysis Collaboration, 1997] STS metastasizes primarily to the lungs but also to bone, liver and other organs, depending on the subtype. Chemotherapy is widely used in the treatment of irresectable advanced disease, basically with a palliative intent, as most initially chemotherapy-sensitive patients will ultimately relapse and present at that point with chemotherapy-resistant disease.<br><br>Clinical efficacy and safety of pazopanib in soft tissue sarcoma patients have been established in a randomized double-blind placebo-controlled Phase III study that enrolled 369 randomized pts (246 pazopanib, 123 placebo). The progression-free survival (PFS) per independent review is significantly prolonged with pazopanib (median: 20 vs 7 weeks; HR=0.31, 95% CI 0.24-0.40 ; P<0.0001). | STS background information updated |

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|---|---|---|---|
| | | The interim analysis for overall survival shows a statistically non-significant improvement of pazopanib vs placebo (median: 11.9 vs 10.4 months, HR=0.83, 95% CI 0.62-1.09). Main on-therapy grade 3-4 toxicities in the pazopanib vs placebo arm respectively: fatigue (13%, 6%), hypertension (7%, nil), anorexia (6%, nil), and diarrhea (5%, 1%). Similarly, thromboembolic events (grade 3-5 ) (3%, 2%), LVEF drop of >15% (8%, 3%). [Van et al, 2011] | |
| 3. PMS design overview | • Indication: Advanced renal cell carcinoma<br>• Votrient will be administered for the treatment of advanced renal cell carcinoma as described the prescribing information of Votrient. | • Indication:<br>1. Advanced renal cell carcinoma<br>***2. Advanced soft tissue sarcoma who have received prior chemotherapy***<br>***: Adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated.***<br>• ***Subjects treated and/or will be treated with Votrient according to the prescribing information will be enrolled.*** | Indication was revised to add STS |
| 4.2 Eligibility criteria | 4.2. Eligibility criteria<br><br>The investigators enroll advanced renal cell carcinoma patients administrated Votrient at the site.<br><br>All subjects must satisfy the following criteria at PMS entry according to KFDA PMS regulation:<br><br>4.2.1. Inclusion criteria<br><br>• Subjects with indication in the prescribing information<br>• Subject who received Votrient as described the prescribing information<br>4.2.2. Exclusion Criteria<br><br>• Subjects have contraindication according to the prescribing information | 4.2. Eligibility criteria<br>The investigators enroll advanced renal cell carcinoma ***or Soft Tissue Sarcoma (STS)*** patients administrated Votrient at the site.<br><br>All subjects must satisfy the following criteria at PMS entry according to KFDA PMS regulation:<br><br>• Subject who received Votrient as described the prescribing information<br>• Subject who don't have contraindication according to the prescribing information<br>• ***Subject is willing and able to provide written informed consent*** | To reflect the Prescribing information, Eligible criteria was amended.<br><br>And the informed consent required due to the revised local regulations. |

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| Table 1 Overview of PMS procedures | The every-8week assessment of AE and tumor will be recommended. Disease assessment will be done by the study site's institutional standard. | The every-***4week*** assessment of AE and tumor will be recommended. Disease assessment will be done by the study site's institutional standard. | Clinically, assessment of tumor made every 4-week |
| 9.4 Recording of AEs and SAEs | From the time a subject ~~prescribed the medicine~~ until one month after he or she has completed Votrient treatment (including any follow-up period), AE/SAE will be reported promptly to GSK | From the time a subject ***agree to his or her participating in this PMS*** until one month after he or she has completed Votrient treatment (including any follow-up period), AE/SAE will be reported promptly to GSK. | To reflect the changes regarding informed consent process |
| 10. Reporting of pregnancy | Any subject who becomes pregnant should be advised to discontinue Votrient. The investigator will collect pregnancy information on any subject who becomes pregnant while participating in this PMS. The investigators will record pregnancy information on the Pregnancy Report Form and submit it to GSK within 24 hours of learning of a subject's pregnancy. The subject will be instructed to investigator of inform pregnancy if investigator get this information this will be forwarded to GSK. While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE.<br><br>Follow the subject to determine the outcome of the pregnancy and forward the outcome information to GSK no later than 6 to 8 weeks following the estimated delivery date. | Any subject ***in person or his or her partner*** who becomes pregnant should be advised to discontinue Votrient. The investigator will collect pregnancy information on any subject ***in person or his or her partner*** who becomes pregnant while participating in this PMS. The investigators will record pregnancy information on the Pregnancy Report Form and submit it to GSK within 24 hours of learning of a subject's pregnancy. The subject will be instructed to investigator of inform pregnancy if investigator get this information this will be forwarded to GSK. While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE.<br><br>Follow the subject to determine the outcome of the pregnancy and forward the outcome information to GSK no later than 6 to 8 weeks following the estimated delivery date | To reflect the changes in the PV code |

