# Non-Interventional Study Protocol
# A-6181218

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

# Statistical Analysis Plan
# (SAP)

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# TABLE OF CONTENTS

# 1 AMENDMENTS TO PREVIOUS VERSIONS

Not applicable, this is version 1.

# 2 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical analyses that will be performed to generate the final report for the TROYA study. This includes a brief summary of the main study characteristics and the aim of the SAP, which corresponds to the statistical analysis plan for this study.

In recent years, a better understanding of the molecular biology of renal cell carcinoma (RCC) has led to an unprecedented development of therapies for this disease. As a result, several 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[1].

Among these new agents, sunitinib, pazopanib and sorafenib are recommended in all the 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, 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 events[7,8]. In fact, temporary dose interruptions are a strategy that is provided for in the summary of product characteristics for this purpose.

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 events 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 events 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 (HFS) 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 complain 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 events 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 event 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.

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.

## 2.1 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 (see ANNEX 1)*** which will be completed by the patient individually after it has been explained to them by the clinician or a person appointed by the investigator (nursing staff, clinical trials coordinator) in the treatment room during the scheduled visits, once the patient understands how to complete the form.
The FACIT–Fatigue questionnaire will be handed out at the following treatment times, which coincide with the visits, according to the site'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

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 2).
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 relevant ***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).
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 regular 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 trials 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.

## 2.2 STUDY OBJECTIVES

Fatigue-related quality of life of patients taking 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 events 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 day of drug administration, napping, 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.

## 3 INTERIM ANALYSES

An interim analysis is scheduled to be performed when all the patients have completed the FACIT-Fatigue at six months.

## 4 HYPOTHESIS TESTING

The statistical significance value is set to $p<0.05$ The SPSS statistical package, V19.0 or later will be used.

# 5 ANALYSIS POPULATION

## 5.1 FULL ANALYSIS SET

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 taking 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 proportion of 10%, assuming a discontinuation rate of 5%.

### 5.1.1 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 treatment with a tyrosine kinase inhibitor.
3) Baseline ECOG ≤2.
4) Patients who give their signed and dated informed consent
5) Committed patients who are able to complete the quality of life questionnaires and patient diary

### 5.1.2 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 stroke within the last 6 months
7) Severe hepatic impairment.
8) Concomitant use of potent inhibitors or inducers of hepatic cytochrome CYP3A4

## 6 OBJECTIVES AND VARIABLES

The primary objective of the study is to study fatigue-related quality of life of patients taking a tyrosine kinase inhibitor evaluated using the validated 13-item FACIT- Fatigue scale for patients with metastatic renal cancer in Spanish.

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. The data will be recorded in the electronic CRF designed for this study, where the following patient information is collected:

**DEMOGRAPHIC 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
6) Date on which the disease was diagnosed
7) Date of diagnosis of advanced stage disease
8) Histological type
9) Smoking

**LIFESTYLE (weekly from baseline visit to month 9)**

1) Napping
2) Aerobic exercise
3) 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 dose changes per treatment cycle
4) Temporary treatment interruptions, number of interruptions per treatment cycle
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 who achieve complete remission (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 the response is documented to the first date that progressive disease is observed.

- **Safety:** The safety of the tyrosine kinase inhibitor will be evaluated describing the incidence and all grades in the event of fatigue and or hand-foot syndrome.

- **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 cases in which 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.**

## 6.1 EFFICACY/EFFECTIVENESS OBJECTIVES

- Progression-Free Survival (PFS): PFS will be studied using Kaplan Maier survival curves, considering progression/death as the event and time to event as the interval from the start of treatment until the first date that progressive disease (PD) is observed according to RECIST criteria (Version 1.1) or until *death*. Patients who have not had an event at the time of the analysis of the study data will be censored on the date of the last available follow-up.

- Objective Response Rate (ORR): defined as the proportion of subjects who achieve complete remission (CR) or partial response (PR). Additionally, the patients with stable disease (SD) will be evaluated. The subjects will be evaluated in accordance with RECIST criteria (Version 1.1).

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

_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.

