Prospective, multicentre, observational study on fatigue- and hand-foot syndrome-related quality of life in patients with metastatic renal cell carcinoma receiving a tyrosine kinase inhibitor as first-line treatment (TROYA Study)

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Prospective, multicentre, observational study on fatigue- and hand-foot syndrome-related quality of life in patients with metastatic renal cell carcinoma receiving a tyrosine kinase inhibitors as first-line treatment
Protocol Code	A 6181218
Protocol Version	1.0
Date of the latest Protocol version	28 October 2015
Active substances	Sunitinib malate, pazopanib, sorafenib
Medicinal products	Sutent®, Votrient®, Nexavar®
Objectives	To know about the quality of life of patients with metastatic renal cell carcinoma who are being treated with sunitinib, pazopanib or sorafenib, and who suffer from fatigue and hand-foot syndrome, with personal inter-variability, and to explore measures that can be taken in terms of both everyday lifestyle and treatment to mitigate or cure such side effects that affect patients.
Clinical Coordinators / Authors	PPD MD PPD Email: PPD MD PPD Tel.: PPD Email: PPD

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse event monitoring
AEMPS	*Agencia Española de Medicamentos y Productos Sanitarios* (Spanish Agency of Medicines and Medical Devices)
AR	Autonomous Regions
AUC	Area Under the Curve
CR	Complete Response
CRF	Case Report Form
CTCAE version 4	Common Terminology Criteria (Common Terminology Criteria for Adverse Events, version 4) of the U.S. Department of Health and Human Services
CVA	Cerebrovascular Accident
DMP	Data management plan
DOR	Duration of response
DP	Disease Progression
ECOG	Eastern Cooperative Oncology Group. Scale to measure the quality of life of oncology patients with scores running from 0 to 5
eCRF	Electronic Case Report Form
EDP	Exposure during pregnancy
FDA	Food & Drug Administration
GCP	Good Clinical Practice
HFS	Hand-Foot Syndrome
IC	Informed Consent

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
mRCC	Metastatic Renal Cell Carcinoma
NIS	Non-interventional study
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PR	Partial Response
RCC	Renal cell carcinoma
SAE	Serious Adverse Event
SAE	Serious Adverse Event
SD	Stable Disease
SRSD	Single reference safety document
TKI	Tyrosine kinase inhibitor
TT	Treatment Time
TTF	Time to Treatment Failure

2. PERSONS RESPONSIBLE FOR THE STUDY

See ANNEX 7 for information on the Principal Investigators.

Study Coordinator

Name	Title	Affiliation	Address
PPD	MD	PPD	Email: PPD

3. ABSTRACT

Prospective, multicentre, observational study in patients with metastatic renal cell carcinoma (mRCC) receiving a tyrosine kinase inhibitor as first-line treatment according to routine clinical practice, designed to evaluate the incidence of fatigue and hand-foot syndrome in order to determine how these affect the baseline characteristics of the patient and his/her disease (age, gender, baseline status, tumour histology, etc.) and the patient's lifestyle as such side effects develop.

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STUDY TITLE

Prospective, multicentre, observational study on fatigue- and hand-foot syndrome-related quality of life in patients with metastatic renal cell carcinoma receiving a tyrosine kinase inhibitor as first-line treatment (TROYA Study)

PROTOCOL CODE: A6181218 (PFI-ITK-2015-01) TROYA

COORDINATING INVESTIGATOR:

The scientific coordinator will be responsible for maintaining the methodological rigour of the study, both in the design phase and in the evaluation of results and writing of the final report.
He will guarantee the ethical conduct of the study, maintaining scientific support for all participating doctors until the results are published.

Dr PPD

STUDY SITES:

It is initially considered optimal to include patients at approximately 35 Spanish sites (see ANNEX 7 to the protocol, which contains the list of proposed sites).

IEC THAT WILL ASSESS THE STUDY

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STUDY OBJECTIVES

PRIMARY OBJECTIVE

Fatigue-related quality of life of patients receiving a tyrosine kinase inhibitor evaluated using the validated 13-item FACIT-Fatigue scale for patients with metastatic renal cancer in Spanish.[1,2]

SECONDARY OBJECTIVES

1) Quality of life in patients with palmar-plantar erythrodysaesthesia (hand-foot syndrome).

2) To assess the following adverse effects according to version 4 of the CTCAE (Common Terminology Criteria for Adverse Events): any grade of fatigue and hand-foot syndrome (HFS).

3) To study what role aerobic exercise (walking quickly, running, swimming, playing tennis, dancing and/or riding a bike) plays in the onset of fatigue before starting and during treatment.

4) To evaluate what impact the time of drug administration, napping, off-treatment periods, temporary treatment breaks and dose reductions have on controlling fatigue and hand-foot syndrome.

5) Time to Treatment Failure (TTF), defined as the time from the start of treatment with a tyrosine kinase inhibitor to tumour progression, treatment discontinuation for any reason or death from any cause.

6) Progression-Free Survival (PFS) (median): time from the start of treatment with a tyrosine kinase inhibitor to tumour progression or death from any cause.

7) Objective Response Rate according to RECIST version 1.1.

DESIGN

Prospective, multicentre, observational, post-authorisation study in patients aged ≥ 18 years diagnosed with metastatic renal cell carcinoma who are to be given a tyrosine kinase inhibitor as first-line treatment.
This is a non-interventional study and therefore the decision to prescribe any treatment will be made prior to and independently of the patient's participation in the study; i.e. patients will receive the same medication whether they participate in the study or not according to the clinical judgement and normal clinical practice of the doctor responsible for the patient. Moreover, no additional tests are to be performed as part of the study.

STUDY CONDITION

Metastatic renal cell carcinoma.

STUDY POPULATION AND TOTAL NUMBER OF SUBJECTS

A population of 100 patients aged 18 years or over and diagnosed with metastatic renal cell carcinoma who are to start first-line treatment with a tyrosine kinase inhibitor according to routine clinical practice is to be studied at 35 Spanish sites.

INCLUSION AND EXCLUSION CRITERIA

3.1.1. Inclusion Criteria

The patients must meet all the inclusion criteria to participate in the study:

1) Patients ≥ 18 years old and diagnosed with metastatic RCC who, in the investigator's opinion, are candidates for starting first-line treatment with a tyrosine kinase inhibitor according to routine clinical practice.
2) Patients who have no contraindications to the treatment.
3) Baseline ECOG ≤ 2.
4) Patients who are able to give informed consent on their own without the need for a legal representative.
5) Committed patients who are able to complete the quality of life questionnaires and patient diary on their own without the need for a legal representative.

3.1.2. Exclusion Criteria

Patients must not meet any of the exclusion criteria described below.

1) Patients who are not candidates for first-line treatment with a tyrosine kinase inhibitor.
2) Patients who are receiving the treatment as second-line or subsequent therapy.
3) Untreated hypothyroidism.
4) Untreated severe anaemia.
5) Pregnancy or breast-feeding.
6) Myocardial infarction or cerebrovascular accidents (CVA) within the last 6 months.
7) Severe hepatic impairment.
8) Concomitant use of potent inhibitors or inducers that interact with hepatic cytochrome CYP3A4.

QUALITY OF LIFE:

1) Fatigue-related quality of life of patients evaluated using the validated 13-item FACIT-Fatigue scale for patients with kidney cancer in Spanish. Company FACIT.ORG (USA) (ANNEX 8).

2) Quality of life in patients with palmar-plantar erythrodysaesthesia (hand-foot syndrome). To be evaluated according to CTCAE Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) with scores running from 1 to 3 (see ANNEX 9).

SCHEDULE

Date of submission to AEMPS for classification: October 2015

Proposed date of submission to the IEC: November 2015

Proposed date of inclusion of the first patient in the study: February 2016

Proposed end-of-recruitment date: August 2017 or after recruiting 100 patients, whichever occurs first.

Recruitment period: 18 months.

Proposed date of the end of data collection: May 2018 or whenever the last patient passes to the 2nd line of treatment, whichever occurs first.

Expected date of Interim study report: After completing the 9 months of fatigue-related quality of life follow-up in all patients, estimated July 2018.

Expected date of Final study report: October 2018

SOURCE OF FUNDING

Pfizer SLU, as sponsor of the study, will provide financial compensation to the participating sites/investigators. Such compensation will be explicit and transparent, without prejudice to the internal rules of their employing agencies and in accordance with specific regulations in the ARs and at the sites where the study is conducted.

Fees are to fund the collection and transcription of clinical and epidemiological data from patients and the quality of life questionnaires to the case report forms.

