NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Axitinib In ADvanced / Metastatic Renal Cell CarcinOma - A Non-Interventional Study of Real World Treatment Outcomes in Patients Receiving 2nd Line Axitinib after 1st Line Sunitinib (**ADONIS**)
Protocol number	A4061078
Protocol version identifier	ADONIS V13
Date of last version of protocol	September 28, 2017
Active substance	Axitinib, Inlyta® Sunitinib, Sutent®
Medicinal product	Axitinib, Inlyta® Sunitinib, Sutent® Pazopanib, Votrient® Sorafenib, Nexavar® Everolimus, Afinitor® Temsirolimus, Torisel®
Product reference	Axitinib, Inlyta® EU/1/12/777 Sunitinib, Sutent® EU/1/06/347
Research question and objectives	ADONIS' objectives aim at assessing the real life usage of Axitinib across Europe and evaluate the impact of Axitinib in 2nd line on the treatment outcomes of mRCC patients treated with Sunitinib 1st line, in the real life setting
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2. LIST OF ABBREVIATIONS

	Definition
ADR	Adverse Drug Reaction
adv/m RCC	advanced/metastatic Renal Cell Carcinoma
AE	Adverse Event
CR	Complete Response
AR	Adverse Reaction
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria For Adverse Events
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
EU	Europe
FGF	Fibroblast Growth Factor
FKSI 19	Functional Assessment of Cancer Therapy-Kidney Symptom Index 19
AXI	Axitinib
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MH	Mental Health
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NI	Non Interventional
ORR	Objective Response Rate
OS	Overall Survival
PDGF	Platelet-Derived Growth Factor
PFS	Progression Free Survival
PR	Partial Response
QoL	Quality of Life
RCC	Renal Cell Carcinoma
RE	Role Emotional
RMM	Repeated mixture models
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SF-36	The Short Form (36) Health Survey
SU	Sunitinib
SU-AXI	–Sunitinib-Axitinib
TKI	Tyrosine Kinase Inhibitors
TSF	Time to Strategy Failure
TTF	Time to Treatment failure
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

3. RESPONSIBLE PARTIES

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4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	25 April 2014	Administrative	10. management and reporting of adverse events/adverse reactions	Additon of precision to inclusion criteria, modification reporting of adverse evevnt; addition of precision in the CRF.	Modification of Pfizer SOP
2	18 Nov 2014	Administrative	10. management and reporting of adverse events/adverse reactions	Addition of paragraph 10.2, 10.2.1, 10.2.2, 10.5, 10.5.1with the reporting obligation of Austria and Switzerland	Needed for Austrian and Swiss regulatory submissions
3	28 Sep 2017	Administrative		Insertion of particularities related to pharmacovigilance specific to Spain and suppression of Austria obligation	Adaptation of the protocol to current locals legislations

5. ABSTRACT

Axitinib in ADvanced / Metastatic Renal Cell CarcinOma - A Non-Interventional Study of Real World Treatment Outcomes in Patients Receiving 2nd Line Axitinib after 1st Line Sunitinib (ADONIS)

- *Rationale and background*

Metastatic disease develops in approximately one third of patients with renal cell carcinoma (RCC). Research on the molecular pathobiology of advanced/metastatic RCC has identified that the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) axis plays a critical role in tumor growth and survival [1]. With the advent of targeted therapies, recent progress has been made in developing effective treatment options for mRCC patients.

Axitinib (Inlyta®) is a vascular endothelial growth factor receptor (VEGFR-1,2,3) tyrosine kinase inhibitor (TKI) and has recently been approved in Europe (EU) for the treatment of adult patients with advanced/metastatic RCC after failure of prior treatment with Sunitinib or a cytokine [1]. This approval is based on the results of the AXIS study showing improved progression free survival compared to sorafenib after failure of prior treatment with sunitinib or a cytokine [2].

Axitinib dose increase or reduction are recommended based on individual safety and tolerability and give the physicians the option and flexibility to tailor the dose to each individual patient in order to optimize outcomes [1]. The most recent ESMO guidelines (2012) [3] provide updated recommendations for the treatment adv/mRCC treatment and recommend sunitinib and axitinib as standard of care with the highest level and grade of recommendation in their respective lines. These changes in recommendations and the increasing number of available agents imply many questions regarding the optimal use of targeted agents and the optimal combined first line (1L) – second line (2L) sequence of available agents.

ADONIS is designed to provide knowledge regarding the use of the SU-INL sequence with respect to efficacy outcomes, adverse events, and health related quality of life (QoL) in the real life setting. ADONIS will also shed some light on the real world use of flexible dosing of Axitinib.

- *Research questions and objectives*

Primary objectives:

- to assess the impact of AXI in 2nd line on progression free survival (PFS) and on time to treatment failure (TTF) for patients with adv/mRCC
- to assess the impact of the SU–AXI sequence on combined PFS and TTF for patients with adv/mRCC

Secondary objectives:

- to assess the objective response rate (ORR) for adv/mRCC patients receiving AXI in 2nd line post SU,
- to describe usage of flexible dosing of AXI in these patients in terms of dosing change, dosing schedules and the average dose received during the AXI period treatment,
- to assess the proportion of titrated patients within adv/mRCC patients receiving AXI in 2nd line post SU,
- to assess the impact of titration on PFS for adv/mRCC patients receiving AXI in 2nd line post SU,
- to assess OS (OS median and 24-month OS) for adv/mRCC patients receiving SU in first line followed by AXI in 2nd line,
- to assess the time to strategy failure (TSF) for adv/mRCC patients receiving the SU–AXI sequence,
- to assess PFS and OS for the combined 1st line SU – 2nd line sequences according to the second line post SU (TKI, mTOR) treatment,
- to describe safety and tolerability of patients receiving the SU–AXI sequence,
- to measure quality of life (QoL) in patients receiving AXI in 2nd line post SU.

- *Study design*

This study is an international (EU), prospective (partly retrospective), non-interventional, non-controlled, observational study. Primary outcome measures will assess progression free survival (PFS) in patients receiving the combined SU-AXI sequence and in patients receiving AXI in second line post SU.

- *Population - "Population" includes the setting and study population*

Patients will be enrolled when they start a treatment with SU in 1st line or AXI in 2nd line post SU treatment. The possible sequences of treatment under investigation (i.e. patient pools) will be:

- SU (prospective) – AXI
- SU (retrospective) – AXI
- SU – not further active treatment (supportive care)
- SU – other second line treatment (sorafenib, pazopanib, everolimus, temsirolimus, other)

- *Data sources*

Data will come from medical records and will be collected in routine clinical practice. Because of the inclusion criteria (Patients being treated with SU in 1st line according to the European approved therapeutic indication and/or being treated with AXI in 2nd line according to the European approved therapeutic indication (except post cytokines)), the medication is prescribed within the regular practice of the physician. As a non-interventional study, there are no specific requirements with regards to the treatment process.

- *Study size*

The study is designed to enroll approximately 750 patients over an enrollment period of 54 months. Out of those 750 patients, 350 are expected to receive the combined SU-AXI sequence and to provide a combined PFS median estimate.

- *Data analysis*

Kaplan-Meier analysis will be provided for PFS and OS. ORR will be assessed and a 2-sided 95% confidence interval will be provided using the Clopper-Pearson formula.

- *Milestones*

The study will enroll patients for 54 months with a minimum of 24 months of follow up.

Milestone	**Planned date**
Start of data collection	01 Feb 2014
End of data collection	30 Apr 2021

6. RATIONALE AND BACKGROUND

Renal cell carcinoma (RCC) accounts for approximately 2% of all cancers worldwide, with the highest rates observed in North America, Australia and Europe [4, 5]. It was estimated that in 2008 more than 190,000 patients worldwide suffered from RCC and about one half of these patients would die from this disease [6]. Approximately 40,000 patients are diagnosed with RCC in Europe each year, leading to an estimated 20,000 deaths [7]. Locally advanced/metastatic RCC ranks at number six of the cancer-related causes of death [8]. Age peak is between 50 and 70 and the incidence in men is twice as high as in women. Contrary to most cancers, prevalence of the RCC continues to rise worldwide with an estimated annual rate of 1.5 to 5.9% [9].

RCC is often asymptomatic or associated with non-specific symptoms such as fatigue, weight loss, malaise, fever and night sweats [10]. At the time of diagnosis, about 50-65% of RCC patients suffer from "localized" (stage I or II) RCC, 20% have "locally advanced" RCC (stage III), and 20-30% "metastatic" RCC (stage IV). In addition, around 30% of the patients with "localized" or "locally advanced" RCC at the time of the diagnosis will relapse [11]. Patients with RCC of stage II, III, or IV have a 5-year survival rate of 80%, 50-60%, or 10%, respectively.

Metastases occur most commonly in the lungs (55%), followed by the lymph nodes (34%) and the liver (33%), and/or the skeletal system (32%). Rarer metastatic sites e.g., pancreas, thyroid may also be observed. Around 75-85% of the cases of RCC are highly vascularized tumors that overexpress a number of growth factors like the vascular endothelial growth factor (VEGF), the platelet-derived growth factor (PDGF), and the fibroblast growth factor (FGF).

Treatment of advanced/metastatic renal cell carcinoma (adv/m RCC) has experienced fundamental changes within a very short period of time. In 2003, the era of cytokines, prognosis for patients with metastatic renal cell carcinoma (mRCC) was poor, with median survival reported at 6-12 months, and two-year survival at about 10% [12].

With the advent of targeted therapies, recent progress has been made in developing effective treatment options for mRCC patients. Research on the molecular pathobiology of advanced/metastatic RCC has identified the VEGF /VEGF receptor (VEGFR) axis and the phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway lying downstream (the "angiogenesis axis") as clinically relevant targets [13-15]. The VEGF/VEGFR axis plays a critical role in tumor growth and survival [14].

Inhibitors of this pathway include the multitargeted receptor tyrosine kinase inhibitors (TKI) sunitinib (Sutent®, Pfizer Inc.), sorafenib (Nexavar®, Bayer HealthCare/Onyx Pharmaceuticals), pazopanib (Votrient®, GlaxoSmithKline Inc) and axitinib (Inlyta®, Pfizer Inc), the VEGF

ligand-binding monoclonal antibody bevacizumab (Avastin®, Genentech, Inc.), usually given in combination with Interferon-alpha, and the mammalian target of rapamycin (mTOR) kinase inhibitors temsirolimus (Torisel®, Pfizer Inc) and everolimus (Afinitor®, Novartis). Cytokines have now been largely superseded by novel agents targeted against specific components of the pathways involved in tumor growth and angiogenesis, such as VEGF/VEGFRs [16.17].

Gap 1 :

Axitinib (Inlyta®) is a small molecule VEGFR TKI and has recently been approved in Europe. Axitinib is indicated (in Europe) "for the treatment of adult patients with adv/mRCC after failure of prior treatment with sunitinib or a cytokine" [1]. The AXIS phase III randomized clinical trial demonstrated superior efficacy of axitinib relative to sorafenib in second line treatment. The overall PFS by independent review (primary endpoint) was 6.7 versus 4.7 months. In patients previously given sunitinib alone or cytokine alone, the PFS were 4.8 versus 3.4 months and 12.1 versus 6.1 months, respectively. The PFS of axitinib post sunitinib was 6.5 months when assessed by investigators [2].