## 6.2 SAFETY OBJECTIVES

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

# 7 HANDLING OF MISSING DATA

No criterion for replacing missing values will be used.

# 8 STATISTICAL ANALYSIS AND METHODOLOGY

## 8.1 STATISTICAL METHODS

The investigator will collect data from the enrolled patients in 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 in turn is associated with a file, "WorkGroup", detailing the user code and permits of the investigator 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, the "Queries" will be programmed in the electronic case form so that when the investigator saves the data, it informs him/her of any doubts 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.

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 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 mxm 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 the survival distributions.

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.

## 8.2 STATISTICAL ANALYSIS

### 8.2.1 Included and evaluable population

The absolute and relative frequency of patients who meet all the inclusion criteria and do not meet any of the exclusion criteria will be presented.

The frequency distribution of the sub-population of non-evaluable patients will be presented depending on the reasons for non-evaluation:

- Patients who are not 18 years or older 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.
- Patients with contraindication for treatment with a tyrosine kinase inhibitor
- Patients without a baseline ECOG of less than or equal to 2
- Patients who does not give their signed and dated informed consent
- Patients not committed and able to complete the quality of life questionnaires and the patient diary
- Patients who are not candidates for first-line treatment with a tyrosine kinase inhibitor
- Patients who are receiving the treatment as second-line or subsequent therapy
- Patients with untreated hypothyroidism
- Patients with untreated severe anaemia
- Pregnant or breastfeeding patients
- Patients who have had a myocardial infarction or stroke (CVA) within the last 6 months
- Patients with severe hepatic impairment.
- Patients concomitantly using potent inhibitors or inducers of hepatic cytochrome CYP3A4.

### 8.2.2 Descriptive analysis

The mean value, standard deviation, median, minimum, maximum, interquartile range (IR) and 95% confidence interval (95%CI) will be given for:

- ❖ Patients' age at baseline visit

- ❖ Time elapsed since the disease diagnosis moment (calculated as the difference between the disease diagnosis date and the baseline visit date)
- ❖ Time elapsed since the advanced diagnosis (calculated as the difference between the advanced stage diagnosis data and the baseline visit date)

The frequency distribution of the patients will be presented according to:

- ✓ Gender
  - o Male
  - o Female

- ✓ ECOG at the time of diagnosis
  - o 0
  - o 1
  - o 2
  - o 3
  - o 4

- ✓ Heng prognostic criteria
  - o Favourable
  - o Intermediate
  - o Poor prognosis

- ✓ Site of metastasis
  - o Lung
  - o Brain
  - o Nodes
  - o Bone
  - o Liver
  - o Kidney

- ✓ Histological type
  - o Clear cells
  - o Chromophobe
  - o Sarcomatoid differentiation
    - ▪ <20%
    - ▪ 20-30%
    - ▪ 31-50%
    - ▪ 51-75%

- >75%

  - Papillary type 1
  - Papillary type 2
  - Mixed
  - Not performed

✓ Smoking
  - No
  - Yes
  - Occasional
  - Former smoker of <6 months

✓ Dose of the tyrosine kinase inhibitor and regimen with which they initiated treatment at baseline visit
  - Sunitinib 50 mg 4/2 regimen
  - Sunitinib 50 mg 2/1 regimen
  - Sunitinib 37.5 mg 4/2 regimen
  - Sunitinib 37.5 mg 2/1 regimen
  - Sunitinib 25 mg 4/2 regimen
  - Sunitinib 25 mg 2/1 regimen
  - Pazopanib 800 mg/24 hours continuous
  - Pazopanib 400 mg/24 hours continuous
  - Sorafenib 400 mg/24 hours continuous
  - Sorafenib 400 mg/12 hours continuous

### 8.2.3 Follow-up analysis

The evolution of the following aspects will be presented for each one of the follow-up visits of the patients at which the variables listed below are recorded:

- **Presence of palmar-plantar erythrodysesthesia:** the absolute and relative frequency of patients who as of month 3 of treatment develop palmar-plantar erythrodysesthesia of any grade will be provided. In the sub-population of patients with hand-foot syndrome, the frequency distribution will be presented according to the degree of severity of these AE, according to CTCAE (Common Terminology Criteria form Adverse Event) version 4:

  - Grade 1
  - Grade 2

- Grade 3

For each one of the evolution visits (month 6 and month 9), a study will be performed to ascertain whether significant changes have occurred in the presence and the grade of the HFS with regard to the previous visit, defined as (improved, maintained or worsened). The Pearson chi-squared test will be used for this purpose (or Fisher's exact test for 2x2 tables or likelihood ratio test for mxn tables, if necessary).