AMENDMENTS AND UPDATES

None

Amendment No.	Date	Substantial or administrative amendment	Amended protocol section(s)	Summary of change(s)	Reason

4. MILESTONES

Milestone	Proposed date
Start of data collection Proposed date of the first patient's first visit, FSFV	February 2016
End of data collection Proposed date of the last patient's last visit, LSLV	May 2018
Interim study report Proposed date of drafting (or remittance) of Interim report	July 2018
Final study report Proposed date of drafting (or remittance) of Final report	October 2018

5. STUDY RATIONALE

BACKGROUND

Over recent years, a better understanding of the molecular biology of renal cell cancer (RCC) has led to an unprecedented development of therapies for this disease. As a result, various targeted agents have been approved and used for the management of RCC that have led to an improvement in both the progression-free survival (PFS) and overall survival (OS) of patients diagnosed with this disease.[3]

Among these new agents, sunitinib, pazopanib and sorafenib are drugs that are recommended in all guidelines for the first-line treatment of RCC. Sunitinib is the targeted agent most widely used in routine clinical practice today. Sunitinib and sorafenib are oral tyrosine kinase inhibitors that inhibit vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), platelet-derived growth factor receptors (PDGFR), c-Kit, RET and FLT3. Pazopanib is an oral tyrosine kinase receptor inhibitor that inhibits vascular endothelial growth factor receptors, platelet-derived growth factor receptors (PDGFR) and c-Kit.

Sunitinib has been approved for the management of patients diagnosed with metastatic RCC (mRCC) based on the results of the randomised, controlled, double-blind, phase III study[4] comparing sunitinib with interferon alpha as first-line treatment for 750 patients with mRCC. The study showed significant improvement in the efficacy of sunitinib compared with interferon with a median PFS (primary endpoint of the study) of 11 months vs. 5 months ($p < 0.001$) for the sunitinib and interferon arms, respectively.

Pazopanib has been approved for patients diagnosed with mRCC based on data from a randomised, multicentre, double-blind, placebo-controlled study that included 435 patients with advanced and/or metastatic RCC who had not received previous treatment, or who had received first-line treatment with IL-2 or interferon alpha. PFS was 9.2 months for the pazopanib group versus 4.2 months for the placebo group (< 0.0000001).[10]

Sorafenib was initially approved for the treatment of mRCC in patients with advanced renal cell carcinoma in whom previous therapy with interferon alpha or interleukin-2 had failed or who were considered unsuitable for such therapy based on the results of a randomised, multicentre, double-blind, placebo-controlled, phase III trial involving 903 patients. The median PFS was 167 days in patients randomised to sorafenib compared to 84 days in patients receiving placebo ($p < 0.000001$). Currently, as a result of the approval of new drugs for the treatment of mRCC, its use in the first-line setting (approval for patients who are not candidates for cytokine therapy) is not very common and it is more habitually used as second-line or subsequent therapy.[11]

With most drugs used for the treatment of mRCC, data indicate the importance of maintaining dose intensity, since it is correlated with response and survival. This is shown, for example, in a meta-analysis of 6 studies including a total of 443 patients with pharmacokinetic data diagnosed with mRCC and treated with sunitinib. This meta-analysis demonstrated that increased exposure

to sunitinib, reflected by a greater area under the curve (AUC), was associated with improved PFS, improved OS and a higher response rate.[5] A relationship has also been found between exposure to pazopanib and efficacy.[6]

In the pivotal phase III clinical trial involving sunitinib, 19% of patients discontinued treatment due to side effects and 38% of patients had to temporarily interrupt treatment, while 50% of patients had to reduce the standard dose in order to control adverse effects.[7,8] In fact, temporary dose interruptions are one strategy contemplated in the summary of product characteristics for this medicinal product.
The most common grade 3-4 toxicity was hypertension (12%), followed by fatigue (11%), diarrhoea (9%) and HFS (9%).[4,7]

In the sunitinib expanded access programme, 8% of patients discontinued treatment due to serious adverse effects while 30% required dose reductions due to toxicity.[9]

Pazopanib: 19% of cytokine-pretreated patients discontinued treatment versus 12% of treatment-naive patients.[10]

10% of patients being treated with sorafenib stopped treatment due to side effects in the pivotal trial.[11]

Although the therapeutic goal in the treatment of metastatic renal cell carcinoma is to prolong the survival of patients, it is equally important to keep treatment-related toxicities as low as possible in order to achieve patient adherence to treatment, thereby maximising dose intensity, which is the determining factor for obtaining better results in the long term. The high incidence of dose reduction and treatment interruptions due to adverse effects could lead to decreased plasma drug exposure and reduced clinical benefit.[5,6] The drug's tolerability may be a barrier when it comes to maximising the potential efficacy of therapy.

Therefore, maintaining the dose is a challenge, with side effects such as fatigue, diarrhoea, hand-foot syndrome or hypertension. In fact, fatigue and diarrhoea are the most worrying symptoms when questioning patients,[12] to such an extent that 50-75% of patients receiving treatment complains about some degree of asthenia, although only 7-11% of cases interfere with the activities of daily living.

In studies, TKI-related fatigue is highly variable in both degree and duration, although it is generally mild to moderate.[13] In the case of sunitinib, this is especially significant since this is a drug that is administered intermittently. Fatigue typically occurs 2-3 weeks after the start of treatment, increases in intensity during weeks 3 and 4, and tends to improve during the 2-week off-treatment period, during which patients are comparatively better than during on-treatment weeks. This has resulted in the use of alternate sunitinib scheduling in clinical practice in order to improve tolerability and maintain effective dose intensity, with the schedule of 14 days on and 7 days off being the most commonly used (2/1 schedule). Results based on the use of these schedules by different groups have recently been published (retrospective analyses).[14,15] The European Association of Urology Guidelines[16] on Renal Cell Carcinoma 2015 describe the

schedule of 2 weeks on and 1 week off treatment for the management of toxicity in patients being treated with sunitinib.

It is not clear what percentage of fatigue is cancer-related and what percentage is attributable to the tyrosine kinase inhibitor as both types of fatigue are very similar and often coexist. The mechanisms of fatigue are not well described. Changes at muscle level can cause peripheral fatigue, whereas central nervous system failure to activate the motor neurons adequately would cause central fatigue.

Fatigue is more common in men, particularly in young men, resulting in repeated treatment interruptions. However, fatigue tends to decrease with increasing treatment cycles. Whether this phenomenon represents an adaptation and/or learning by the patient or a true lower incidence is unknown.

It is important to rule out other causes that may cause or exacerbate fatigue, such as dehydration, hypothyroidism, hypercalcaemia, anaemia or depression. These adverse effects must be monitored every 2-3 cycles.[13]

In the phase I study published by Faivre,[17] asthenia was associated with an increase in daytime napping and night-time somnolence. Age and baseline status (ECOG) at the start of the study did not predict asthenia.

Patient education is crucial. It is necessary to explain that this adverse effect will quite probably appear and we have strategies to manage it if it occurs.
It is interesting to see fatigue in the context of the disease and to readjust the patient's expectations, explaining that it will be necessary to adapt his/her everyday activities to save energy.[13]

Some authors recommend training with aerobic exercises for 30 minutes 3 times a week. Randomised clinical trials have demonstrated better responses in oncology patients using resistance training. It is important to take into account the patients' previous level of activity and cardiac output before recommending exercise.

RATIONALE FOR THIS STUDY

In view of the above, we believe it is appropriate to initiate a study to prospectively assess fatigue-related quality of life in patients with mRCC who are starting treatment with a tyrosine kinase inhibitor.
The patients' quality of life will be evaluated using the FACIT-Fatigue questionnaire and a Patient Diary (both to be completed by the patient) every 6 weeks.

To our knowledge, no fatigue-related quality of life studies in European patients with this condition have been published to date.

6. OBJECTIVES

PRIMARY OBJECTIVE

Fatigue-related quality of life of patients receiving a tyrosine kinase inhibitor evaluated using the validated 13-item FACIT-Fatigue scale for patients with metastatic renal cancer in Spanish.[1,2]

SECONDARY OBJECTIVES

1) Quality of life in patients with palmar-plantar erythrodysaesthesia (hand-foot syndrome).

2) To assess the following adverse effects according to version 4 of the CTCAE (Common Terminology Criteria for Adverse Events): any grade of fatigue and HFS.

3) To study what role aerobic exercise (walking quickly, running, swimming, playing tennis, dancing and/or riding a bike) plays in the onset of fatigue before starting and during treatment.

4) To evaluate what impact the time of drug administration, napping, off-treatment periods, temporary treatment breaks and dose reductions have on controlling fatigue and hand-foot syndrome.

5) Time to Treatment Failure (TTF), defined as the time from the start of treatment with a tyrosine kinase inhibitor to tumour progression, treatment discontinuation for any reason or death from any cause.