The AXIS study has established axitinib (Inlyta®) as a standard of care in 2nd line mRCC patients. However, the real life impact of second line Axitinib post Sunitinib remains to be established and the non-interventional real-life study ADONIS will lead to an increased knowledge and answer important questions about Axitinib in terms of efficacy, safety, dose titration practices and quality of life.

Gap 2 :

A number of publications support the hypothesis that dose titration of axitinib in a select group of patients who tolerate the drug at the standard starting dose may improve the efficacy [18-20].

Indeed, there is a variable level of drug exposure between patients and a significant percentage of patients are below the therapeutic drug threshold. Pharmacokinetic data suggest that normalization of plasma exposures can be achieved with dose titration [20, 21].

Clinical parameters for dose titration based on individual tolerability are useful for identifying patients with sub-therapeutic axitinib exposure at the 5 mg BID starting dose. Recent studies support an association between hypertension, Axitinib dose/plasma concentration and clinical outcome [22]. A retrospective analysis across 5 phase II studies of axitinib for the treatment of different solid tumor types shows that axitinib efficacy correlated with diastolic blood pressure ≥90 mm Hg [23]. Recent results of a pharmacokinetic analysis also support axitinib dose titration to increase plasma exposure in patients who tolerate axitinib and demonstrate diastolic blood pressure as a potential marker of efficacy [20].

In a randomized phase II clinical trial with axitinib for first-line metastatic RCC, the best response rate was obtained in patients with the highest rate of hypertension (82%) at baseline and thus who were not titrated. It suggests that these patients had adequate plasma exposure at the starting dose and that diastolic blood pressure could be considered as a marker of efficacy [24].

Dose increase or dose reduction of axitinib (Inlyta®) is labeled in the SmPC. The flexible dosing gives the physicians the option and flexibility to tailor the dose to each individual patient in order to optimize outcomes. Blood pressure appears as a potential predictive biomarker to define the suitable dose schedule. Though, the association between hypertension, Axitinib titration and clinical outcome needs to be further investigated.

ADONIS will allow assessing flexible dosing usage across Europe in real life and evaluate the impact of dose titration on the treatment outcomes of Axitinib in 2nd line mRCC patients post Sunitinib.

Gap 3 :

The ESMO guidelines for the treatment of adv/mRCC have recently been updated. The current update represents a step forward in the management of mRCC and recommends sunitinib and axitinib as standard of care with the highest level and grade of recommendation in their respective lines, with a third-line option with everolimus [3]. The recent availability of several new targeted agents raises many questions regarding their optimal use and the optimal combined first line (1L) – second line (2L) sequence of available agents. The optimal sequencing of targeted agents will therefore become increasingly important for achieving prolonged disease control [25-27].

Sunitinib (SU) and Axitinib (AXI) have been studied in sequence as 1st and 2nd line therapies in the AXIS trial. In this phase III trial, among those treated with SU in 1st line, approximately 50% of patients were then treated with AXI and saw an improvement in PFS over sorafenib [2].

The pivotal everolimus trial RECORD-1 comparing adv/mRCC patients (n= 410) treated with everolimus after one or more TKIs vs placebo showed a superior PFS in the active treatment arm relative to placebo and best supportive care (4.9 versus 1.9 months). However, in this study, most patients received multiple agents prior to randomization between everolimus and best supportive care and in fact only 21% patients were true second line patients [28]. Furthermore, out of these 21% only 43 patients received everolimus post sunitinib [29].

The INTORSECT phase 3 trial randomized a total of 512 patients to receive temsirolimus or sorafenib after sunitinib progression. Results showed that there was no significant difference in terms of PFS between the two therapies (4.28 versus 3.91 months; p = 0.19). However, an

improvement in OS was reported in favor of sorafenib (16.4 versus 12.3 months, p = 0.014). [30].

Based on these phase III data (AXIS, INTORSECT, RECORD-1), a reasonable sequencing scheme for mRCC patients seems to consist of sunitinib, followed by axitinib, followed by everolimus. This sequence is supported by the ESMO guidelines [3]. However, as there are many treatment options available, many questions remain regarding the optimal use of the new targeted agents, including which agent to use, in which setting, and the optimal sequence of available agents. The aim of ADONIS will be to address part of this question prospectively and contribute to the collective knowledge by assessing the impact of SU-AXI sequence in the real life setting; The other sequences received by patients will also be described to draw an overview of therapeutics strategies post SU in 1st line across Europe.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Questions

ADONIS objectives are dual and aim at primarily increasing the knowledge regarding the outcomes from the use of AXI post SU on one hand and outcomes from the combined SU-AXI sequence on the other hand. This will be addressed across Europe and in individual country cohorts to understand specificities and differences in use and outcomes.

7.2. Study Objectives

7.2.1. Primary objectives

In the real life setting:

- to assess the impact of AXI in 2nd line post-SU on progression free survival (PFS) and on time to treatment failure (TTF) for patients with adv/mRCC
- to assess the impact of the SU–AXI sequence on combined PFS and TTF for patients with adv/mRCC

7.2.2. Secondary objectives:

In the real life setting:

- to assess the objective response rate (ORR) for adv/mRCC patients receiving AXI in 2nd line post SU,
- to describe usage of flexible dosing of AXI in these patients in terms of dosing change, dosing schedules and the average dose received during the AXI period treatment,
- to assess the proportion of titrated patients within adv/mRCC patients receiving AXI in 2nd line post SU,
- to assess the impact of titration on PFS for adv/mRCC patients receiving AXI in 2nd line post SU,
- to assess OS (OS median and 24-month OS) for adv/mRCC patients receiving SU in first line followed by AXI in 2nd line,
- to assess the time to strategy failure (TSF) for adv/mRCC patients receiving the SU–AXI sequence,
- to assess PFS and OS for the combined 1st line SU – 2nd line sequences according to the second line post SU (TKI, m TOR),
- to describe safety and tolerability of patients receiving the SU–AXI sequence,
- to measure quality of life (QoL) in patients receiving AXI in 2nd line post SU.

8. - RESEARCH METHODS

8.1. Study design

8.1.1. Global design

ADONIS is an international (EU), prospective (partly retrospective), non-interventional, non-controlled, observational multicenter study.

Patients can be enrolled from several EU countries including Austria, Belgium, Denmark, France, Finland, Germany, Greece, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, The Netherlands and UK (non-exhaustive list).

Investigators will be specialists in charge of adv/mRCC. The sites involved (at least when performing feasibility) will be representative of their respective country in terms of practice. Participating physicians will not be influenced in their decision making and routine proceedings in any way.

The study will enroll approximately 750 adv/mRCC patients at the 1st and 2nd line treatment level. Patients will be enrolled when they start a treatment with SU in 1st line or AXI in 2nd line post SU treatment.

Patients enrolled at SU initiation, will be followed-up whatever the post SU 2nd line treatment is (AXI, other drugs, no further active treatment, (supportive care)). The possible 1st and 2nd line sequences of treatment under investigation (i.e. patient pools) are (Figure 1):

- SU (prospective) – AXI
- SU (retrospective) – AXI
- SU – not further active treatment (supportive care)
- SU – other second line treatment (sorafenib, pazopanib, everolimus, temsirolimus, other)

The study will include a retrospective and/or prospective data collection period :

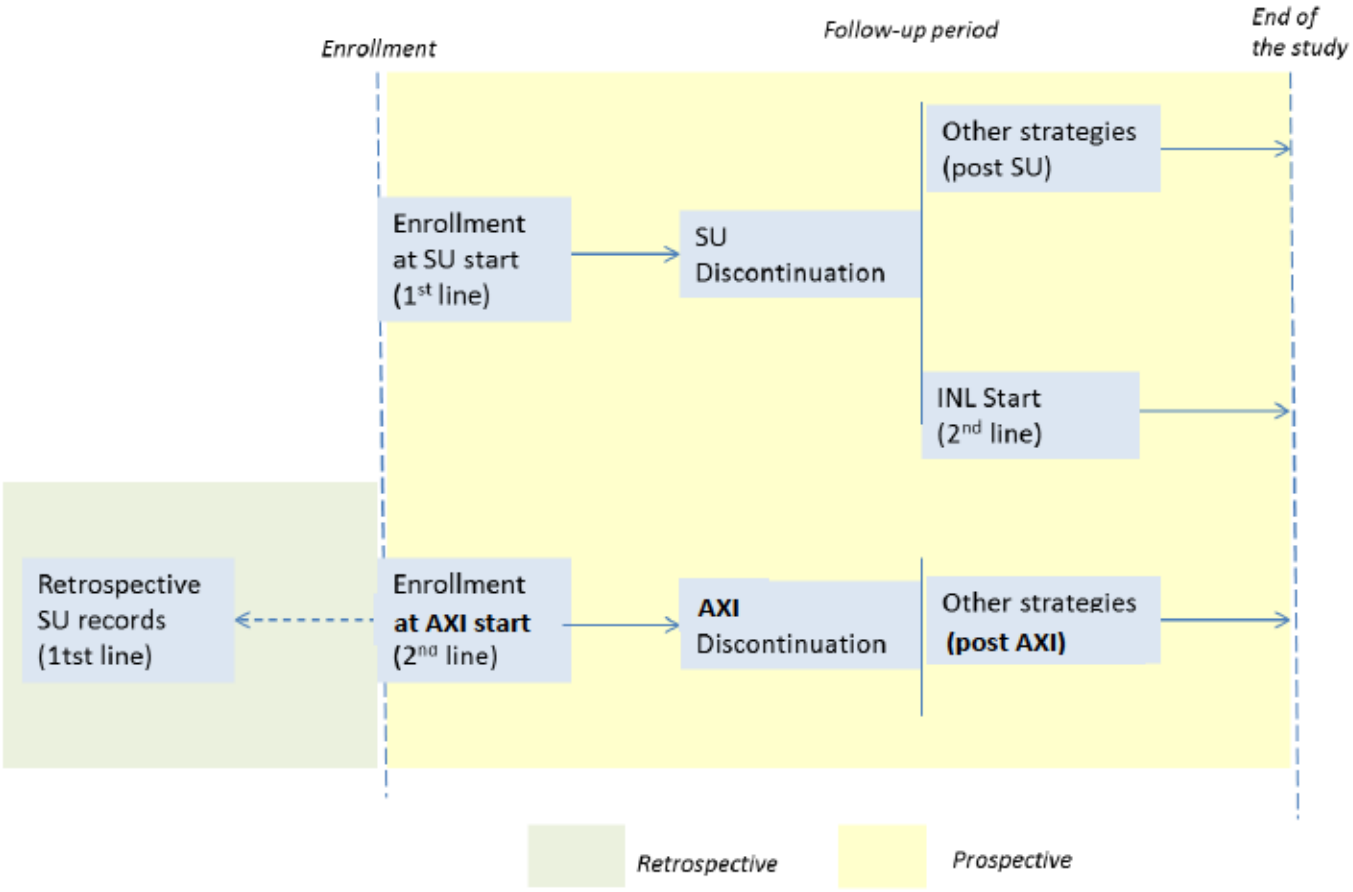
- Retrospective data, consisting of SU 1st line treatment records, will be collected for patients who start the study with AXI in 2nd line.

- Prospective data in terms of medical treatment records, will be collected for all 2nd line AXI patients.