- **Presence of fatigue:** the absolute and relative frequency of patients with the presence of fatigue of any degree since the baseline visit will be provided. In the sub-population of patients with fatigue, the frequency distribution will be presented according to the degree of severity, according to CTCAE (Common Terminology Criteria form Adverse Event) version 4:

  - Grade 1
  - Grade 2
  - Grade 3
  - Grade 4

  For each one of the evolution visits (month 3, month 6 and month 9), a study will be performed to ascertain whether significant changes have occurred in the grade of fatigue with regard to the previous visit, defined as (improved, maintained or worsened). Significant associations will be sought between the habits of daytime rest, physical aerobic exercise, medication taken, dose and treatment schedule changes, dose interruptions and the number of days of treatment interruption depending on the evolution of the presence and degree of fatigue in the last twelve weeks. The Pearson Chi-squared test will be used for this purpose (or Fisher's exact test for 2x2 tables or likelihood ratio test for mxn tables, if necessary).

- **Patient diary data (weekly):** the distribution of patient frequencies will be presented according to the following habits:
  - **Napping**
    - Every day
    - Weekend and/or holidays
    - Sporadically, between 2 or 6 days
    - Has not taken a nap any day

- **Physical exercise:**
  - I have not done any kind of physical exercise
  - I have done at least 45 minutes of physical exercise 2-3 days a week
  - I have done 45 min of physical exercise 4-5 days a week for at least 6 months
  - I have done at least 45 minutes of physical exercise every day

- **Has taken the medication:**
  - In the morning (between 7 am and 12 noon)
  - In the afternoon (between 1 pm and 7 pm)
  - At night (between 8 pm and 6 am)
  - I have not taken any medication this week

For each one of the weekly habits described above, a summary calculation will be made (after three months) of each patient's habits in terms of daytime rest, physical exercise and taking their medication, taking the options marked with greater frequency in the last 12 weeks into account.

- **FACIT_Fatigue:** The main measures of centrality and dispersion measures will be calculated (mean, standard deviation, median, minimum, maximum, IR and 95%CI ) from the score obtained in the FACIT_Fatigue quality of life scale, calculated as described in ANNEX 1. The absolute and relative frequency of patients with severe fatigue, being those with a score of less than 30 points on the FACIT_Fatigue scale, will also be presented.

  For each one of the evolution visits (week 6, week 12, week 18, week 24, week 30 and week 36), a study will be performed to ascertain whether significant changes have occurred in fatigue-related quality of life versus the previous evaluation, and defined as:

  - **Improvement:** if there is an increase of more than 4 points in the FACIT_Fatigue scale score versus the previous evaluation
  - **Maintenance:** if the score on the quality of life scale does not vary by more than 4 points versus the previous evaluation
  - **Worsening:** if the score obtained on the Facit_Fatigue scale decreases by more than four points versus the previous evaluation.

  Significant associations will be sought between the habits of daytime rest, the practice of physical aerobic exercise, medication taken, dose and treatment schedule changes, dose interruptions and the number of days of treatment

interruption depending on the evolution in the evaluation of the fatigue in the FACIT_Fatigue over the last six weeks. The Pearson chi-squared test will be used for this purpose (or Fisher's exact test for 2x2 tables or likelihood ratio test for mxn tables, if necessary).