6) Progression-Free Survival (PFS) (median): time from the start of treatment with a tyrosine kinase inhibitor to tumour progression or death from any cause.

7) Objective Response Rate according to RECIST version 1.1.

7. METHODS OF INVESTIGATION

7.1. Study design

Prospective, multicentre, observational, post-authorisation study in patients aged ≥ 18 years diagnosed with metastatic renal cell carcinoma who are to be given a tyrosine kinase inhibitor as first-line treatment.

The study will evaluate measures to improve patients' quality of life, such as time of drug administration, napping, temporary treatment breaks and dose reductions.

Fatigue-related quality of life will be evaluated using the Spanish version of the ***FACIT*–Fatigue Questionnaire**, which will be completed by the patient individually after having been explained by the clinician or a person appointed by the investigator (nursing staff, clinical trial coordinator)

in the treatment room or another room during the scheduled visits, once the patient understands how to complete the form.

The FACIT–Fatigue questionnaire will be handed out together with the patient diary at the following treatment times, which coincide with the visits, according to the department's protocol:

1) **Baseline** (before starting the treatment)
2) **Month 3**
3) **Month 6**
4) **Month 9** or upon treatment discontinuation
5) **Additional visits according to the oncology department's clinical practice:** additional visits may be recorded on the case report form (e.g. at 15 days)

The patient will also complete this FACIT-Fatigue questionnaire at home **at the start of each cycle** (for sorafenib and pazopanib a cycle will be 6 weeks of treatment), even if this does not coincide with scheduled visits to the hospital.

The hand-foot syndrome-related quality of life evaluation that patients may be asked to take part in will be performed on the basis of the CTCAE V4.03 2010 with scores running from 1 to 3 (see ANNEX 9).

7.2. Scope

The study will start at each site after the contract has been signed by all parties and all documentation and information on the procedures and objectives of the study have been received by the person appointed by the sponsor.

Recruitment will be competitive between all the participating sites (estimating between 1 and 4 patients per site) and will finish once 100 patients have been recruited.

The investigator will be guided by routine clinical practice at all times when making decisions regarding the best available treatment option for the patient.

At the Baseline Visit, patients will sign the informed consent form and their participation in the TROYA study will be recorded in their medical records.

There should be evidence of a signed and personally dated ***informed consent*** document indicating that the patient (or his/her legal representative) has been informed of all aspects of the study and the ***patient information sheet***, with a record being made in the patient's medical records that the patient received a copy.

All patients who are about to start first-line treatment with a tyrosine kinase inhibitor and who meet all the inclusion criteria and no exclusion criterion are candidates for this study.

The information requested at all of the study visits will be recorded on the electronic CRF (Case Report Form) attached in Annex 2.

Different aspects for improving the quality of life of patients, such as drug administration time, weekly mild-moderate aerobic exercise and napping, will be evaluated. For this purpose the patient will complete this information in a diary (***Patient Diary***).

Other aspects, such as temporary treatment interruptions and dose reductions, will be recorded on the CRF at each visit.

Quality of life will be evaluated at the Baseline visit, the 3 month visit (coinciding with the first control CT according to routine clinical practice), the 6 month visit (second CT) and the 9 month visit (third CT) using the validated Spanish version of the **FACIT–Fatigue** questionnaire. Other evaluations may also be conducted using this questionnaire at any additional visits scheduled for the patient according to the site's clinical practice.

Each patient will complete the questionnaire after it has been explained by the clinician or a person appointed by the investigator (nursing staff, clinical trial coordinator).

Any adverse events experienced by the patient will be recorded according to clinical practice, in compliance with the toxicity manuals of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

7.2.1. Inclusion Criteria

The patients must meet all the inclusion criteria to participate in the study:

1) Patients ≥ 18 years old and diagnosed with metastatic RCC who, in the investigator's opinion, are candidates for starting first-line treatment with a tyrosine kinase inhibitor according to routine clinical practice.
2) Patients who have no contraindications to the treatment.
3) Baseline ECOG ≤ 2.
4) Patients who are able to give informed consent on their own without the need for a legal representative.
5) Committed patients who are able to complete the quality of life questionnaires and patient diary on their own without the need for a legal representative.

7.2.2. Exclusion Criteria

Patients must not meet any of the exclusion criteria described below.

1) Patients who are not candidates for first-line treatment with a tyrosine kinase inhibitor.
2) Patients who are receiving the treatment as second-line or subsequent therapy.
3) Untreated hypothyroidism.
4) Untreated severe anaemia.
5) Pregnancy or breast-feeding.
6) Myocardial infarction or cerebrovascular accidents (CVA) within the last 6 months.
7) Severe hepatic impairment.

8) Concomitant use of potent inhibitors or inducers of hepatic cytochrome CYP3A4.

7.3. Variables

The variables to be analysed for this study will be obtained from the patients' medical records, quality of life questionnaires and Patient Diaries in accordance with the protocol. Data will be recorded on the electronic CRF design for this study (ANNEX 2). The following data will be included:

DEMOGRAPHICS AND DISEASE INFORMATION

1) Age at the baseline visit
2) Gender
3) ECOG at the time of diagnosis (0,1 2)
4) Heng prognostic criteria
5) Site of metastasis and number thereof
6) Date on which the disease was diagnosed
7) Date of diagnosis of advanced stage disease
8) Type of histology

LIFESTYLE

1) Napping
2) Aerobic exercise
3) Smoking
4) FACIT – Fatigue questionnaire score at the scheduled visits

TREATMENT

1) Time when the oral treatment is taken
2) Tyrosine kinase inhibitor dose and treatment regimen
3) Number of changes to dose and which cycle they occur in
4) Temporary treatment interruptions, number of interruptions and which cycle they occur in
5) Best response achieved with first-line treatment
6) Mean duration of treatment
7) Time to treatment failure
8) How long each patient stays on first-line treatment / No. of cycles received
9) Reason for discontinuing the first-line drug
10) Date of disease progression and/or death

Through the analysis of the collected variables the following aspects will be assessed:

- **Progression-Free Survival (PFS)**: defined as the interval from the start of treatment to the date of the first documentation of objective tumour progression or death from any cause.

- **Objective Response Rate (ORR):** defined as the proportion of subjects achieving either complete response (CR) or partial response (PR). In addition, subjects with stable disease (SD) will also be evaluated to obtain clinical benefit along with subjects with tumour progression. Subjects will be evaluated according to RECIST 1.1.

- **Duration of Response (DOR):** in patients with PR or CR, it will be defined as the interval from the date response is documented to the first date that disease progression is observed.

- **Safety:** the safety of the tyrosine kinase inhibitor will be evaluated by describing the incidence of serious adverse effects, side effects in the potential drug risk management plan (described in the table) and all grades if fatigue and/or hand-foot syndrome are present.

- **Fatigue-related quality of life of patients:** this will be measured based on the results obtained after completion of the FACIT-Fatigue questionnaire by the patient.

- **HFS-related quality of life of patients** in those cases where HFS is present with a score from 1 to 3 according to version 4 of the CTCAE (Common Terminology Criteria for Adverse Events).

- **Date of disease progression and/or death**.

7.4. Source documents

The investigator will, at all times, be fully responsible for the accuracy and authenticity of all clinical and epidemiological data reported by the patient and included on the CRFs.
The source documents will be the medical records of each patient and any tests performed in relation to the disease, plus all quality of life questionnaires and the Patient Diary. The investigator undertakes to safeguard these records together with the study documentation for review by the clinical monitor appointed.

The information on the CRFs should be consistent with the data in the medical records.
The sponsor will establish the monitoring plan.

7.5. Sample size (statistics)

Plans are to include 100 patients in the study to receive first-line treatment over the course of 18 months at 35 sites.

This is a descriptive study; therefore, a specific number of patients is not required to calculate the sample size.

In order to study the fatigue-related quality of life of patients who are receiving a tyrosine kinase inhibitor, evaluated using the validated 13-item FACIT-Fatigue scale for patients with metastatic renal cancer on Spanish, the inclusion of 100 patients with metastatic renal carcinoma who are about to receive first-line treatment with a tyrosine kinase inhibitor and who meet the screening criteria of the study is proposed.

This sample size will allow us to estimate percentages of patients with fatigue (severe/non-severe) during follow-up, with a 95% level of significance and an estimated replacement rate of 10%, assuming a replacement rate of 5%.

7.6. Data processing (statistics)

The investigator will collect data from the recruited patients using an electronic Case Report Form specially designed for this study.

The patient number we provide is a serial number devoid of any identifying value.

The information is stored in an Access database, which is in turn associated with a file, "WorkGroup", detailing the user code and the investigator's permissions within the database. People not within this working group cannot access the database.