- Prospective data will also be collected for all patients enrolled in the study at the SU 1st line level, irrespective of 2nd line treatment, or no further active treatment.

The inclusion period of eligible patients is planned for 54 months, with a minimum 2-year follow-up period. Patients will be followed-up from their enrollment to the end of the study follow up period.

Figure 1 : study flow chart



8.1.1. Study endpoints

Primary endpoints:

Progression Free Survival (PFS) :

- PFS for patients with adv/mRCC receiving AXI in 2nd line post SU as defined as the time from when the patient receives the first dose of AXI to the time of progression or death due to any cause, whichever occurs first

- Combined PFS for patients with adv/mRCC receiving the SU–AXI sequence as defined as the time from when the patient receives the first dose with SU in first line, until progression or death due to any cause with AXI in 2nd line, whichever occurs first during the SU-AXI sequence

(Time to Treatment Failure) TTF:

- TTF for the AXI 2nd line as defined as from when the patient receives the first dose of AXI to the time of AXI discontinuation (date completed by the physician).
- TTF for the SU–AXI sequence as defined as the time from when the patient receives the first dose with SU in first line to the time of AXI discontinuation (date completed by the physician).

Secondary endpoints:

- Objective Response Rate (ORR) for adv/mRCC patients receiving AXI in 2nd line post SU defined as the percentage of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST criteria v1.1.

- Overall survival (OS) for adv/mRCC patients receiving SU in first line followed by AXI in 2nd line as measured from date of first SU dose to the date of death of any cause. The OS median and the overall survival at month 24 (24 month OS) will be measured.

- Time to strategy failure (TSF) for patients receiving the SU-AXI sequence is defines as the time from when the patient receives the first dose with SU in first line to the time of AXI discontinuation (date completed by the physician) without the time between discontinuation of SU and start of AXI.

- Description of real life usage of flexible dosing across Europe with description of treatment schedules (dosing change, dosing schedule, average dose received during the period treatment)

- Proportion of titrated patients: titration is defined as described in the SmPC. A patient is considered as titrated when an AXI dose increase is maintained for at least 4 weeks.

- PFS for titrated and non-titrated patients when they receive AXI in 2nd line post SU

- Efficacy parameters (PFS, OS) for the combined 1st line SU – 2nd line sequences according to the second line post Sunitinib (other than SU-AXI):

    - SU in 1st line – other TKI in 2nd line (sorafenib, pazopanib)

    - SU in 1st line / mTOR in 2nd line. (temsirolimus, everolimus)

- Safety description with AE listing in patients receiving AXI: frequencies of patients experiencing at least one AE will be displayed by body system

- QoL using the questionnaire Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) and the Mental Health (MH) and Role-Emotional (RE) domains of the SF-36 questionnaire.

8.2. Setting

The study will enroll patients according to the eligibility criteria in participating countries across Europe. The recruiting centers will be representative of each country involved in terms of care management systems, of size and of practices (at least when performing feasibility).

Any patient who meets the eligibility criteria will be invited to participate in the study with no selection by the investigators. The enrollment visit will be performed at the time of the patients' inclusion, after the patients' acceptation of enrollment in the study.

Data will come from medical records and will be collected in routine clinical practice. The enrollment visit will comprise a first section on patients' eligibility for every patient whatever pool they belong to and a second section depending on the treatment started (SU or AXI) at the inclusion.

For patients enrolled in the study when AXI is started as a 2nd line therapy, a retrospective section will be completed at patients' inclusion, to collect data on SU 1st line treatment.

For patients who start AXI when SU is discontinued during the study, the AXI initiation visit will resume baseline data that need to be updated.
Follow-up will be ensured during visits in the context of usual patients' care management (non-interventional study). No visits will be required by the protocol of the study. As long as the

patients are treated with SU or AXI, every visit to the center will be recorded. In accordance with ESMO guidelines and physicians clinical practice is real life, follow-up visits are approximately expected:

- during SU treatment : every 6 weeks (every cycle) with tumor assessment approximately every 3 months with respect to the clinical practice
- during AXI treatment : every 4 weeks (every cycle) with tumor approximately assessment every 2 months with respect to the clinical practice

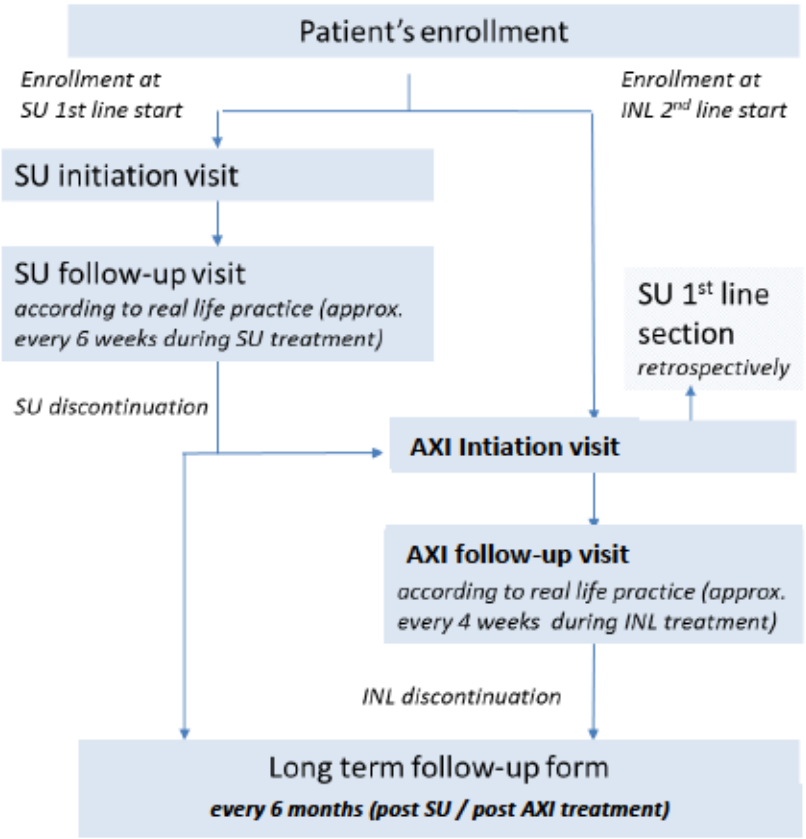
When patients come off SU treatment (i.e. are not receiving AXI) or come off Axitinib (after receiving the SU-AXI sequence) they will be followed up every 6 months (separate form) for survival until the end of the study.

Because of the inclusion criteria (Patients being treated with SU in 1st line according to the European approved therapeutic indication and/or being treated with AXI in 2nd line according to the European approved therapeutic indication (except post cytokines)), the medication is prescribed within the regular practice of the physician. Because of the non-interventional nature of the study, there will be no specific requirements with regards to the treatment process. The physician will determine dosage and duration of the treatment, guided by the SmPC and according to his assessment of the individual therapeutic needs of the patient.

The QoL questionnaire will be completed at baseline and then every month for patients receiving AXI. QoL will also be measured at the discontinuation of AXI treatment. Patients will complete the QoL questionnaire at their homes once per month and return it using pre-stamped envelopes. If not done before, the questionnaire will be completed at the site preferentially prior to the follow-up visit(s).

If QoL objective is locally non-compliant with a non-interventional study design, patients will be exempted from performing the questionnaires.

Figure 2 : visit scheme



8.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Histologically confirmed diagnosis of advanced/metastatic renal carcinoma (clear cell RCC as well as non-clear cell RCC) with measurable disease according to RECIST 1.1

2. Patient 18 years of age and over

3. Patients being treated with SU in 1st line according to the European therapeutic indication and/or being treated with AXI in 2nd line according to the European approved therapeutic indication (except post cytokines)

4. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

8.2.2. Non inclusion criteria

Patients meeting any of the following criteria will not be included in the study:

5. Patients being treated with cytokines or any other treatment outside of SU in 1st line
6. Patients receiving anti –tumor treatment beyond a second line
7. Patients already under Sunitinib, already under Axitinib: enrolment must occur at the beginning of each line of treatment (before or at the first follow up visit)

8.3. Variables

Variable	Role	Data source(s)
Patient demographics (year of birth, gender, height, weight)	*baseline characteristics*	Initiation visit
Performance status (ECOG, Karnofsky)	*baseline characteristics, potential confounder*	Initiation visit Follow up visit
Risk groups (MSKCC risk, Heng risk)	*baseline characteristics, potential confounder*	Initiation visit
Comorbidities	*baseline characteristics, potential confounder*	Initiation visit
Lab tests (abnormal findings – levels when abnormal)	*baseline characteristics, potential confounder*	Initiation visit Follow up visit
Blood Pressure measurement (Y/N, date of exam and level, antihypertensive treatment)	*baseline characteristics, outcome*	Initiation visit Follow up visit
Electrocardiogram (Y/N/date of exam/ abnormal findings)	*baseline characteristics,*	Initiation visit
Echocardiography (Y/N/date of exam/ abnormal findings, LVEF)	*baseline characteristics,*	Initiation visit
Tumor history (date of first diagnosis, TNM, Grade at diagnosis /at enrolment, Histology)	*baseline characteristics*	Initiation visit
Metastasis (date of first detection and	*baseline characteristics*	Initiation visit

localisation)		
Previous treatments for RCC (Surgery, radiotherapy, other / for primary tumor/ for metastasis)	*baseline characteristics, potential confounder*	Initiation visit
Sunitinib therapy (starting date and dose, dose change, change of schedule)	*exposure*	Initiation visit Follow up visit
Axitinib therapy (starting date and dose, dose titration up, dose reduction, change of schedule)	*exposure, effect modifier/sub-group identifier*	Initiation visit Follow up visit
Additional anti tumor treatment (name and dose)	*exposure, potential confounder*	Inclusion visit Follow up visit
Comedications (name of products, starting and ending dates)	*exposure, potential confounder*	Initiation visit Follow up visit
Sunitinib / Axitinib Progression (Y/N and date)	*outcome*	Initiation visit Follow up visit
Sunitinib / Axitinib Tumor Response	*outcome*	Initiation visit Follow up visit
Sunitinib / Axitinib Safety : AE description andAE grade (according CTCAE)	*outcome*	Initiation visit Follow up visit
Sunitinib / Axitinib discontinuation	*outcome*	Follow up visit
Axitinib QoL (FKSI-19, and MH and RE domains of SF-36)	*outcome*	Initiation visit Follow up visit End of treatment
Death (Y/N,date, Cause)	*outcome*	Follow up visit

Table 1 : variables collected during study

Detailed definitions will be included in the Statistical Analysis Plan

8.4. Data sources

A Case Report Form (CRF) will be used for data recording. In this protocol, the term case report form (CRF) should be understood to refer to medical records in either paper or electronic data form. The data collection method used will be:

- eCRF for physicians (in English, a translated paper copy will be available)
- paper questionnaires for patients:

As regards the scope of the patient data relevant to drug safety, this is subject to the same high company standards as the CRFs of clinical trials. The stipulations of the documentation form must be observed so that the data can be analyzed with reference to the afore-mentioned objectives.

As the study is retrospective/prospective and non-interventional, it will only document cases that were observed during the documentation period and the documentation should illustrate the usual procedure in the practice.