- **Treatment:** For each one of the treatment cycles received by patients during the 9-month follow-up, the following will be studied:

  - **Dose change:** the absolute and relative frequency of patients who have changed doses since the last cycle will be provided. In the sub-population of patients with dose changes in the last cycle, their frequency distribution will be presented according to:
    - Number of dose changes received
      - 1 change _ New dose
        - Sunitinib 50 mg 4/2 regimen
        - Sunitinib 50 mg 2/1 regimen
        - Sunitinib 37.5 mg 4/2 regimen
        - Sunitinib 37.5 mg 2/1 regimen
        - Sunitinib 25 mg 4/2 regimen
        - Sunitinib 25 mg 2/1 regimen
        - Pazopanib 800 mg/24 hours continuous
        - Pazopanib 400 mg/24 hours continuous
        - Sorafenib 400 mg/24 hours continuous
        - Sorafenib 400 mg/12 hours continuous
      - 2 changes_ New dose
        - Sunitinib 50 mg 4/2 regimen
        - Sunitinib 50 mg 2/1 regimen
        - Sunitinib 37.5 mg 4/2 regimen
        - Sunitinib 37.5 mg 2/1 regimen
        - Sunitinib 25 mg 4/2 regimen
        - Sunitinib 25 mg 2/1 regimen
        - Pazopanib 800 mg/24 hours continuous
        - Pazopanib 400 mg/24 hours continuous
        - Sorafenib 400 mg/24 hours continuous
        - Sorafenib 400 mg/12 hours continuous

  - **Treatment interruptions:** the absolute and relative frequency of patients who have interrupted the treatment since the last cycle will be given. In

the sub-population of patients with treatment interruptions, their frequency distribution will be presented according to:

- Number of treatment interruptions
  - 1
  - 2
  - 3
  - 4
  - 5
  - ...
- Total calculation of days of treatment interruption
  - <7 days
  - 7-14 days
  - >14 days

In order to study the evolution of patients in terms of the presence of AEs (HFS and fatigue), patient habits in terms of daytime rest, aerobic physical exercise and taking medication, paired data comparisons will be performed between each one of the visits with the results of the previous visit, as well as of each one of the visits with regard to the results presented at the baseline visit, using, for this purpose, the non-parametric sign tests for categorical variables or the McNemar test in the case of dichotomous variables.
In order to ascertain whether there is a significant evolution in the score obtained on the FACIT_Fatigue scale throughout the study, comparisons of paired data will be performed for each one of the assessments with regard to the baseline value and with regard to the previous evaluation using the Student t-test for paired data or the non-parametric Wilcoxon test, as appropriate.

### 8.2.4 Efficacy analysis

For the patient efficacy analysis, the following will be studied on completion of the first-line treatment or else on the date of the patient's last follow-up when the cut-off is decided:

- **Number of treatment cycles received**, presenting the frequency distribution of patients according to the number of cycles of treatment with the tyrosine kinase inhibitor in first line.
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6

- ...

- **Best response rate achieved**, presenting the frequency distribution of the patients based on the best response achieved with tyrosine kinase in first line.
  - CR
  - PR
  - SD
  - DP

- **ORR**, the absolute and relative frequency of patients who have achieved an objective response rate will be given (CR+PR).

- **CBR**, the absolute and relative frequency of patients who have achieved a clinical benefit rate will be given (CR+PR+SD).

- **DOR,** for the sub-population of patients who have achieved ORR, the time from the date of the response to the date of progression will be calculated, providing the value of the mean, standard deviation, median, range, interquartile range and 95% confidence interval.

- **Time to the best response**, calculated as the difference between the treatment start date and the date on which the best response is achieved. Providing the main measures of centrality and dispersion.

- **Time on treatment**, calculated as the difference between the treatment start date and the treatment end date or the date of the last follow-up if the patient is still on first-line at the time of the cut-off. It will be studied using the value of the mean, standard deviation, median, range, interquartile range and 95% confidence interval.

- **Reason for terminating treatment**, providing the frequency distribution of the patients according to the reason for terminating the treatment:
  - Unacceptable toxicity
  - Progression
  - Death
  - Other

- **Time to Treatment Failure (TTF).** TTF will be studied by means of a Kaplan Meier survival analysis, calculated as the time elapsed from the start of treatment with a tyrosine kinase inhibitor to tumour progression, treatment discontinuation for any reason or death from any cause.