A Data Management Plan (DMP) will be developed, and once approved by the person responsible for the study, "Queries" will be programmed in the electronic case report form so that when the investigator saves the data, he/she will be informed of any queries regarding the data.

All changes made by the investigators during the collection of data will be stored in a table specially designed for this purpose, indicating the user, date, modified field, the old value and the new value.

7.7. Data analysis (statistics)

The fatigue-related quality of life of the patients and the quality of life of patients with palmar-plantar erythrodysaesthesia (hand-foot syndrome) will be studied using the mean, standard deviation and confidence intervals if they follow normal distribution, or the median, minimum, maximum and interquartile range if they do not follow Gaussian distribution. The Wilcoxon test will be used to analyse the inter-visit correlation for patients' quality of life.

The objective response rate according to RECIST version 1.1 will be studied using absolute and relative frequencies.

In order to study the impact of drug administration time, napping, temporary treatment interruptions and dose reductions on fatigue and hand-foot syndrome control, independent samples will be compared using Pearson's chi-square test (or Fisher's exact test for 2x2 tables or likelihood ratio test for MxN tables, if necessary) in the case of qualitative variables and Student's t-test, one-way ANOVA test or non-parametric equivalents, such as the Mann-Whitney U test or Kruskal-Wallis H test in the case of quantitative variables.

The Kaplan-Meier survival estimate will be used to study both the PFS and TTF of patients. The log-rank test will be used to compare survival estimates.

The assumptions of normality and homoscedasticity of the variables will be studied for the use of parametric tests. Estimates will be calculated with a 95% confidence level and the SPSS statistical analysis software package, V19.0 or later, will be used.

7.8. Quality control

As this is a post-authorisation study, the same procedures will be followed by the investigator as in routine clinical practice.

However, the investigators are responsible for ensuring that the protocol and principles of Good Clinical Practice (GCP) are complied with.

Study sites may be subject to face-to-face or remote monitoring by the person appointed by the sponsor (at least 20% of patients monitored face-to-face) and review by the Independent Ethics Committee (IEC) and/or quality assurance audits conducted by the relevant regulatory authorities and the study sponsor.

Case Report Form/Electronic data collection

The CRF is required and must be completed for each patient included.

The investigator will be responsible for reviewing and approving the CRFs, for ensuring that they are completed and for ensuring that the patients complete the **quality of life questionnaires** and the **Patient Diary**.

The investigator will, at all times, be fully responsible for the accuracy and authenticity of all clinical data included on the CRFs.

Storing the records

In order to allow monitoring of the study by the sponsor or assessments or audits by the regulatory authorities, the investigator agrees to keep records, including the identity of all participating patients (enough information to link the records, e.g. CRFs and hospital records), all original signed informed consent forms, copies of all serious adverse events forms and source documents. The records must be kept by the investigator in accordance with ICH guidelines or local regulations, or as specified in the contract, whichever is longer.

7.9. Limitations of the research methods

The Patient Diary will contain epidemiological data that cannot be confirmed by the Investigator, although guidelines will be provided during the initial visit to each site to standardise the collection of such data.
PFS will be evaluated by each investigator in line with routine clinical practice with no centralised evaluation.

7.10. Further aspects

Not applicable.

8. PROTECTION OF STUDY SUBJECTS

The study will be conducted according to routine clinical practice as described in the protocol, the International Conference on Harmonisation's Guideline for Good Clinical Practice and applicable local requirements and laws (Order SAS/3470/2009 of 16 December).

8.1. Patient information and consent

All parties will ensure that personal data are protected and will not include patients' names on any of the sponsor's forms, reports, publications or any other text for disclosure, unless so required by law. For data transfer, Pfizer will maintain a high level of confidentiality and protection of patients' personal data.

The informed consent form must comply with local legal and regulatory requirements. The informed consent form used in this study and any changes made during the course of the study must be prospectively approved by the IEC and by Pfizer prior to implementation.

The investigator must ensure that each study patient or his/her legal representative is informed of the nature and objectives of the study and possible risks associated with his/her participation therein. The investigator, or a person appointed by the same, will obtain written informed consent from each patient or his/her legal representative before performing any study-specific procedure. The investigator will retain the original of each patient's signed informed consent form.

The Patient Information Sheet and Informed Consent document must comply with ICH GCP, local administrative regulations and legal requirements.

The informed consent form used in the study and all amendments must be approved by the independent ethics committee prior to use. The investigator will keep the original consent documents signed by subjects.

8.2. Withdrawal of patients

Patients may leave the trial at any time voluntarily or they may be withdrawn at the discretion of the investigator or the sponsor for safety, behaviour or administrative reasons. In any event, every effort should be made to document the results of any such patient. The investigator should inquire about the reason for the withdrawal and conduct follow-up on the patient in relation to any unresolved adverse event.

If the patient leaves the study and also withdraws his/her consent for future disclosure of information, no further data evaluation or collection should be performed. The sponsor may retain and continue to use any data collected before the withdrawal of consent.

8.3. IEC

Pfizer, as the study sponsor, is responsible for obtaining the prospective approval of the study protocol, amendments and informed consent forms, and other relevant documents, if necessary, from the IEC. All correspondence with the IEC should be kept in the Investigator's File.

The requirements of local regulations will be followed for the submission and management of initial approvals or amendments to the protocol.

All correspondence with the central IEC and AEMPS should be kept in the Investigator's File. Any notification or opinion of the IECs or competent bodies of each AR should be sent to the study sponsor.

8.4. Ethical considerations of the study

The study will be conducted in accordance with legal and regulatory requirements and scientific rigour, respect and responsibility, and will follow the generally accepted research practices described in ***Guidelines for Good Pharmacoepidemiology Practices (GPP)*** published by the International Society for Pharmacoepidemiology (ISPE), ***Good Epidemiological Practice (GEP) guidelines*** published by the International Epidemiological Association (IEA), ***Good Practices for Outcomes Research*** published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), ***International Ethical Guidelines for Epidemiological Research*** published by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims and/or equivalent.

8.5. Interference with the physician's prescribing habits

There will be no interference with the investigator's decision on the most appropriate treatment for the patient.

This is a non-interventional study and therefore the decision to prescribe any treatment will be made prior to and independently of the patient's participation in the study; i.e. patients will receive the same medication whether they participate in the study or not according to the clinical judgement and normal clinical practice of the doctor responsible for the patient. Moreover, no additional tests are to be performed as part of the study.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/REACTIONS

The following table summarises requirements for the recording of safety events on the case report form (CRF) and for reporting safety events to the Department of Drug Safety at Pfizer, using the "*Non-Interventional Study (NIS) Adverse Event Monitoring (AEM) Report Form*" (ANNEX 10).

These requirements are set out for three types of events: (1) Serious Adverse Events (SAEs); (2) Non-serious Adverse Events (AEs) (as appropriate); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast-feeding, medication errors, overdose, incorrect use of the drug, extravasation and occupational exposure.

These events are defined in the "Definitions of safety events" section.

Safety Event	**Recorded on the Case Report Form**	**Reported on the NIS AEM Report Form to the Department of Drug Safety at Pfizer within 24 hours of becoming aware of the same**
SAE (Serious Adverse Event)	All	All
AE (Non-serious Adverse Event)	All	Carcinogenicity Reproductive and developmental toxicity Retinal detachment Other potential cardiac events Ischaemic events Tachycardia events Conduction events
Scenarios involving exposure to a drug during the study, including exposure during pregnancy, exposure during breast-feeding, medication error, overdose, incorrect use of the drug, extravasation, lack of efficacy and occupational exposure	All (regardless of whether they are associated with an AE), **except occupational exposure**	All (regardless of whether they are associated with an AE)
In paediatric patients and patients with impaired liver and heart function	All AEs (including non-serious AEs)	

For each AE, the investigator must obtain adequate information to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as an SAE (see the "Serious Adverse Events" section below).

The safety events listed in the table above must be reported to Pfizer within **24 hours** of the investigator becoming aware of the event, **regardless of whether the investigator determines that it is related to the study drug**. In particular, if the SAE has resulted in death or is life-threatening, it must be reported to Pfizer immediately, regardless of the amount of information available on the event. This period should also apply to any additional new information (follow-up) on previously reported safety events. In the unlikely event that the investigator does not immediately detect a safety event, he/she must report it within 24 hours of becoming aware of the same and document the date and time he/she became aware for the first time.