Follow-up visits should be documented only when these correspond to routine medical practice and/or take place for medical and therapeutic need, i.e. the patient must on no account be given an appointment because of the NIS. Follow-up visits are not expected to be more frequent than one visit every 6 weeks with SU and every 4 weeks with AXI.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has the final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the CRF.

8.5. Study size

The primary endpoints of this study in patients with adv/mRCC are PFS and TTF for patients receiving AXI in 2nd line and the combined PFS and TTF for patients receiving the SU-AXI sequence. In this non-interventional real life study, the objective is only descriptive and the sample size will rely on the precision of the estimate.

The expected precision of the median PFS can be calculated with the Greenwood's formula. The formula provides an estimate of the variance of S(t) (Kaplan-Meier estimate) as follows:

$$\hat{Var}[\hat{S}(t)] = [\hat{S}(t)]^2 \sum_{j:t_j \leq t} \frac{d_j}{n_j(n_j - d_j)}$$

where *tj* is the times of events, *dj* the number of events at these times and *nj* the sample size at risk.

Assuming the absence of right-censoring before the median survival and the occurrence of a single event for each event time, Greenwood's formula for median survival can be simplified as follows:

$$\hat{Var}[\hat{S}(t)] = \frac{0,5^2}{n}.$$

The different variances and CI of S(t) can therefore be calculated as a function of n and accuracy.

$s(t)^2$	n	Variance $(s(t)^2/n)$	Accuracy
	150	0.001666667	0.080
	175	0.001428571	0.074
	200	0.00125	0.069
	225	0.001111111	0.065
0.25	250	0.001	0.062
	300	0.00083	0.056
	350	0.0007143	0.052

Table 2 : sample size and accuracy of PFS

Inclusion of 350 patients with the SU-AXI sequence will allow demonstration of median progression free survival as well as time to treatment failure with an accuracy of 5.2%.

The SU-AXI 350-patient sample is expected to comprise two thirds of patients enrolled in the AXI 2nd line pool (approx. 225 patients) and one third of patients enrolled in the SU 1st line pool then receiving an AXI 2nd line (approx. 125 patients).

This last group (125 patients) implies initial inclusion of 525 patients in the SU 1st line pool. Based on current EU market research and 2014 forecasts, it is expected that 68% of the SU 1st line pool has a 2nd line treatment (357 patients); and that 35% are expected to initiate 2nd line treatment with AXI (125 patients).

ADONIS is therefore targeting approximately 750 patients: 225 in the AXI pool and 525 in the SU pool. These estimates will allow for an approximate SU-AXI 350- patient group to meet primary outcome objectives and a SU – other 2nd line treatment group of 230 patients to meet secondary objectives.

This sample size of 125 SU-AXI patients in the prospective group will also allow for comparisons with the AXIS-trial with respect to PFS and to demonstrate that the AXI PFS is no worse than 25% of the PFS measured by investigators in the AXIS study (i.e. at least 4.9 months

based on AXIS PFS of 6.5 months when assessed by investigators [2] (80% power, Brookmeyer-Crowley type test, One-sided alpha level (Type I error rate) set at 0.1).

8.6. Data management

The database and data management plan will be generated to include the following as a minimum:

- Data Flow Plan
- Case Report Form Completion Guidelines
- Data Entry Methods and Guidelines
- Data Validation Document
- Data Handling Conventions

A Data Clarification Form (DCF) process will be used for handling data discrepancies.

Data management and statistical analysis will be performed with SAS software (version 9.1, SAS Institute, North Carolina USA).

8.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The primary population for evaluating all efficacy and safety endpoints as well as patient characteristics will include all patients enrolled in this study.

Descriptive analysis of qualitative and ordinal variables will comprise sample size and the frequency of each modality. Descriptive analysis of quantitative variables will comprise the mean, standard deviation and their confidence intervals as well as the median and range. Univariate analysis will be performed on data of CRF and questionnaire.

Baseline descriptive results will be presented separately for the prospective group (SU start – patients starting a first line) and for the retrospective / prospective one (IN start- patients starting a second line).

Missing data management will be addressed in the SAP.

8.7.1. Efficacy Analysis

Progression-Free Survival (PFS)

Combined PFS of the SU-AXI sequence is defined as the time from when the patient receives the the first dose with SU in first line, until progression or death due to any cause with AXI in 2nd line, whichever occurs first during the SU-AXI sequence. PFS in patients receiving AXI in 2nd line is defined as the time from when the patient receives the first dose of AXI to the time of progression or death due to any cause, whichever occurs first.

Patients who remain progression free at the end of AXI treatment will be evaluated until death, disease progression or the start of a new anticancer therapy.

For the primary endpoints, PFS will be assessed using the Kaplan-Meier method. This method will be applied to derive, survival curves, median event time and a 95% confidence interval for the median.

Kaplan-Meier estimates will also be provided for sub-group analysis of interest:

- Titrated and non-titrated patients, defined in the following section (titration description section), receiving AXI in 2nd line
- Patients receiving AXI in 2nd line post SU depending on the response to SU in 1rst line.
- Country cohorts where feasible (pool size)
- SU 2nd groups depending on the 2nd line treatment :
    - SU in 1st line- AXI in 2nd line,
    - SU in 1st line – other TKI in 2nd line (sorafenib, pazopanib)
    - SU in 1st line / mTOR in 2nd line. (temsirolimus, everolimus)

Potential influences of baseline patient characteristics (eg, age, sex, MSKCC risk group) on the primary PFS will be evaluated by Cox proportional regression method.

Time to Treatment to Failure (TTF) and Time to Strategy Failure (TSF)

TTF for the AXI 2nd line is defined as from when the patient receives the first dose of AXI to the time of AXI discontinuation (date completed by the physician) whatever the reason for discontinuation is and whatever the following therapeutic strategy. In case of death while the patient is still treated with AXI, date of death will be considered as date of discontinuation.

TTF for the SU–AXI sequence is as defined as the time from when the patient receives the first dose with SU in first line to the time of AXI discontinuation (date completed by the physician).

TSF for SU-AXI sequence is defined as the time from when the patient receives the first dose with SU in first line to the time of AXI discontinuation (date completed by the physician) without the time between discontinuation of SU and start of AXI.

Similar to PFS, Kaplan-Meier analyses will be performed for TTF and TSF.

Objective Response Rate (ORR)

ORR is defined as the percentage of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST V1.1, relative to all patients who have baseline measurable disease. Confirmed responses are those that persist on repeat imaging study ≥4 weeks after initial documentation of response.

Patients who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. A patient, who initially meets the criteria for a PR and then subsequently becomes a confirmed CR, will be assigned a best response of CR.

ORR will be assessed and a 2-sided 95% confidence interval will be provided using the Clopper-Pearson formula.

Overall Survival (OS)

OS is defined as the date from first SU dose to the date of death due to any cause. For patients not experiencing the event, their survival times will be censored at the last date they are known to be alive. Similar to PFS, Kaplan-Meier analyses will be performed for OS. The share of patients alive (OS) at 2 year will be measured for the sequence.

8.7.2. Analysis of other Endpoints

Titration of Axitinib

Titration is defined as described in the Axitinib (Inlyta ®) SmPC [1] (the active version at the date of patient's AXI Initiation).

Treatment titration schedules (dose changes, average daily dose over the treatment (in mg), dosing schedule) will be described in patients receiving AXI. A non-titrated and a titrated group will be defined based on the changes in dosing and the titration duration set up. Reason for non-

titration will be identified (hypertension, Grade 3/4 Adverse Drug Reaction): patients will be considered as titrated when an AXI dose increase is maintained at least 4 weeks.

Quality of life

QoL will be measured via the questionnaire Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) and the Mental Health (MH) and Role-Emotional (RE) domains of the SF-36 questionnaire.

QoL as measured by FKSI-19 will be the sum of the scores from the FKSI-19 questionnaire. FKSI-19 will be reported using means (with standard deviations and 95% confidence intervals) and medians at each assessment point, based on the observed values as well as changes from baseline. Similar statistics will be provided for the RE and MH domains of SF-36.

QoL will also be assessed according to the response to AXI.

8.7.3. Safety Analysis

Summaries and listings of AEs and other safety parameters will be provided by period of treatment (Sunitinib, Axitinib).

Frequencies of patients experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Summary tables will present the number of patients observed with AEs and corresponding percentages.

The description will be conducted for all the reported AEs whether related to the drug or not, and then for the AEs related to SU or AXI.

Adverse event reported by patients through the quality of life questionnaires will also be described.

8.8. Quality control

8.8.1. Investigational site set up

Appropriate training relevant to the study will be given to investigational staff. Any new information relevant to the performance of this NIS will be forwarded to the staff during the study.

8.8.2. Investigational site monitoring

Regular contacts with the sites will be planned to provide information and support to the investigator(s) and verify that study sites procedures are compliant with the protocol and that data are being accurately recorded in the CRFs.

Additional monitoring tasks will be described in a monitoring plan according to Pfizer SOP; monitoring visit at investigators sites will ensure that:

- information letters have been given to the patients and consents have been signed
- study is conducted according to the protocol
- data reported on case report forms is compliant with source documents.
- study documents are correctly archived in accordance with the investigator's study file.

8.8.3. Study coordination

Regular progress reports presenting key indicators at a national and EU level will be regularly prepared and forwarded to the study coordinating team. Based on these status reports, different actions will be decided by the study coordinating team to ensure a satisfactory progress and an appropriate quality of data.

Different signals (Protocol deviations etc as identified by monitoring) will be used as potential identification of low protocol compliance by investigators. If compliance is an issue, the situation will be evaluated and specific action plans will be implemented to correct the situation.

8.8.4. Quality and accuracy of records

The investigator will have the responsibility for collecting and reporting of all clinical, safety and laboratory data entered int the CRFs and/or any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports).

8.8.5. Storage of record

The records should be retained by the investigator according to local regulations, and/ or as specified in the Clinical Study Agreement.

8.9. Limitations of the research methods

8.9.1. Investigational site selection

The voluntary participation of physicians constitutes a selection bias observed for this type of study. Investigational sites will be recruited within a representative list of the country's centres in terms of size, care management system and practices.

8.9.2. Patients selection

This constitutes another potential selection bias classically associated with NI studies. Voluntary or involuntary selection of patients in a study by investigators is inevitable, but this bias can be limited by systematic attempts to enroll patients in the study.

8.9.3. Patients lost to follow-up

The pragmatic nature of this study (which involves non-intervention on usual patient management practices) complicates the collection of follow-up data and may increase the number of patients lost to follow-up. Electronic monitoring and the final evaluation questionnaire in the CRF should minimize this number of patients as well as the history and the severity of the studied disease.

8.9.4. Measurement biases

Measurement biases will be related to difference in sites' procedures to manage patients in real life setting. As no further examinations are expected within the study, tumor response will be assessed by physicians based on their own practices and can differ from one site to another. ORR assessment as well as PFS assessment will include this slight margin of error which is inherent to any NIS study in oncology [31]. To limit the bias, investigators will mention the use or not of RECIST criteria when they assess the tumor response.

8.10. Other aspects

If a physician agrees to participate in this NIS, a written agreement will be concluded with this physician which contains the amount of allowance paid for the documentation of one subject.