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| 11. Data analysis and statistical consideration | 11.1.Primary endpoint<br>• Occurrence of adverse events after Votrient administration.<br><br>11.2.Secondary endpoints<br>• Occurrence of unexpected or serious adverse event after Votrient administration<br>• Effectiveness of Votrient by indication<br>• (...)<br><br>11.5.Analysis population<br>Two populations will be considered in the analysis:<br>- Safety population<br>All subjects who receive at least one dose of the drug and at least once safety assessment will be safety population. This is the primary population for the analyses of the safety data.<br>- Effectiveness population<br>All subjects who complete all procedure according to this protocol will be efficacy population. This is the primary population for the analyses for the effectiveness data. | 11.1.Primary endpoint<br>• Occurrence of adverse events after Votrient administration ***by indication***<br><br>11.2.Secondary endpoints<br>• Occurrence of unexpected or serious adverse event after Votrient administration ***by indication***<br>• Effectiveness of Votrient ***by indication***<br>• (...)<br><br>11.5.Analysis population<br>Two populations will be considered in the analysis:<br>- Safety population<br>All subjects who receive at least one dose of the drug and at least once safety assessment will be safety population. This is the primary population for the analyses of the safety data.<br>- Effectiveness population<br>All subjects who complete all procedure according to this protocol will be efficacy population. This is the primary population for the analyses for the effectiveness data.<br><br>***Both analysis will be conducted based on each indications.*** | Major analysis will be performed indication |
| 12.7 Personal Information and Data Protection | NA | Records of personally identifiable information will be not included in the study results and managed by a serial number so they will not be included on publication and disclosure of study results.<br>Investigators take responsibility for protecting from personal and medical information leaking. | To protect the patients privacy |

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|---|---|---|---|
| Reference | | 20. Storm HH. Survival of adult patients with cancer of soft tissues or bone in Europe. Eur J Cancer 1998; 34: 2212-2217.<br>21. Leibel S.A., Tranbaugh R.F., Wara W.M. et al.: Soft tissue sarcomas of the extremities. Survival and patterns of failure with conservative surgery and postoperative irradiation compared to surgery alone. Cancer 50: 1076-1083, 1982.<br>22. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised respectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 350: 1647-54<br>23. Verweij J., van Oosterom A.T. and Pinedo H.M.: Melanomas, soft tissue and bone sarcomas. Eur. J. Cancer Clin. Oncol. 4 (suppl): 75-85, 1985.<br>24. Van Oosterom A.T., Mouridsen H.T., Nielsen O.S. et al: Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in firs:- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur. J. Cancer 38: 2397-2406, 2002.<br>25. Van Der Graaf W. T., Blay J., Chawla S. P. et al: PALETTE: A randomized, double-blind, phase III trial of pazopanib versus placebo in patients (pts) with soft-tissue sarcoma (STS) whose disease has progressed during or following prior chemotherapy—An EORTC STBSG Global Network Study (EORTC 62072). J Clin Oncol. Vol 29, No 18_suppl (June 20 Supplement), 2011: LBA10002 | Reference added |
| Appendix 4. | NA | Amendment to the protocol | |