For safety events that are considered serious or that are identified in the right-hand column of the above table, which should be reported to Pfizer within 24 hours of becoming aware of them, the investigator is required to obtain and provide Pfizer with any additional information within 24 hours. Pfizer may also require that an investigator obtain specific follow-up information in an expeditious manner. This information is more detailed than that recorded on the CRF. In general, it should include a description of the adverse event in sufficient detail to allow a full medical evaluation of the case and an independent determination of the possible causality. Any relevant information related to the event should be provided, such as medication and comorbidities. In the case of the death of a patient, a summary of available post-mortem findings must be sent as soon as possible to Pfizer or its appointed representative.

Reporting period

For each patient, the safety event reporting period begins when the patient receives the first dose of sunitinib, sorafenib or pazopanib or signs the informed consent if he/she has already been exposed to sunitinib, sorafenib or pazopanib and it lasts until the end of the study observation period, which should cover at least 28 calendar days after the last administration of the study drug; a report must be sent to the Department of Drug Safety at Pfizer (or its appointed representative) in the event that any of the types of safety events listed in the above table occur during this period. In this study, for patients included retrospectively without signing the ICF, the reporting period will run from administration of the first dose until 28 calendar days after administration of the last dose. If a patient receives a study drug on the last day of the observation period, the reporting period should be extended 28 calendar days after the end of the observation period. The date of informed consent frequently coincides with the date of recruitment. In some situations, there may be a delay between the date of informed consent and the date of recruitment. In these situations, if a patient gives his/her informed consent but is never included in the study (e.g. the patient changes his/her mind about participating, screening failure, etc.), the reporting period ends on the date on which it is decided not to recruit the patient.
If the investigator is aware of an SAE occurring at any time after completion of the study and believes that the SAE is related to sunitinib, sorafenib or pazopanib, the SAE should also be reported to the Department of Drug Safety at Pfizer.

Causality assessment

The investigator is obliged to assess and record the causal link. For all AEs, the investigator should obtain sufficient information to determine the causality of each adverse event. For sunitinib, sorafenib or pazopanib-related AEs, the investigator is required to follow the AE until the event and/or its consequences are resolved or stabilised to an acceptable level from their point of view, and Pfizer agrees with that assessment.

The causality assessment by the investigator is to determine whether there is a reasonable possibility that sunitinib, sorafenib or pazopanib caused or contributed to an adverse event. If the final determination of causality by the investigator is "unknown" and he/she is unable to determine whether sunitinib, sorafenib or pazopanib caused the event, it must be reported within 24 hours.

If the investigator cannot determine the aetiology of the event but has determined that sunitinib, sorafenib or pazopanib was not the cause, this should be recorded on the CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse Events

An AE is any unwanted medical event that happens to a patient who has received a drug. The event does not necessarily have a causal link with the treatment.

Below are some examples of adverse events:

- Abnormal test results (see below for the circumstances under which an abnormal test result is an adverse event);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependence.

In addition, for medications, such events may include signs and symptoms arising from:

- Drug overdose;
- Drug discontinuation;
- Incorrect use of the drug;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast-feeding;
- Medication error;
- Occupational exposure.

Abnormal test results

The criteria for determining whether an abnormal result of an objective test should be reported as an adverse event are:

- The test result is associated with accompanying symptoms; and/or
- The test result requires additional diagnostic tests or medical or surgical intervention; and/or
- The test result leads to modification of the study dosage or withdrawal from the study, requires a major additional concomitant drug treatment or another kind of treatment; and/or
- The investigator or the sponsor considers the test result to be an adverse event.

Simply repeating a test with an abnormal result in the absence of the above conditions is not an adverse event. It is not necessary to report as adverse events any abnormal test results that are found to be not correct.

Serious adverse events

A serious adverse event is any undesirable medical episode in a patient who has received a drug or nutritional product (including paediatric formulations) of any dose that:

- Causes death;
- Is life-threatening;

- Requires hospitalisation of the patient or prolongation of existing hospitalisation (see below for the circumstances that do not constitute an adverse event);

- Causes persistent or significant disability/incapacity (significant disruption of the ability to perform the functions necessary to lead a normal life);

- Causes a congenital anomaly or birth defect.

The progression of the cancer being studied (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is death during the study or during the reporting period. Hospitalisation due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignant tumour is fatal during the study or in the reporting period, the death-causing episode should be recorded as a serious adverse event with grade 5 severity.

Medical and scientific judgement should be applied to determine whether a particular episode is a medically important adverse event. It is possible that a medically important adverse event is not immediately life-threatening or does not cause death or hospitalisation. However, if it is determined that the adverse event may endanger the patient and/or may require intervention to prevent one of the other outcomes included in the above definitions, the adverse event should be reported as serious.

These events comprise, for example, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or seizures that do not require hospitalisation or development of drug dependency or abuse.

Suspected transmission of an infectious, pathogenic or non-pathogenic agent through a Pfizer product is considered serious. The event may be suspected due to clinical symptoms or laboratory results indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and are managed as serious and expeditious by the pharmacovigilance staff. These cases are also considered for reporting as product defects, if deemed appropriate.

Hospitalisation

Hospitalisation is defined as any initial admission (even if less than 24 hours) to a medical facility or any extension if already admitted. Also considered as admission is transfer within the hospital to an acute care or intensive care unit (e.g. from a psychiatric ward to a medical ward, from a medical ward to the coronary care unit, from a neurology ward to a tuberculosis unit). Attending A&E does not necessarily constitute hospitalisation; however, an event that causes the patient to go to A&E should be evaluated to determine its medical relevance.

Hospitalisations in the absence of a medical adverse event are not considered an adverse event as such and need not be reported. For example, the following reports of hospitalisation without adverse events need not be reported:

- Social hospitalisation (e.g. if the patient has nowhere to spend the night)

- Administrative hospitalisation (e.g. for an annual check-up)
- Optional hospitalisation not precipitated by an adverse event (e.g. for elective cosmetic surgery)
- Hospitalisation for observation without an adverse medical event
- Hospitalisation for the treatment of a pre-existing condition not associated with the development of a new adverse event or aggravation of a pre-existing condition (e.g. investigation of pre-existing laboratory abnormalities)
- Hospitalisation described in the protocol during the study (e.g. for a procedure required by the study protocol)

Situations that need reporting to the Department of Drug Safety at Pfizer within 24 hours

Situations involving exposure during pregnancy, exposure during breast-feeding, medication error, overdose, incorrect use of the drug, extravasation, lack of efficacy and occupational exposure are described below.

Exposure during pregnancy

Exposure during pregnancy (EDP) takes place if:

1. A woman becomes pregnant or discovers that she is pregnant while receiving sunitinib, sorafenib or pazopanib or having been directly exposed (whether in treatment or through environmental exposure) to sunitinib, sorafenib or pazopanib; or if the woman becomes pregnant or discovers she is pregnant after stopping or having been directly exposed to sunitinib, sorafenib or pazopanib (maternal exposure);

An example of environmental exposure would be a case involving direct contact of a pregnant woman with a Pfizer product (e.g. a nurse reports that she is pregnant and has been exposed to chemotherapy agents).

2. A man has been exposed, whether in treatment or through environmental exposure, to sunitinib, sorafenib or pazopanib before or around the time of conception and/or exposed during the pregnancy of the partner (paternal exposure).

As a general rule, exposure during pregnancy, prospective and retrospective of any kind, is reportable regardless of whether it involves an AE and the procedures for reporting SAEs should be followed.

If a study participant or a participant's partner becomes pregnant or discovers that she is pregnant while receiving treatment with sunitinib, sorafenib or pazopanib, this information must be reported to Pfizer using the *NIS AEM Report Form* and the EDP Supplemental Form, regardless of whether it involves an adverse event.

Also, information relating to environmental exposure to sunitinib, sorafenib or pazopanib in a pregnant woman (e.g. she reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be reported using the *NIS AEM Report Form* and the EDP Supplemental Form. This should be done regardless of whether there has been an AE.

The information reported shall include expected delivery date (see information related to abortion below).

Follow-up should be performed to obtain general information on the pregnancy; also, for all EDP reports where the outcome of the pregnancy is unknown, the case should be followed up to obtain information on the outcome. The pregnancy will be followed up to the end or until termination (e.g. abortion) and Pfizer will be notified of the outcome. This information will provided as follow-up to the initial EDP report. In the case that the birth takes place, the structural integrity of the newborn can be assessed at the time of birth. In the case of abortion, the reasons for the termination should be established and, if clinically possible, the structural integrity of the foetus should be evaluated by visual inspection (unless there are previous conclusive laboratory findings that denote congenital anomalies and these findings are reported).

If the pregnancy outcome meets SAE criteria (e.g. ectopic pregnancy, spontaneous abortion, intrauterine foetal death, neonatal death or congenital anomaly [in a child born alive, post-abortion foetus, intrauterine foetal death or neonatal death]), the procedures for reporting SAEs must be followed.