Since no other examinations will be performed than the usual clinical examinations and laboratory tests, the medical services provided and the drugs will be reimbursed by the health insurer. The agreed allowance is paid for the workload involved in the documentation of the treatment on the specific Case Report Form.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient withdrawal

Patients may withdraw from the study at any time on their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

Treatment discontinuation or loss to follow-up do not constitute patient withdrawal

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued 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.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. REQUIREMENTS

The table below summarizes the requirements for recording safety events on the eCRF of the study and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the *eCRF of the Study*	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
non-serious AE	All	***Potential risks (SUNITINIB RMP V14.0)*** Carcinogenicity Other Potential Cardiac events: Conduction defect events, Ischemic events, Tachycardia events Retinal detachment Reproductive and developmental toxicity ***Missing Information (SUNITINIB RMP V14.0)*** Use in pediatric subjects Use in pregnant and lactating women Use in severe hepatic impairment subjects Use in cardiac impairment subjects ***Potential risks (AXITINIB RMP V8.0)*** Wound healing complications Congestive heart failure/cardiomyopathy QT prolongation Reproductive and developmental toxicity Microangiopathy Carcinogenicity Osteonecrosis of the jaw Drug Drug interactions with CYP1A2, CYP2C8 and P-glycoprotein substrates ***Missing information (AXITINIB RMP V8.0)*** Risks in pregnant and lactating women, Risks in pediatric subjects,

		Risks in patients with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min), Risks in subjects with severe hepatic impairment (>Child-Pugh Class B), Risks in patients with brain metastasis, spinal cord compression, or carcinomatous meningitis, Risks in subjects with recent myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, deep vein thrombosis, or pulmonary embolism, Risks in patients with active peptic ulcer disease, **Appendix 1.1.1.** Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks).
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

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

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific

follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF of the study. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of *Sunitinib and/or Axitinib* or the time of the patient's informed consent if s/he is already exposed to *Sunitinib and/or Axitinib*, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to *Sunitinib and/or Axitinib*, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to *Sunitinib and/or Axitinib*, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that *Sunitinib and/or Axitinib* caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether *Sunitinib and/or Axitinib* caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that *Sunitinib and/or Axitinib* did not cause the event, this should be clearly documented on the eCRF of the study and the NIS AEM Report Form.

10.2. COUNTRY REQUIREMENT

10.2.1. Switzerland requirements :

Because of the inclusion criteria (Patients being treated with SU in 1st line and/or being treated with AXI in 2nd line after having received Su in 1st line), the medication is prescribed within the regular practice of the physician. Because of the non-interventional nature of the study, there will be no specific requirements with regards to the treatment process. The physician will determine dosage and duration of the treatment, guided by the **Swiss Prescribing Information** and according to his assessment of the individual therapeutic needs of the patient.

Safety event	Recorded on the *eCRF of the Study*	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
non-serious AE	All	All
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

10.2.2. Spain requirements:

The following table summarizes the requirements for recording adverse events / adverse reactions on the eCRF of the study and reporting adverse events / adverse reactions on the non-interventional adverse event form (NIS AEM Report Form) to the department of safety of the Pfizer drug. These requirements are described for three types of events: (1) severe adverse events (SAE); (2) non-severe AE (as applicable); and (3) cases involving exposure to the drug, including exposure during pregnancy, exposure during lactation, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the "Definitions of adverse events" section.

Safety event	Recorded on the *eCRF of the Study*	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All

non-serious AE	All	***Potential risks (SUNITINIB RMP V14.0)*** Carcinogenicity Other Potential Cardiac events: Conduction defect events, Ischemic events, Tachycardia events Retinal detachment Reproductive and developmental toxicity ***Missing Information (SUNITINIB RMP V14.0)*** Use in pediatric subjects Use in pregnant and lactating women Use in severe hepatic impairment subjects Use in cardiac impairment subjects ***Potential risks (AXITINIB RMP V8.0)*** Wound healing complications Congestive heart failure/cardiomyopathy QT prolongation Reproductive and developmental toxicity Microangiopathy Carcinogenicity Osteonecrosis of the jaw Drug Drug interactions with CYP1A2, CYP2C8 and P-glycoprotein substrates ***Missing information (AXITINIB RMP V8.0)*** Risks in pregnant and lactating women, Risks in pediatric subjects, Risks in patients with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min), Risks in subjects with severe hepatic impairment (>Child-Pugh Class B), Risks in patients with brain metastasis, spinal cord compression, or carcinomatous meningitis, Risks in subjects with recent myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, deep vein thrombosis, or pulmonary embolism, Risks in patients with active peptic ulcer disease, Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks).

Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

In addition to the notification to the Pfizer safety department, suspected serious adverse reactions detected during the course of the study will be notified to the point of contact designated by the competent bodies in term of pharmacovigilance of the autonomous community from where the health professional exercises, within a maximum period of 15 calendar days since the suspicion of adverse reaction was known. This notification will be made electronically by the Pfizer pharmacovigilance manager.

Adverse Reactions (AR)

An AR is any harmful and unintended reaction to a research drug, regardless of the dose administered. Unlike an AA, in the case of an adverse reaction, there is a suspicion of a causal relationship between the investigational drug and the adverse event, and there is also talk of suspected RA (SAR).

10.3. DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event/AR*);

* Spain requirement only

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event/AR* are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

* Spain requirement only

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event/AR*. Any abnormal test result that is determined to be an error does not require reporting as an adverse event/AR*.

Serious adverse events/SAR*

A serious adverse event/SAR* is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events/AR*);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event/SAR* unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event/SAR*. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event/SAR* and as a serious adverse/SAR* event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event/reaction* is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event/reaction* may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

* Spain requirement only

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event/reaction* may be suspected from clinical symptoms or laboratory findings 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 handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE/AR* is not in itself an AE/AR* and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

* Spain requirement only

- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) *Sunitinib and/or Axitinib*, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to *Sunitinib and/or Axitinib* (maternal exposure).

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

2. A male has been exposed, either due to treatment or environmental exposure to *Sunitinib and/or Axitinib* prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE/SAR* reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with *Sunitinib and/or Axitinib*, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to *Sunitinib and/or Axitinib* in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

* Spain requirement only

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs/SAR* follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs/SAR* when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

<u>Exposure during breastfeeding</u>

* Spain requirement only

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE/RA*. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE/RA* associated with such a drug's administration, the AE/RA* is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

* Spain requirement only

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

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

10.4. ADVERSE EVENT REPORTING IN THE RETROSPECTIVE SETTING

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the *eCRF of this study* and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information

known regarding these adverse events. No follow-up on related adverse events will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)*" and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

10.5. COUNTRY REQUIREMENT

10.5.1. Switzerland Adverse Event Reporting in the Retrospective Setting

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) **regardless of possible attribution to a Pfizer drug**.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs that appear in the reviewed information must be recorded on the *eCRF of this study* and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

10.5.2. Notification of adverse events / adverse reactions in the retrospective area of Spain

This notification has not been expressly requested by the AEMPS at the time of registration of the study.

11. REFERENCES

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12. LIST OF TABLES

13. LIST OF FIGURES

ADONIS CRF

Subject ID:

ANNEX 1. CASE REPORT FORM

ADONIS

Axitinib In ADvanced / Metastatic Renal Cell CarcinOma - A Non-Interventional Study Of Real World Treatment Outcomes In Patients Receiving 2nd Line Axitinib After 1st Line Sunitinib

CASE REPORT FORM

Center identifier
Patient identifier

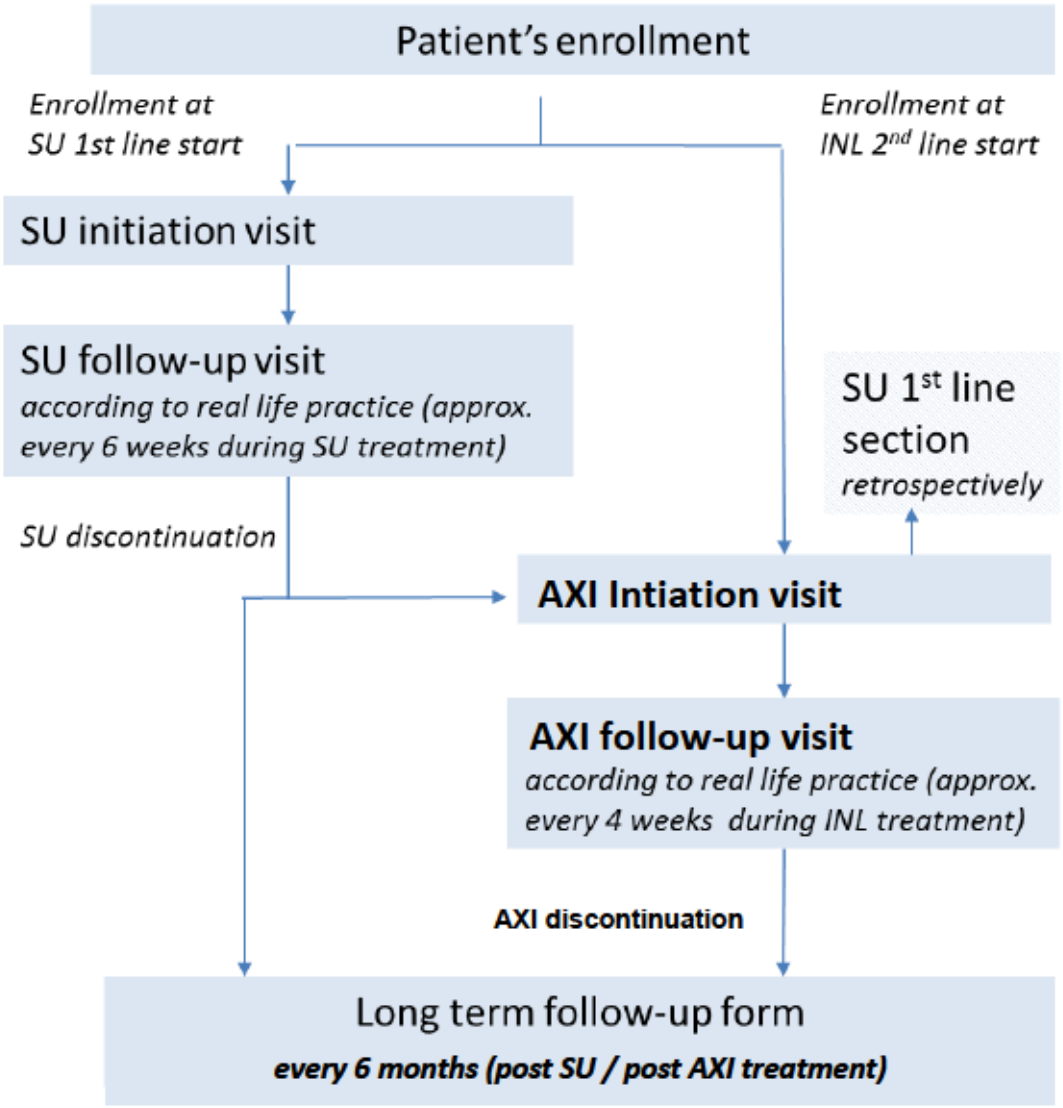
CRF V12.2 – 05 December 2014

ADONIS CRF

Subject ID:

1. STUDY PLAN

1.1. Visit Scheme



ADONIS CRF

Subject ID:

1.2. Study plan

Variable	At SU initiation visit	At SU follow-up visit	At AXI initiation visit	At AXI follow-up visit	Long term follow up
Patient demographics	x		x*		
Performance status	x	x	x	x	x
MSKCC risk, Heng risk	x		x		
Description of primary tumor	x		x*		
Metastasis	x		x		
Comorbidities	x		x		
Lab tests	x	x	x	x	
Blood Pressure measurement / antihypertensive treatment	x	x	x	x	
Electrocardiogram	x		x		
Echocardiography	x		x		
Sunitinib therapy	x	x	x**		
Axitinib therapy			x	x	
Other anti tumor treatment	x	x	x	x	x
Concomitant treatment	x	x	x	x	
Tumor Response		x		x	x
Safety	x	x	x	x	
Quality of life (FKSI-19, and MH and RE domains of SF-36)			x	x	
Death		x		x	x

** : only if patient is enrolled at Axitinib start / ** : retrospective records*

ADONIS CRF

Subject ID:

2. ENROLLMENT

Inclusion Date _|_|_ / _|_|_ / 20_|_|_ (DD/MM/YYYY) **Patient identifier** _|_|-_|_|_|_|_|

Inclusion criteria

1. Histologically confirmed diagnosis of advanced/metastatic renal carcinoma (clear cell RCC as well as non-clear cell RCC) with measurable disease according to RECIST 1.1 ☐ Yes ☐ No
2. Patient 18 years of age and over ☐ Yes ☐ No
3. Patients being treated with SU in 1st line according to the European approved therapeutic indication and/or being treated with AXI in 2nd line according to the European/ approved therapeutic indication except post cytokines) ☐ Yes ☐ No
4. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study ☐ Yes ☐ No

   date signed _|_|_ / _|_|_ / 20_|_|_ (DD/MM/YYYY)

"If one of these boxes is ticked "No", the patient must not be included in the study"

Non-inclusion criteria

5. Patients being treated with cytokines or any other treatment outside of Sunitinib in first line ☐ Yes ☐ No
6. Patients receiving anti –tumor treatment beyond a second line ☐ Yes ☐ No
7. Patients already under Sunitinib, already under Axitinib: enrollment must occur at the beginning of each line of treatment (before or at first follow up visit) ☐ Yes ☐ No

"If one of these boxes is ticked "Yes", the patient must not be included in the study"

After review all criteria above, is the patient included in the study? ☐ Yes ☐ No

If Yes, date of inclusion _|_|_ / _|_|_ / 20_|_|_ (DD/MM/YYYY)

If No, why? _____

Patient's Demographic data

Year of birth _|_|_|_|_ (YYYY) Body height _|_|_ cm

Sex ☐ male ☐ female Body weight _|_|_|,_| kg

The patient is included in the study with:

☐ SUNITINIB in first line ☐ AXITINIB in second line

If SUNITINIB is started, please go to the SUNITINIB section and complete the SUNITINIB initiation visit

If AXITINIB is started, please go to the AXITINIB section and complete the AXITINIB initiation visit

ADONIS CRF

Subject ID:

3. SUNITINIB FIRST LINE VISITS

Sunitinib Initiation Date _|_|/_|_|/20_|_| (DD/MM/YYYY) **Patient identifier** _|_|-_|_|-_|_|_|

3.1. SUNITINIB INITIATION VISIT

Patient characteristics when SUNITINIB is initiated

ECOG

Eastern Cooperative Oncology Group (ECOG) available ☐ Yes ☐ No

If yes, _|_| _|_|_|_|

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Karnofsky performance status

Karnofsky statusavailable ☐ Yes ☐ No

Classification to determine a patient's performance status

_|_| _|_| _|_|

Normal status, no complaints, no evidence of disease	☐	100%
Minor signs and symptoms of disease	☐	90%
Normal activities with efforts	☐	80%
Unable to carry on normal activity, unable to work, able to care for self	☐	70%
Requires occasional assistance	☐	60%
Requires nursing and medical care and assistance, not permanently bedridden	☐	50%
Bedridden, requires special care	☐	40%
Severely disabled, requires hospital care	☐	30%
Requires hospital care and supportive treatment	☐	20%
Moribund, disease progressing rapidly	☐	10%

MSKCC risk (first line) *(definition pop-up sur le site)*

☐ Good ☐ Poor

☐ Intermediate ☐ NA

Heng risk factors *(definition pop-up sur le site)*

☐ Good ☐ Poor

☐ Intermediate ☐ NA

ADONIS CRF

Subject ID:

Description of the disease

Primary Tumor

Date of Primary Tumor diagnosis *(histologically confirmed)* __/__ / __/__/__/__ (MM/YYYY)

pTNM state at patient' tumor diagnosis *(histologically confirmed)* T____ N____ M_____

Grading when primary tumor was diagnosed ☐ G1 ☐ G2 ☐ G3 ☐ G4 ☐ Unknown

Grading at patient' enrollment ☐ G1 ☐ G2 ☐ G3 ☐ G4

Type ☐ clear cell RCC ☐ non-clear cell RCC

Previous treatment for primary tumor

Surgery ☐ Yes ☐ No

If yes ☐ Right kidney ☐ Left kidney ☐ Both

Right side:	Left side:
☐ radical nephrectomy	☐ radical nephrectomy
☐ partial nephrectomy	☐ partial nephrectomy
Adrenalectomy ☐ Yes ☐ No	Adrenalectomy ☐ Yes ☐ No
Lymphadenectomy ☐ Yes ☐ No	Lymphadenectomy ☐ Yes ☐ No
☐ open path ☐ laparoscopic ☐ robotic	☐ open path ☐ laparoscopic ☐ robotic

Radiotherapy ☐ Yes ☐ No

Other ☐ Yes ☐ No

If yes, _____

Metastasis localization (confirmed by imaging procedure)

Metastasis : ☐ Yes ☐ No

Date of first metastasis detection __/__ / __/__/__/__ (MM/YYYY) ☐ Not applicable

Number of mestastis sites (localization) : __/__

Current localization

Lung	☐ Yes	☐ No	☐ Unknown	Skeletal system	☐ Yes	☐ No	☐ Unknown
Lymph node	☐ Yes	☐ No	☐ Unknown	Suprarenal gland	☐ Yes	☐ No	☐ Unknown
Liver	☐ Yes	☐ No	☐ Unknown	Kidney (contralateral)	☐ Yes	☐ No	☐ Unknown
CNS	☐ Yes	☐ No	☐ Unknown				
Other	☐ Yes : _____						

ADONIS CRF

Subject ID:

Treatment for metastasis

Surgery ☐ Yes ☐ No

If yes Number of surgeries __|__

Radiotherapy ☐ Yes ☐ No

Other ☐ Yes ☐ No

If yes, _____

Comorbidities

Comorbidity? ☐ Yes ☐ No

If yes, please specify

- ☐ Hypertension
- ☐ Chronic heart failure LVEF: _____ %
- ☐ Peripheral arterial occlusive disease
- ☐ History of myocardial infarction
- ☐ History of stroke (transient ischemic attack)
- ☐ History of venous thromboembolism
- ☐ Diabetes mellitus
- ☐ Lipopathy
- ☐ Impaired glucose tolerance
- ☐ Hyperthyroidism
- ☐ Hypothyroidism
- ☐ Chronic renal failure If yes ☐ mild ☐ moderate ☐ severe ☐ dialysis
- ☐ Chronic liver failure If yes ☐ mild ☐ moderate ☐ severe
- ☐ Chronic gastrointestinal disorders If yes, which _____
- ☐ Other cancer disease (malignant) If yes, which _____
- ☐ Dementia
- ☐ Depression
- ☐ Other *(please enter diagnosis)*:

1. _____
2. _____
3. _____

ADONIS CRF

Subject ID:

Concomitant treatment

Comedications ongoing or stopped in the last 15 days (other than tumor therapy) : ❑ Yes ❑ No

Please record all medications including non-prescription drugs which the patient is taking.

Drug name	Starting date	Status
_____	_I_I / _I _I_I_I (MM/YYYY)	□ Ongoing □ Discontinued End date _I_I / _I _I_I_I (MM/YYYY))
_____	_I_I / _I_I_I_I (MM/YYYY)	□ Ongoing □ Discontinued End date _I_I / _I _I_I_I (MM/YYYY))
_____	_I_I / _I_I_I_I (MM/YYYY)	□ Ongoing □ Discontinued End date _I_I / _I _I_I_I (MM/YYYY))

(new lines can be added if more than 3 treatments are received)

Please note that this table will be updated at each follow up visit

ADONIS CRF

Subject ID:

Laboratory test results ❑ Yes ❑ No

For the following parameters, please complete the table

Date of lab tests _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

LABORATORY PARAMETERS	LEVEL OBTAINED	LEVEL*	UNIT	OTHER UNIT, IF APPLICABLE
Hemoglobin	☐ Yes ☐ No		g/dL	
Calcium	☐ Yes ☐ No		mmol/L	
Albumin	☐ Yes ☐ No		g/L	
LDH	☐ Yes ☐ No		U/L	
Platelets	☐ Yes ☐ No		10^9/L	
Neutrophils	☐ Yes ☐ No		%	

Together with the Karnofsky performance status scale, the data obtained for hemoglobin, calcium, albumin, and LDH will be used to calculate the MSKCC risk score (in first line). For the Heng score, platelet and neutrophil are used.

For other biological parameters, please: indicate abnormal findings

LABORATORY PARAMETERS	Abnormal findings	*For abnormal findings, level	UNIT	OTHER UNIT, IF APPLICABLE
Creatinine	☐ Yes		mg/dL	
ALT (GPT)	☐ Yes		U/L	
AST (GOT)	☐ Yes		U/L	
Alkaline phosphatase	☐ Yes		U/L	
Total bilirubin	☐ Yes		mg/dL	
TSH	☐ Yes		mU/L	
fT3	☐ Yes		pmol/L	
fT4	☐ Yes		pmol/L	
Hematocrit	☐ Yes		%	
Phosphate	☐ Yes		mmol/L	
Glucose	☐ Yes		mmol/L	
Lymphocytes	☐ Yes		%	
Leucocytes	☐ Yes		10^9/L	
Sodium	☐ Yes		mmol/L	
Potassium	☐ Yes		mmol/L	
Magnesium	☐ Yes		mmol/L	
Cholesterol	☐ Yes		mmol/L	
Triglycerides	☐ Yes		mmol/L	

*** in case of clinically significant abnormal findings, also fill in "Comorbidities / Physical examination"** section *(the investigator can be redirected to this table to completed comorbidities)*

ADONIS CRF

Subject ID:

Other exams

At Sunitinib initiation, medical history of hypertension? ☐ Yes ☐ No

In case of hypertension, also complete "Comorbidities / Physical examination" with hypertension

Is the patient receiving an antihypertensive treatment? ☐ Yes ☐ No

If yes, please check that ongoing antihypertensive treatments are recorded in the concomitant treatment table (the table of concomitant treatment is displayed and the investigator can update the table if appropriate)

Blood pressure measurement :

Date of last measurement : _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Please specify levels of blood pressure; if several measurements have been done, please specify levels for every measurement

		Systolic (mmHg)	Diastolic (mmHg)
Measurement 1	☐ Not done	_|_|_	_|_|_
Measurement 2	☐ Not done	_|_|_	_|_|_
Measurement 3	☐ Not done	_|_|_	_|_|_

Electrocardiogram

☐ Yes ☐ No ⟶ If yes, please specify date: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Abnormal findings? ☐ Yes ☐ No