- **Progression-Free Survival (PFS)** Progression-free survival will be studied by means of a Kaplan Meier survival analysis, calculated as the time elapsed from the date of the start of treatment with a tyrosine kinase inhibitor to the date of progression/death, if the event occurs, or else it will be censored on the date of

the patient's last follow-up

**Death:** the frequency distribution of deaths will be presented according to the reason:

- Adverse event
- Progression
- Other cause

## 9 LIST OF TABLES AND TABLE OF CONTENTS

| Table/Graph number | | | | Table/Graph title |
|---|---|---|---|---|
| **1.** | | | | Included and evaluable population |
| **2.** | | | | Descriptive analysis |
| | **.1** | | | Demographic and disease information |
| | | **.1** | | Age |
| | | **.2** | | Time from diagnosis and from the advanced diagnosis of the disease |
| | | **.3** | | Gender |
| | | **.4** | | ECOG at time of diagnosis, Heng prognostic criteria and site of metastasis |
| | | **.5** | | Histological type |
| | | **.6** | | Smoking |
| | **.2** | | | Dosage and treatment regimen of tyrosine kinase with which the patient begins treatment |
| **3.** | | | | Analysis of evolution |
| | **.1** | | | Presence of palmar-plantar erythrodysesthesia of any grade (month 3, month 6, month 9) |
| | | **.1** | | Association between medication intake habits and evolution of hand-foot syndrome (every three months) |
| | | **.2** | | Association between dose changes and evolution of hand-foot syndrome (every three months) |
| | | **.3** | | Association between dose, treatment regimen received and the evolution of hand-foot syndrome (every three months) |
| | | **.4** | | Association between temporary treatment interruptions and evolution of hand-foot syndrome (every three months) |
| | **.2** | | | Presence of fatigue of any grade (baseline, month 3, month 6, month 9) |
| | | **.1** | | Association between daytime rest habit and fatigue evolution (every three months) |
| | | **.2** | | Association between daytime physical exercise and fatigue evolution (every three months) |
| | | **.3** | | Association between daytime medication-taking habits and fatigue evolution (every three months) |
| | | **.4** | | Association between daytime dose changes and fatigue evolution (every three months) |
| | | **.5** | | Association between doses, daytime treatment regimen and fatigue evolution (every three months) |

| | | | | |
|---|---|---|---|---|
| | | **.6** | | Association between temporary daytime interruptions and fatigue evolution (every three months) |
| | **.3** | | | Data from the patient diary |
| | | **.1** | | Daytime rest (weekly) |
| | | **.2** | | Physical exercise (weekly) |
| | | **.3** | | Has taken the medication (weekly) |
| | **.4** | | | Quality of life (FACIT_Fatigue) (every six weeks) |
| | | **.1** | | Association between daytime habit and evolution on the Facit_Fatigue (every six weeks) |
| | | **.2** | | Association between daytime physical exercise and evolution on the Facit_Fatigue (every six weeks) |
| | | **.3** | | Association between daytime medication-taking habits and evolution on the Facit_Fatigue (every six weeks) |
| | | **.4** | | Association between daytime dose changes and evolution on the Facit_Fatigue (every six weeks) |
| | | **.5** | | Association between doses, daytime treatment regimen and evolution on the Facit_Fatigue (every six weeks) |
| | | **.6** | | Association between temporary daytime interruptions and evolution on the Facit_Fatigue (every six weeks) |
| | **.5** | | | Treatment, dose changes and temporary interruptions |
| | **.7** | | | Efficacy analysis |
| | | **.1** | | Number of treatment cycles received |
| | | **.2** | | Best response rate achieved with first-line treatment |
| | | **.3** | | ORR, DOR |
| | | **.4** | | Time on treatment and time to best response |
| | | **.5** | | Time to Treatment Failure (TTF) |
| | | **.6** | | Progression-free survival (PFS) |
| | | **.7** | | Reason for termination of treatment and reason for death |