Additional information on the outcome of the pregnancy that should be reported as SAEs:

- Spontaneous abortion includes natural miscarriage and retained products of conception

- Neonatal deaths that occur within a month of birth should be reported as SAEs, regardless of causality. Also, deaths that occur after the first month must be reported as SAEs when the investigator qualifies them as related or possibly related to exposure to the investigational medicinal product

Additional information regarding exposure during pregnancy may be requested. The need for increased follow-up of the birth outcome will be determined on an individual basis (e.g. monitoring of premature infants to identify developmental delays).

In the case of paternal exposure, the participant in the study will be provided with a "Pregnant Partner Release of Information Form" to give to his partner. It must be documented that this document was provided to the participant to give to his partner.

<u>Exposure during breast-feeding</u>

Cases of exposure during breast-feeding should be reported, regardless of the presence of an associated AE. A report of exposure during breast-feeding will not be generated when a Pfizer drug specifically approved for use in breastfeeding women (e.g. vitamins) is administered according to the authorised use. However, if the child experiences an AE associated with

administration of the drug, the AE should be reported along with the exposure during breast-feeding.

Medication error

A medication error is an unintended mistake in the prescription, dispensing or administration of a drug that may cause or lead to inappropriate use of the medication or patient harm when the medication is under the control of the healthcare professional, the patient or the consumer. These events may be related to professional practice, products, healthcare procedures and systems, including: prescription, order form, package leaflet, packaging and nomenclature; composition, dispensing, distribution; administration; education, monitoring; and use.

Medication errors include:

- Potential medication errors, whether or not linked directly to a patient (e.g. unintentional/incorrect administration, which may be an accidental off-label use or prescription of the product by the healthcare professional or the patient/consumer)
- Confusion related to trademarks (e.g. trade name, brands)

The investigator must notify Pfizer of the following medication errors, regardless of the occurrence of an associated AE/SAE:

- Medication errors in which the patient has been exposed to the drug, whether or not the error is accompanied by an AE
- Medication errors that do not involve a patient directly (e.g. potential medication errors). When a medication error does not involve a patient being exposed to the drug, the following minimum reporting criteria are required:
    - An identifiable reporter;
    - A suspect drug;
    - Medication error.

Overdose, Incorrect use of the drug, Extravasation

Reports of overdose, incorrect use of the drug and extravasation associated with using a Pfizer product should be reported to Pfizer by the investigator, regardless of the presence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy of a Pfizer product should be reported to Pfizer by the investigator, regardless of the presence of an associated AE/SAE or the indication of the Pfizer product.

Occupational exposure

Reports of occupational exposure to a Pfizer product should be reported to Pfizer by the investigator, regardless of the presence of an associated AE/SAE.

9.1. Single reference safety document

The Summary of Product Characteristics of the medicinal product will be used as the single reference safety document (SRSD) during the study, which will be used by the Department of Drug Safety at Pfizer to evaluate any safety event reported to Pfizer by the Investigator during the course of the study.

The SRSD should be used by the investigator as a guideline for prescribing and evaluating any event relating to patient safety in relation to the drug received.

Evaluation of severity

The investigator will use the following definitions of severity according to version 4.0 of the CTCAE to describe the maximum severity of the adverse event. If the adverse event is serious, the CTCAE grade reported in the adverse events section of the CRF should match the description of the CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	**Clinical description of severity**
0	No change from the normal or reference range (this grade is not in version 4.0, but may be used in certain circumstances)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO an adverse event

Note the distinction between the severity and seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (significantly interferes with the subject's normal functioning), but would not be classified as serious unless it met one of the serious adverse event criteria listed above.

The incidence of AEs leading to discontinuation of the investigational medicinal product and/or

Reporting requirements

An adverse event report form (*Non-Interventional Study (NIS) Adverse Event Monitoring (AEM) Report Form)* is included as annex 10 to the protocol, which, once COMPLETED, will be

forwarded to the Department of Drug Safety at Pfizer Spain and the contact person for the study on behalf of the sponsor via the following communication channels:

To the Pharmacovigilance Department:

- By **fax: 900 866 211**

- Or by **email**: ESP.AEReporting@pfizer.com

A copy should also be forwarded to the contact person for the study, either by fax: PPD or by email: PPD

10. PUBLICATION OF RESULTS

All information obtained as a result of this study will be considered confidential.

The Scientific Coordinator of the study, together with the sponsor, will undertake to disclose the results through the usual scientific means.

The authors listed in the publication of the study results must meet the following requirements:

• Substantial contribution to the proposal and design of the study or to the collection, analysis and interpretation of study data

• Involvement or contribution in writing and/or reviewing the publications with regard to intellectual content

• Contribution to final approval of the published version

• Agreement to act responsibly in all aspects of the publication of the data to ensure that issues relating to the accuracy or integrity of any part of the work are investigated and appropriately addressed

CCI

INCIDENT REPORTING

In the event that a ban or restriction (e.g. temporary suspension) is imposed by a competent authority in any part of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer must be immediately informed thereof.

The investigator will also inform Pfizer immediately of any urgent safety measures taken to protect the study patients from any danger and any violation of the protocol of which he/she is aware.

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12. LIST OF TABLES

Not applicable

13. LIST OF CHARTS

Not applicable

ANNEX 1. LIST OF INDEPENDENT DOCUMENTS

Number	Date	Title
Annex 1	N/A	List of Annexes to the Protocol
Annex 2		Case Report Form
Annex 3	N/A	Coordinating Investigators' Statement
Annex 4	N/A	Reference IEC Approval
Annex 5	Version 1.0	Patient Information Sheet/Informed Consent Form
Annex 6	Version 1.0	Schedule of Payments/Financial Report
Annex 7	Version 1.0	List of Sites and Investigators
Annex 8	Version	Quality of Life Questionnaire
Annex 9	Version	Quality of Life - Hand-Foot Syndrome
Annex 10	Version 4.0_July 2014	Serious Adverse Event Report Form
Annex 11	N/A	Summary of Product Characteristics for Sutent, Votrient and Nexavar

ANNEX 2. CASE REPORT FORM

Attached as a separate document

ANNEX 3: COORDINATING INVESTIGATOR'S STATEMENT

Attached as a separate document

ANNEX 4. IEC APPROVAL

Attached as a separate document

ANNEX 5. PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

Pfizer	**INFORMED CONSENT DOCUMENT FOR A NON-INTERVENTIONAL STUDY**	**Page:** 41 of 56
INN	**Protocol number:**	**Version date**: 01/ October/ 2015
Language:	**Site No.:** 01	**Country:** Spain

CONSENT TO PARTICIPATE IN A NON-INTERVENTIONAL RESEARCH STUDY

Name of the research study: **Prospective, multicentre, observational study on fatigue- and hand-foot syndrome-related quality of life in patients with metastatic renal cell carcinoma receiving a tyrosine kinase inhibitor as first-line treatment (TROYA Study)**

Protocol number: **A6181218**

Name of the company sponsoring the research study: **PFIZER SLU**

Name of the principal investigator (study doctor): **Dr** PPD

Address of the research site:

Daytime telephone number:

24-hour telephone number:

This consent document includes important information about the non-investigational research study that you have been asked to take part in. A non-interventional study only gathers information. Your doctor will give you the same treatment as you would be receiving if you were not participating in this study.

Read this information carefully before deciding whether to take part. Nobody can force you to participate and you can leave the study at any time. If you decide to participate in this research study, you should sign this consent document and you will receive a copy of the signed document for your records.

This research study will be conducted by the oncologist responsible for your care and his/her team. Pfizer is sponsoring the study and will pay the doctor and the hospital for conducting the study.

The following sections describe the research study. Before deciding whether to participate, take all the time you need to ask the site staff any questions you may have and to talk to your family and friends, your GP or another healthcare professional. The site staff will answer all of your questions in detail before you make a decision**.**

1. WHAT IS THE AIM OF THE STUDY?

You are being asked to take part in this research study because you are going to receive treatment for your disease (kidney cancer) in the form of an oral drug from the group of drugs called tyrosine kinase inhibitors and we are investigating the effect that these drugs have on your quality of life.

The treatment may cause adverse effects, such as fatigue (tiredness) or hand-foot syndrome (skin changes on the hands and/or feet), among other side effects that your doctor will explain to you before starting the treatment. Knowing more about these effects in clinical practice may help prevent or improve them.

This study is going to assess the impact of fatigue on your everyday life and the effect that this treatment may have on the skin on the palms of your hands and the soles of your feet.

The study also aims to evaluate the influence of lifestyle (habits such as exercise, smoking or napping) on the development of fatigue (tiredness) or skin changes and how these adverse effects can be managed by taking breaks during the treatment, reducing the dose received or temporarily interrupting drug administration.