⟶ If yes, please specify*

- ☐ Atrial fibrillation
- ☐ Ventricular rhythm disorder
- ☐ AV-block
- ☐ Other _____

*** in case of clinically significant abnormal findings, also fill in "Comorbidities / Physical examination"section**
(the investigator can be redirected to this table to fill in comorbidities)

Echocardiography

☐ Yes ☐ No ⟶ If yes, please specify date: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

LVEF _|_| %

Abnormal findings? ☐ Yes ☐ No

If yes, please specify* _____

*** in case of clinically significant abnormal findings, also fill in "Comorbidities / Physical examination" section**
(the investigator can be redirected to this table to fill in comorbidities)

ADONIS CRF

Subject ID:

ADONIS CRF

Subject ID:

First line treatment

Therapy started with Sunitinib in first line

Therapy started with Sunitinib on _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

Dose: ☐ 50 mg/day, 4 weeks, then paused for 2 weeks

☐ other: _____

Additional anti-tumor treatment *(bisphosphonates, other)*

☐ Yes ☐ No

If yes please complete the table :

Medication	Dosage	Starting date	Status
_____ *(trade name)*	_|_|_|_| / _____ *(dose)* *(unit)*	_|_| / _| _|_|_| (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :_|_| / _|_|_|_| (MM/YYYY)
_____ *(trade name)*	_|_|_|_| / _____ *(dose)* *(unit)*	_|_| / _| _|_|_| (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :_|_| / _|_|_|_| (MM/YYYY)

(new lines can be added if more than 2 medications are received)

Please note that supportive treatment (eg. pain killers) are completed in the concomitant table :

Radiotherapy

☐ Yes ☐ No

Please complete the "Follow-up visit" at each visit until discontinuation of Sunitinib

Follow up visits are not scheduled by the study ; they are based on routine care visits (approximately every 6 weeks)

ADONIS CRF **Subject ID:**

3.2. SUNITINIB Follow up VISIT

Sunitinib follow-up visit Date _|_|/_|_|/20_|_| (DD/MM/YYYY) Patient identifier _|_|

Tumor assessment according to RECIST criteria (v1.1)

Was tumor assessment done since last visit? ☐ **Yes** ☐ **No**

Date of the assessment _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

Imaging procedure *(multiple selections possible)*

☐ CT ☐ Chest X-ray ☐ MRI ☐ Ultrasound ☐ Bone scan

Response to therapy :

☐ CR (Complete Remission)

☐ PR (Partial Remission)

☐ SD (Stable Disease)

☐ PD (Progressive Disease)

☐ NA (Not Assessable) Reason: _____

Clinical parameters

Eastern Cooperative Oncology Group (ECOG) available ☐ **Yes** ☐ **No**

If yes, ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Blood pressure measurement

☐ Yes ☐ No If yes, please specify date: _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

Please specify levels; if several measurements have been done, please specify levels for every measurement

		Systolic (mmHg)	Diastolic (mmHg)
Measurement 1	☐ Not done	_|_|_	_|_|_
Measurement 2	☐ Not done	_|_|_	_|_|_
Measurement 3	☐ Not done	_|_|_	_|_|_

Changes in the antihypertensive treatment since last visit: ☐ Yes ☐ No

If yes, Date _|_|/_|_|/_|_|_|_| (DD/MM/YYYY

If yes, changes in the antihypertensive treatment were

☐ dose increase
☐ dose reduction
☐ changes of drugs
additional antihypertensive therapy

If changes of drugs, please update the concomitant treatment table *(the table of concomitant treatment is displayed and the investigator can update the table if appropriate)*

ADONIS CRF **Subject ID:**

ADONIS CRF **Subject ID:**

Laboratory test results

New lab test results ☐ Yes ☐ No (the CRF displays the date of lab test results at the last visit)

if yes date of the last lab test results _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

If yes please complete the table with new results

For the following parameters, please complete the table

LABORATORY PARAMETERS	LEVEL OBTAINED	LEVEL*	UNIT	OTHER UNIT, IF APPLICABLE
Hemoglobin	☐ Yes ☐ No		g/dL	
Calcium	☐ Yes ☐ No		mmol/L	
Albumin	☐ Yes ☐ No		g/L	
LDH	☐ Yes ☐ No		U/L	
Platelets	☐ Yes ☐ No		10^9/L	
Neutrophils	☐ Yes ☐ No		%	

For other biological parameters, please: indicate abnormal findings

LABORATORY PARAMETERS	LEVEL OBTAINED	LEVEL*	UNIT	OTHER UNIT, IF APPLICABLE
Creatinine	☐ Yes		mg/dL	
ALT (GPT)	☐ Yes		U/L	
AST (GOT)	☐ Yes		U/L	
Alkaline phosphatase	☐ Yes		U/L	
Total bilirubin	☐ Yes		mg/dL	
TSH	☐ Yes		mU/L	
fT3	☐ Yes		pmol/L	
fT4	☐ Yes		pmol/L	
Hematocrit	☐ Yes		%	
Phosphate	☐ Yes		mmol/L	
Glucose	☐ Yes		mmol/L	
Lymphocytes	☐ Yes		%	
Leucocytes	☐ Yes		10^9/L	
Sodium	☐ Yes		mmol/L	
Potassium	☐ Yes		mmol/L	
Magnesium	☐ Yes		mmol/L	
Cholesterol	☐ Yes		mmol/L	
Triglycerides	☐ Yes		mmol/L	

ADONIS CRF **Subject ID:**

Sunitinib therapy

(the CRF displays the dosage scheduled at the previous visit)

Have Sunitinib dosage and/or schedule been changed since the last documented visit (including during this visit)?

☐ Yes ☐ No

If yes please specify every change :

Date	Change of dosage	If yes, new dosage (mg/day)	Change of schedule	If yes, new schedule
__ / __ / _____ (DD/MM/YYYY)	☐ Yes ☐ No	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ 75 ☐ Other: __	☐ Yes ☐ No	_____ _____
__ / __ / _____ (DD/MM/YYYY)	☐ Yes ☐ No	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ 75 ☐ Other: __	☐ Yes ☐ No	_____ _____

(new lines can be added if more than 2 changes have occurred)

Has Sunitinib been temporarily interrupted since last visit ? ☐ Yes ☐ No

If yes please specify every interruption :

First day of interruption	Duration in days	If yes, reason :
__ / __ / _____ (DD/MM/YYYY)	__	☐ Adverse events ☐ Radiotherapy ☐ Surgery ☐ Other _____
__ / __ / _____ (DD/MM/YYYY)	__	Adverse events ☐ Radiotherapy ☐ Surgery ☐ Other _____

(new lines can be added if more than 2 interruptions have occurred)

ADONIS CRF **Subject ID:**

Other treatments

Additional anti-tumor treatment *(e.g. bisphosphonates, other)*

(the previous visit anti-tumor treatment table is dispalyed)

Has additional anti-tumor treatment been changed since last visit (including during this visit)? ☐ Yes ☐ No

If yes please update the table :

Medication	Dosage	Starting date	Status
_____ *(trade name)*	_____ / _____ *(dose)* *(unit)*	___ / __ _____ (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :___ / _____ (MM/YYYY)
_____ *(trade name)*	_____ / _____ *(dose)* *(unit)*	___ / __ _____ (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :___ / _____ (MM/YYYY)

(new lines can be added if more than 2 medications are received)

Radiotherapy : ☐ Yes ☐ No

Comedications (other than tumor therapy) :

(the previous visit comedication table is displayed)

Have comedications been changed since last visit (including during this visit)? ☐ Yes ☐ No

If yes please update the table :

Drug name	Starting date	Status
_____	___ / __ _____ (MM/YYYY)	☐ Ongoing ☐ Discontinued End date ___ / __ _____ (MM/YYYY))
_____	___ / ______ (MM/YYYY)	☐ Ongoing ☐ Discontinued End date ___ / __ _____ (MM/YYYY))

(new lines can be added if more than 3 treatment s are received)

ADONIS CRF **Subject ID:**

Occurrence of adverse events

Has the patient experienced adverse events since last visit? ☐ Yes ☐ No

If yes please report the adverse events in the following table and asses the grade using the CTCAE V4.03 (this version is reachable via ta click)

Adverse event description	Starting date	Grade (CTCAE V4.03)
_____	___ /___ / __ _____ (DD/MM/YYYY)	☐ 1 ☐ 2 ☐ 3 ☐ 4
_____	___ /___ / __ _____ (DD/MM/YYYY)	☐ 1 ☐ 2 ☐ 3 ☐ 4

(new lines can be added if more than AR have occured)

Please completed an AE form per AE reported in the table (AE form is attached in annex 2)

(The eCRF, automatically completes any section when data are already available ; the pre-completed sections are still editable /An AE form per AE is completed

The safety requirement as described in the protocol are reminded via a click)

ADONIS CRF **Subject ID:**

Actions done at the end of this visit with Sunitinib

☐ Continuation : ***Please completed this same form at the next visit***

☐ Temporary Interruption ***Please update the temporary interruption table***
(the table is displayed to the investigator)

☐ Discontinuation

If discontinuation, reasons of discontinuation (no multiple selections)

☐ Progression, Date __/__/____ (DD/MM/YYYY)

☐ Intolerability Date __/__/____ (DD/MM/YYYY)

main reason: _____

☐ Death Date of death __/__/____ (DD/MM/YYYY)

Cause: ☐ tumor-related

☐ other cause _____

Please observe the definitions and AE reporting requirements as defined in the protocol

If discontinuation, will the patient start a 2nd line therapy? ☐ Yes ☐ No

If yes, which drug will the patient receive?

☐ Axitinib, Date of start __/__/____ (DD/MM/YYYY)

Please complete the "Axitinib initiation visit" section

☐ Other,

Name of the drug _____

Date of start __/__/____ (DD/MM/YYYY)

Dose ____

Scheduled _____

Please completed the long term follow-up visit every 6 months

Please complete the "Follow-up visit" at each visit until discontinuation of Sunitinib

Follow up visit s are not scheduled by the study but are based on routine care visits. They are not expected to be more frequent than every 6 weeks

ADONIS CRF **Subject ID:**

4. AXITINIB SECOND LINE VISITS

4.1. AXITINIB INITIATION VISIT

Axitinib Initiation Date _|_| / _|_| / 20_|_| (DD/MM/YYYY) **Patient identifier** _|_|

This visit is performed when the patient starts Axitinib in second line.