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# 11 APPENDICES

## 11.1 ANNEX 1: FATIGUE FACIT QUALITY OF LIFE QUESTIONNAIRE

**Spanish version of Fatigue FACIT scale (Version 4)**

**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 | Muchísimo |
|---|---|---|---|---|---|---|
| | Me siento agotado(a) | 0 | 1 | 2 | 3 | 4 |
| | Siento debilidad en todo el cuerpo | 0 | 1 | 2 | 3 | 4 |
| | Me siento decaído(a) | 0 | 1 | 2 | 3 | 4 |
| | Me siento cansado(a) | 0 | 1 | 2 | 3 | 4 |
| | Tengo dificultad para comenzar las cosas porque estoy cansado(a) | 0 | 1 | 2 | 3 | 4 |
| | Tengo dificultad para terminar las cosas porque estoy cansado(a) | 0 | 1 | 2 | 3 | 4 |
| | Tengo energía | 0 | 1 | 2 | 3 | 4 |
| | Soy capaz de hacer mis actividades habituales (trabajar, ir a la escuela, hacer las compras) | 0 | 1 | 2 | 3 | 4 |
| | Necesito dormir durante el día | 0 | 1 | 2 | 3 | 4 |
| | Estoy demasiado cansado(a) para comer | 0 | 1 | 2 | 3 | 4 |
| | Necesito ayuda para hacer mis actividades habituales | 0 | 1 | 2 | 3 | 4 |
| | Estoy frustrado(a) porque estoy demasiado cansado(a) para hacer las cosas que quiero hacer | 0 | 1 | 2 | 3 | 4 |
| | Tengo que limitar mis actividades sociales debido al cansancio | 0 | 1 | 2 | 3 | 4 |

Spanish (Universal)


17 December 2010
Page 1 of 1

**Functional Assessment of Chronic Illness Therapy (FAC1T) Fatigue Scale (Version 4)**

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days**

| | | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I feel fatigued | 0 | 1 | *2* | 3 | **4** |
| 2 | I feel weak all over | 0 | 1 | *2* | 3 | **4** |
| 3 | I feel listless ("washed out") | 0 | 1 | *2* | 3 | **4** |
| 4 | I feel tired | 0 | 1 | *2* | 3 | **4** |
| 5 | I have trouble starting things because I am tired | 0 | 1 | *2* | 3 | **4** |
| 6 | I have trouble finishing things because I am tired | 0 | 1 | *2* | 3 | **4** |
| 7 | I have energy | 0 | 1 | *2* | 3 | **4** |
| 8 | I am able to do my usual activities | 0 | 1 | *2* | 3 | **4** |
| 9 | I need to sleep during the day | 0 | 1 | *2* | 3 | **4** |
| 10 | I am too tired to eat | 0 | 1 | *2* | 3 | **4** |
| 11 | I need help doing my usual activities | 0 | 1 | *2* | 3 | **4** |
| 12 | I am frustrated by being too tired to do the things I want to do | 0 | 1 | *2* | 3 | **4** |
| 13 | I have to limit my social activity because I am tired | 0 | 1 | *2* | 3 | **4** |

Scoring: Items are scored as follows: 4=Not At all. 3=A Little bit; 2=Somewhat; l=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Score range 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

| Item Number | Reverse Item? | | Item Response | Item Score |
|---|---|---|---|---|
| 1 | 4 | - | | = |
| 2 | 4 | - | | = |
| 3 | 4 | - | | = |
| 4 | 4 | - | | = |
| 5 | 4 | - | | = |
| 6 | 4 | - | | = |
| 7 | 0 | + | | = |
| 8 | 0 | + | | = |
| 9 | 4 | - | | = |
| 10 | 4 | - | | = |
| 11 | 4 | - | | = |
| 12 | 4 | - | | = |
| 13 | 4 | - | | = |

**Sum individual item scores: _____**
**Multiply by 13: _____**
**Divide by number of items answered: _____**

For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines on-line at www.facit.org.

Source: Webster, K, Celia, D, & Yost, K. (2003). The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications and interpretation. *Health and Quality of Life Outcomes, 1(79),* 1-7.

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## 11.2 ANNEX 2. 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 oedema | Soft or non-pitting | Indurated or pitting oedema; topical intervention indicated | Oedema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal haemorrhage; 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. | | | | | |