The appearance of these side effects has been associated with a greater response to treatment. It has also been observed that maintaining the medication dose leads to a greater possibility of tumour reduction and therefore greater effectiveness of the drug. It is therefore important to find out how to maintain the dose of medication without having to suffer from severe side effects.

As a result, Pfizer is carrying out a prospective, non-interventional study, without a comparison medicine, in accordance with clinical practice to gather more information about the good and bad effects of tyrosine kinase inhibitors, like the one prescribed by your doctor.

2. HOW MANY PEOPLE WILL PARTICIPATE IN THE STUDY AND HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

There will be approximately 100 people enrolled in this study. This study is being carried out at approximately 35 different hospitals in Spain. Approximately 3 people will take part at this hospital.

3. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

You will participate in this study for approximately 9 months and will have to visit the hospital the same number of times as if you were not part of the study since your

doctor's usual clinical practice will be followed. Therefore, you will have to visit the hospital at least 4 times during the study.

4. WHAT WILL HAPPEN DURING THE STUDY?

If you are included in the study, you will receive the same treatment as you would if you were not part of the study and you will not have any medical tests other than those ordered by your doctor to diagnose and monitor your disease**.** Your participation in the study will therefore not require any additional visits to the hospital other than visits scheduled according to clinical practice, which will be approximately every 3 months. You will also not require any procedures other than those deemed necessary by your doctor to diagnose and assess your disease.

You will be asked to complete some questionnaires about different aspects of your habits and quality of life. This will take you approximately 15 minutes.

One of the questionnaires, the fatigue scale, will include 13 questions about how you feel during the day and how the treatment is affecting your usual activities. This questionnaire should be completed every 6 weeks; therefore, you will sometimes complete it during your hospital visit and on other occasions the questionnaire will be given to you and explained so that you can complete it at home. You will have to take it with you to the hospital the next time you have a visit scheduled by your doctor and give it to the doctor.

You will be asked about whether you do any aerobic exercise, such as walking quickly, swimming, dancing, riding a bike, playing tennis or running, and whether you take naps or smoke before starting the treatment. During treatment, you will be asked to complete a patient diary every week (one day a week, for example every Sunday) about whether you take a nap and whether you do any type of physical exercise.
Your oncologist will ask you whether you have any discomfort affecting the palms of your hands and the soles of your feet at each visit.

5. WHAT ARE THE RISKS AND POTENTIAL INCONVENIENCES OF PARTICIPATING IN THIS STUDY?

Tyrosine kinase inhibitor drugs can cause some side effects, as described in the package leaflet or patient information sheet attached to your prescription. Any negative effects you may experience must be reported to your doctor. If you experience a serious adverse event, such as a disease or condition requiring hospitalisation, even if you are treated at another hospital and for another reason not related to the study treatment you are receiving, tell your study doctor immediately.

As this is a non-interventional study and you are going to be treated with a tyrosine kinase inhibitor drug as part of your normal healthcare, an adverse reaction to the tyrosine kinase inhibitor may not be considered a research-associated complication.

If you or your partner becomes pregnant during the study, tell the study doctor immediately. Also tell the doctor responsible for your care during your pregnancy that you were taking [tyrosine kinase inhibitor]. The study doctor will ask you if you/your partner or the doctor responsible for providing care during the pregnancy are willing to provide information on the pregnancy and its outcome. If you/your partner consent, this information will be given to the study sponsor so that the sponsor can carry out follow-up activities to monitor safety.

6. WHAT OTHER OPTIONS ARE AVAILABLE BESIDES PARTICIPATING IN THIS STUDY?

This study is to be conducted for the sole purpose of research. You can decide not to participate in his study and to continue with your usual healthcare/treatment.

7. WHAT ARE THE POSSIBLE BENEFITS OF MY PARTICIPATION IN THIS STUDY?

This study is to be conducted for the sole purpose of research. You will not obtain any direct benefit from your participation in the study since you will receive your usual healthcare and treatment. However, the information gathered during the study may help others in the future.

8. IS PARTICIPATION IN THE STUDY VOLUNTARY?

Yes. You decide whether or not to take part in this study. You can choose not to participate or you can change your mind and withdraw from (leave) the study at a later date. There will be no penalty and you will not lose any of the benefits you are currently receiving or are entitled to receive.

Your decision will not affect your access to healthcare in the future.

9. WHAT WILL I HAVE TO PAY FOR IF I PARTICIPATE IN THIS STUDY?

You will not have to pay anything to participate in this study.

As this study is only being carried out to obtain information and the healthcare you usually receive will not be modified in any way, the sponsor will not pay for any treatment or procedure you may receive during your participation in this study or for the tyrosine kinase inhibitor prescribed by your doctor.

10. WILL I RECEIVE ANY PAYMENT FOR MY PARTICIPATION IN THIS STUDY?

You will not receive any payment for participating in this study.

11. IF I PARTICIPATE IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

Access to your medical records
For the purpose of this study, the study team may need to access your medical records, even if just to take only the necessary information from your clinical history and the results of earlier tests. On signing this consent form, you are authorising the study team to contact the other healthcare professionals who provide you with care and to access the healthcare information in their power.

According to the current data protection act, you expressly agree to information from your medical records and other data obtained through your participation in the study being included in a personal information file kept by the Site.

Confidentiality of your medical information
Your medical information may include data regarding physical examinations and also results from medical, analytical or testing procedures. All medical information will be confidential. Your medical information will not be disclosed outside the research site, unless required by law and in the cases explained below.

Access to your personal information will be limited to the study doctor and his/her collaborators, health authorities, Independent Ethics Committee and representatives of the sponsor, companies from the sponsor's group and representatives from the authorised services that will control and audit the study. When checking the study data and procedures, everyone has a professional duty to guarantee that confidentiality is maintained according to current guidelines.

These persons will be able to see materials that can identify you to ensure that the study is being conducted properly and that you and the other individuals participating in the study are protected.

Use and disclosure of coded medical information
All the individuals involved in the study, including the study sponsor and the study team, recognise the importance of data protection and their legal obligations to protect your privacy and your well-being. The study team will therefore take measures to protect your privacy and you will only be identified with a code in all study documents. This will allow your medical information to be used, processed and disclosed without identifying you. Only the study team will have access to the code key (the key allows the study team to identify participants). Reports or publications generated during this study will not identify you in any way.
Some of the entities that have access to your coded medical information may be based in other countries, such as the United States and other countries where data protection and privacy laws may be less strict than in your country of residence. Nevertheless, the study sponsor and the institution will take all the necessary measures to protect your information. The sponsor is involved in the U.S.-EU Safe Harbor program and meets requirements thereof for handling your information. For more information on the Safe Harbor program, go to the website of the U.S. Department of Commerce: http://www.export.gov/safeharbor.

Future research

Your medical information may be used for related research in the future. On signing this consent form, you are authorising use of your medical information for future research in the area of oncology.

Withdrawal from the study
If you decide to withdraw from the study, tell the study doctor. If you withdraw your consent for this study, you will no longer be able to participate in the study. If you withdraw from the study without telling your study doctor, your information may be used to contact you again to confirm whether you want to continue with the study.
If you withdraw from the study, the study team will not continue to gather information about you, although you give authorisation for information already obtained to continue to be used, processed and shared as described above. Additionally, during and after your participation in the study, your study doctor must give the sponsor information relating to all serious adverse effects you may have suffered during your participation in the study. If you have any questions or concerns about this, we recommend asking your study doctor.

Storage of research data
All data obtained during the research will be kept for a period of 15 years.

Your right to access the research data
You have the general right to access your medical information and to ask for any incorrect information to be corrected. Requests to access or modify the information must be addressed to your study doctor.
Your right to access your information may have to be postponed until after the study has been completed in order to protect the scientific integrity of the study. If your right to access your medical information needs to be postponed, you will be guaranteed access to such information as soon as it is reasonably possible.

Compliance with current regulations on the confidentiality of your medical information
Pfizer undertakes to guarantee compliance with the principles established in Spanish Law 14/2007 on Biomedical Research, Spanish Organic Law 15/1999 on Personal Data Protection and Spanish Royal Decree 1720/2007 approving Regulations to implement Organic Law 15/1999.

Finally, Pfizer undertakes to ensure that you can exercise your rights of access, rectification, cancellation and opposition under the terms stipulated in Spanish Organic Law 15/1999 on Personal Data Protection. For this purpose, you must contact the site where the study is being conducted.

Consent
On signing this informed consent form, you are explicitly giving authorisation for your medical information to be collected, recorded, stored, transferred or disclosed as described above. You understand that you will not be allowed to participate in the study if you do not consent to the obtaining and use of your medical information.

12. WHO CAN I CONTACT ABOUT MY RIGHTS OR IF I HAVE A QUESTION?

Before signing this document, you must ask about anything you do not understand. The site staff will answer any questions you may have before, during and after the study. If you feel that your question has not been fully answered or you do not understand the answer, please continue to ask questions until you are happy.

If you have any concerns or complaints about this study or about how it is being conducted, express your concerns to the site staff.

13. CONSENT

I have read and understand the information contained in this informed consent document. I have been able to ask questions and they were all answered satisfactorily. I have had enough time and opportunities to ask about details of the study and to decide whether to participate or not. I voluntarily agree to take part in this study. On signing this consent document, I do not waive any of my legal rights.

□ Yes, I agree

□ No, I do not agree

I have been told that I will receive a signed and dated copy of this document.

_____

Name of the study participant in block capitals

_____	_____	_____
Signature of the study participant	Date signed[§]	Time (if necessary)*

[§]The patient / legal representative / impartial witness should personally date his/her signature.

* The time is only necessary if the information was provided on the same day as consent was given, or if consent is given on the same day as study-specific activities are to be carried out.

[†]The investigator, or a person with adequate training and experience appointed by the investigator to carry out the informed consent process, must sign and date the consent document at the same time as the patient.

[‡] Impartial witness: a person who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process

if the patient or the patient's legal representative cannot read and who reads the informed consent form and any other written information supplied to the patient. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.

PERSON OBTAINING CONSENT

Name of the person obtaining consent in block capitals		
Signature of the person obtaining consent †	Date signed	Time (if necessary)*

ANNEX 6: SCHEDULE OF STUDY PAYMENTS

Financial Report attached as a separate document

ANNEX 7: LIST OF SITES, LIST OF INVESTIGATORS AND CONTACT INFORMATION

Principal Investigator(s)

Attached as a separate document

ANNEX 8: FACIT-FATIGUE QUALITY OF LIFE QUESTIONNAIRE

Escala FACIT de fatiga (Versión 4)

A continuación encontrará una lista de afirmaciones que otras personas con su misma enfermedad consideran importantes. **Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días.**

		Nada	Un poco	Algo	Mucho	Muchí-simo
H7	Me siento agotado(a)	0	1	2	3	4
H12	Siento debilidad en todo el cuerpo	0	1	2	3	4
An1	Me siento decaído(a)	0	1	2	3	4
An2	Me siento cansado(a)	0	1	2	3	4
An3	Tengo dificultad para comenzar las cosas porque estoy cansado(a)	0	1	2	3	4
An4	Tengo dificultad para terminar las cosas porque estoy cansado(a)	0	1	2	3	4
An5	Tengo energía	0	1	2	3	4
An7	Soy capaz de hacer mis actividades habituales (trabajar, ir a la escuela, hacer las compras)	0	1	2	3	4
An8	Necesito dormir durante el día	0	1	2	3	4
An12	Estoy demasiado cansado(a) para comer	0	1	2	3	4
An14	Necesito ayuda para hacer mis actividades habituales	0	1	2	3	4
An15	Estoy frustrado(a) porque estoy demasiado cansado(a) para hacer las cosas que quiero hacer	0	1	2	3	4
An16	Tengo que limitar mis actividades sociales debido al cansancio	0	1	2	3	4

ANNEX 9. QUALITY OF LIFE HAND-FOOT SYNDROME

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails.					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin.					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

ANNEX 10. SERIOUS ADVERSE EVENT REPORT FORM

Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
(Including Pragmatic Clinical Studies [Non-Medicinal Intervention])

For Pfizer internal use only	
Local #	Date Reported to Pfizer

AER # (Insert when known)

PROTOCOL # A6181218 **SUBJECT #**

Protocol Title: Estudio observacional, prospectivo y multicéntrico de calidad de vida en relación con la fatiga y el síndrome mano-pie de los pacientes con carcinoma renal metastásico tratados con un inhibidor de la tirosina quinasa en primera línea (Estudio TROYA)

☐ Initial Report ☐ Follow Up Report

Country where event occurred: Spain

Patient Data	Date of Birth ☐ Male ☐ Female	Height ☐ in ☐ cm Weight ☐ lb ☐ kg	**Ethnicity:** Asian ☐ Black ☐ Hispanic ☐ Native American ☐ White ☐ Cannot ask per local regulations ☐ Other (specify)
If patient has died:	Date of Death	Cause(s) of Death	Determined by Autopsy: Y ☐ N ☐ Unknown ☐ *If yes, what was the autopsy determined cause of Death:*

Patient History ☐ None ☐ Unknown *Provide relevant medical history below Include other illnesses present at time of event and pre-existing medical conditions. If additional space is necessary, use addiitonal copies of this page.*

Illness (specify)	Onset Date	Stop Date	Check box if Ongoing	Pertinent Details *Include surgical procedures and dates*
			☐	
			☐	
			☐	
			☐	

Study Drug (Trade and Generic), Formulation, Route, Indication	Check box if Pfizer Drug	Dose	Units	Frequency	Start Date	Stop Date	Check box if Ongoing
	☐						☐
	☐						☐
	☐						☐
	☐						☐

Concomitant Drugs
☐ None
☐ Unknown

List below concomitant drugs taken within two weeks before the event onset. Exclude all drugs only administered more than two weeks before the event, and any drug used to treat the event or taken after event onset. If additional space is necessary, use additional copies of this page.

Drug Name (Trade and Generic)	Reason for Use	Route	Start Date	Stop Date	Check box if Ongoing
					☐
					☐
					☐
					☐

Relevant Tests *List only relevant confirmatory test results for adverse event(s), for example, from blood tests, diagnostic imaging. If additional space is necessary, use additional copies of this page.*

Test	Date	Result	Units	Normal Range Low	Normal Range High	Comments

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Non-Interventional Study Adverse Event Report Form
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AER # *(insert when known)*

PROTOCOL # A6181218 **SUBJECT #**

ADVERSE EVENTS *(if more than two, use additional copies of this page)*
Specify diagnosis if known, rather than symptoms or signs

Adverse Event Term	**Adverse Event Term**
Onset Date:	Onset Date:
Is the event serious? ☐ Yes ☐ No **If yes, identify seriousness criteria below:**	**Is the event serious?** ☐ Yes ☐ No **If yes, identify seriousness criteria below:**
Seriousness Criteria (Check all that apply): ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/Incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event	**Seriousness Criteria (Check all that apply):** ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/Incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event
Status at date of report or at death: ☐ Recovered } ☐ Recovered with sequelae } ☐ Recovering ☐ Not Recovered ☐ Unknown Date of Recovery:	**Status at date of report or at death:** ☐ Recovered } ☐ Recovered with sequelae } ☐ Recovering ☐ Not Recovered ☐ Unknown Date of Recovery:
Is there a reasonable possibility that the event is related to Study Drug? ☐ Yes ☐ No **If yes, specify Study Drug:**	**Is there a reasonable possibility that the event is related to Study Drug?** ☐ Yes ☐ No **If yes, specify Study Drug:**
Is there a reasonable possibility that the event is related to Concomitant Drug? ☐ Yes ☐ No **If yes, specify Concomitant Drug:**	**Is there a reasonable possibility that the event is related to Concomitant Drug?** ☐ Yes ☐ No **If yes, specify Concomitant Drug:**
Last Action Taken In Response to Event(s); specify drug name:	**Last Action Taken In Response to Event(s); specify drug name:**
☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable ☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable ☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
Did an SAE/AE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:	Did an SAE/AE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:

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Non-Interventional Study Adverse Event Report Form
For Protocols with Stipulated Active Collection of Adverse Events
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AER # (*Insert when known*)

PROTOCOL # A6181218 **SUBJECT #**

Event Narrative

Provide any information regarding the circumstances, sequence, diagnosis and treatment of the event(s) not otherwise reported on this form. If additional space is necessary, use additional copies of this page.

Reporter Comments:

Reporter: - -

First Name | Last Name (*Please* PRINT) | Date: DD-MMM-YYYY

Address: /

Street | City / State | Zip Code | Country

Telephone: Fax: Email:

Investigator's Name: _____ **Investigator/Designee Signature:**

Investigator/Designee Awareness Date: - - DD-MMM-YYYY

Report this form to Pfizer within 24 hours of awareness or immediately in case of death and life-threatening SAEs.

RECORD ALL PERTINENT INFORMATION ON THE FORM. DO NOT ATTACH SOURCE DOCUMENTS.

ANNEX 11. SUMMARY OF PRODUCT CHARACTERISTICS FOR SUTENT, VOTRIENT, NEXAVAR

Attached as a separate document