- **If the patient was enrolled in the study when Sunitinib started in first line, please only fill in sections that need an update**
- **If the patient is enrolled at this stage (Axitinib start) please complete every section as well as the Sunitinib retrospective section that you will find at the end of the visit**

Patient characteristics at Axitinib initiation

Weight |__|__|__| Kg *(only for patient enrolled at Sunitinib start),*

ECOG

Eastern Cooperative Oncology Group (ECOG) available ☐ **Yes** ☐ **No**

If yes, _|_| _|_|_|_|

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Karnofsky performance status

Karnofsky status available ☐ **Yes** ☐ **No**

Classification to determine a patient's performance status

_|_| _|_| _|_|

Normal status, no complaints, no evidence of disease	☐ 100%
Minor signs and symptoms of disease	☐ 90%
Normal activities with efforts	☐ 80%
Unable to carry on normal activity, unable to work, able to care for self	☐ 70%
Requires occasional assistance	☐ 60%
Requires nursing and medical care and assistance, not permanently bedridden	☐ 50%
Bedridden, requires special care	☐ 40%
Severely disabled, requires hospital care	☐ 30%
Requires hospital care and supportive treatment	☐ 20%
Moribund, disease progressing rapidly	☐ 10%

MSKCC risk (second line line) *(the definition of 2nd line MSKCC is reachable via a click)*

☐ Good ☐ Poor

☐ Intermediate ☐ NA

ADONIS CRF **Subject ID:**

Description of the disease

Primary Tumor *(only for patient enrolled at Axitinib start)*

Date of Primary Tumor diagnosis *(histologically confirmed)* _|_| / _|_|_|_| (MM/YYYY)

pTNM state at patient' tumor diagnosis *(histologically confirmed)* T____ N____ M_____

Grading when primary tumor was diagnosed ☐ G1 ☐ G2 ☐ G3 ☐ G4 ☐ Unknown

Grading at patient' enrollment ☐ G1 ☐ G2 ☐ G3 ☐ G4

Type ☐ clear cell RCC ☐ non-clear cell RCC

Previous treatment for primary tumor *(only for patient enrolled at Axitinib start)*

Surgery ☐ Yes ☐ No

If yes ☐ Right kidney ☐ Left kidney ☐ Both

Right side:	Left side:
☐ radical nephrectomy	☐ radical nephrectomy
☐ partial nephrectomy	☐ partial nephrectomy
Adrenalectomy ☐ Yes ☐ No	Adrenalectomy ☐ Yes ☐ No
Lymphadenectomy ☐ Yes ☐ No	Lymphadenectomy ☐ Yes ☐ No
☐ open path ☐ laparoscopic ☐ robotic	☐ open path ☐ laparoscopic ☐ robotic

Radiotherapy ☐ Yes ☐ No

Other ☐ Yes ☐ No

If yes, _____

Metastasis localization (confirmed by imaging procedure)

please update this section if changes have occurred ☐ No changes *(for patient enrolled at Sunitinib start),*

Metastasis : ☐ Yes ☐ No

Date of first metastasis detection _|_| / _|_|_|_| (MM/YYYY) ☐ Not applicable

Number of mestastis sites (localization): _|_|

Current localization :

Lung	☐ Yes	☐ No	☐ Unknown	Skeletal system	☐ Yes	☐ No	☐ Unknown
Lymph node	☐ Yes	☐ No	☐ Unknown	Suprarenal gland	☐ Yes	☐ No	☐ Unknown
Liver	☐ Yes	☐ No	☐ Unknown	Kidney (contralateral)	☐ Yes	☐ No	☐ Unknown
CNS	☐ Yes	☐ No	☐ Unknown				
Other							

ADONIS CRF **Subject ID:**

Treatment for metastasis

only for patient enrolled at Sunitinib start), **please update this section if changes have occurred** ☐ No changes

Surgery	☐ Yes	☐ No
	If yes	Number of surgeries ___
Radiotherapy	☐ Yes	☐ No
Other	☐ Yes	☐ No
	If yes,	_____

Comorbidities

ADONIS CRF **Subject ID:**

(only for patient enrolled at Sunitinib start), **please update this section if changes have occurred** ☐ No changes

Comorbidity ☐ Yes ☐ No

If yes, which?

- ☐ Hypertension
- ☐ Chronic heart failure LVEF: _____ %
- ☐ Peripheral arterial occlusive disease
- ☐ History of myocardial infarction
- ☐ History of stroke/(transient ischemic attack)
- ☐ History of venous thromboembolism
- ☐ Diabetes mellitus
- ☐ Lipopathy
- ☐ Impaired glucose tolerance
- ☐ Hyperthyroidism
- ☐ Hypothyroidism
- ☐ Chronic renal failure If yes ☐ mild ☐ moderate ☐ severe ☐ dialysis
- ☐ Chronic liver failure If yes ☐ mild ☐ moderate ☐ severe
- ☐ Chronic gastrointestinal disorders If yes, which _____
- ☐ Other cancer disease (malignant) If yes, which _____
- ☐ Dementia
- ☐ Depression
- ☐ Other *(please enter diagnosis)*:
  1. _____
  2. _____
  3. _____

ADONIS CRF **Subject ID:**

Concomitant treatment

(for patient enrolled at Axitinib start)

Comedications ongoing or stopped in the last 15 days (other than tumor therapy) : ❑ Yes ❑ No

(for patient enrolled at Sunitinib start)

(the comedication table is shown to the investigator)

Have comedications been changed since last visit? ☐ Yes ☐ No

If yes please complete / update the following table :

Drug name	Starting date	Status
_____	_I_I / _I _I_I_I (MM/YYYY)	☐ Ongoing ☐ Discontinued End date _I_I / _I _I_I_I (MM/YYYY))
_____	_I_I / _I_I_I_I (MM/YYYY)	☐ Ongoing ☐ Discontinued End date _I_I / _I _I_I_I (MM/YYYY))
_____	_I_I / _I_I_I_I (MM/YYYY)	☐ Ongoing ☐ Discontinued End date _I_I / _I _I_I_I (MM/YYYY))

(if the patients started the study with Sunitinib, the table completed during SU follow up is displayed to be updated / new lines can be added if more than 3 treatment s are received)

Please note that this table will be updated at each follow up visit

ADONIS CRF **Subject ID:**

Laboratory test results: ❑ Yes ❑ No

☐ No new lab tests since Sunitinib discontinuation *(for patient enrolled at Sunitinib start)*

☐ New lab tests results date _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

For the following parameters, please complete the table

LABORATORY PARAMETERS	LEVEL OBTAINED	LEVEL*	UNIT	OTHER UNIT, IF APPLICABLE
Hemoglobin	☐ Yes ☐ No		g/dL	
Calcium	☐ Yes ☐ No		mmol/L	
Albumin	☐ Yes ☐ No		g/L	
LDH	☐ Yes ☐ No		U/L	
Platelets	☐ Yes ☐ No		10^9/L	
Neutrophils	☐ Yes ☐ No		%	

For other biological parameters, please: indicate any abnormal finding

LABORATORY PARAMETERS	Abnormal finding	For abnormal finding, level	UNIT	OTHER UNIT, IF APPLICABLE
Creatinine	☐ Yes		mg/dL	
ALT (GPT)	☐ Yes		U/L	
AST (GOT)	☐ Yes		U/L	
Alkaline phosphatase	☐ Yes		U/L	
Total bilirubin	☐ Yes		mg/dL	
TSH	☐ Yes		mU/L	
fT3	☐ Yes		pmol/L	
fT4	☐ Yes		pmol/L	
Hematocrit	☐ Yes		%	
Phosphate	☐ Yes		mmol/L	
Glucose	☐ Yes		mmol/L	
Lymphocytes	☐ Yes		%	
Leucocytes	☐ Yes		10^9/L	
Sodium	☐ Yes		mmol/L	
Potassium	☐ Yes		mmol/L	
Magnesium	☐ Yes		mmol/L	
Cholesterol	☐ Yes		mmol/L	
Triglycerides	☐ Yes		mmol/L	

*** in case of clinically significant abnormal findings, also enter at "Comorbidities / Physical examination"** *(the investigator can be redirected to this table to completed comorbidities)*

ADONIS CRF **Subject ID:**

ADONIS CRF **Subject ID:**

Other exams

At Axitinib initiation, medical history of hypertension? ☐ Yes ☐ No

In case of hypertension, also complete "Comorbidities / Physical examination" with hypertension

Blood Pressure measurement

Date of last measurement : _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Please specify levels of blood pressure; if several measurements have been done, please specify levels for every measurement

		Systolic (mmHg)	Diastolic (mmHg)
Measurement 1	☐ Not done	_|_|_	_|_|_
Measurement 2	☐ Not done	_|_|_	_|_|_
Measurement 3	☐ Not done	_|_|_	_|_|_

Is the patient receiving an antihypertensive treatment? ☐ Yes ☐ No

Changes in the antihypertensive treatment since last visit : ☐ Yes ☐ No *(for patient enrolled at Sunitinib start)*

If yes, Date _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

If yes, changes in the antihypertensive treatment were

☐ dose increase

☐ dose reduction

☐ changes of drugs

additional antihypertensive therapy

If changes of drugs, please update the concomitant treatment table *(the table of concomitant treatment is displayed and the investigator can update the table if appropriate)*

Electrocardiogram

☐ Yes ☐ No → If yes, please specify date: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Abnormal findings? ☐ Yes ☐ No

If yes, please specify ☐ Atrial fibrillation

☐ Ventricular rhythm disorder

☐ AV-block

☐ Other _____

*** in case of clinically significant abnormal findings, also fill in "Comorbidities / Physical examination"section** *(the investigator can be redirected to this table to fill in comorbidities*

ADONIS CRF **Subject ID:**

Echocardiography

☐ Yes ☐ No → If yes, please specify date: __ __ / __ __ / __ __ __ __ (DD/MM/YYYY)

LVEF __ __ %

Abnormal findings? ☐ Yes ☐ No

If yes, please specify* _____

*** in case of clinically significant abnormal findings, also fill in "Comorbidities / Physical examination" section**
(the investigator can be redirected to this table to fill in comorbidities

ADONIS CRF **Subject ID:**

Tumor second line treatment

Therapy started with Axitinib in 2nd line

Therapy started with Axitinib on _|_|/_|_|/_|_|_|_|

Dose: ☐ 5 mg/2x/day

☐ other: _____

Additional anti-tumor treatment *(e.g. bisphosphonates, other)*

☐ Yes ☐ No

If yes please complete the table :

Medication	Dosage	Starting date	Status
_____ *(trade name)*	_|_|_|_| / _____ *(dose)* *(unit)*	_|_| / _| _|_|_| (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :_|_| / _|_|_|_| (MM/YYYY)
_____ *(trade name)*	_|_|_|_| / _____ *(dose)* *(unit)*	_|_| / _| _|_|_| (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :_|_| / _|_|_|_| (MM/YYYY)

(if the patients started the study with Sunitinib, the table completed during SU follow up is displayed to be updated - new lines can be added if more than 2 medications are received)

Radiotherapy

☐ Yes ☐ No

If the patient is enrolled in the study when AXITINIB is started, please complete the page "Prior treatment with Sunitinib in first line"

If the patient was enrolled in the study when SUNITINIB was started in first line, please complete the page "Follow-up visit with Axitinib" at each visit until discontinuation of Axitinib (approximately every 1 month)

Please, remit the quality of life questionnaire to the patient and ask him/ her to complete it at every month at home (i.e Day 0 Day 30 Day 60 etc.)

ADONIS CRF **Subject ID:**

Prior treatment with Sunitinib in first line

Please only fill in this section, if patient is enrolled In the study at Axitinib start

Baseline characteristics at the start of Sunitinib

Eastern Cooperative Oncology Group (ECOG) available ☐ **Yes** ☐ **No**

If yes, _|_| _|_|_|_|

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

MSKCC risk **(first line)** *(the definition of 1st line MSKCC is reachable via a click on the study website)*

☐ Good ☐ Poor

☐ Intermediate ☐ NA

Heng risk factors (*the definition is reachable via a click on the study website)*

☐ Good ☐ Poor

☐ Intermediate ☐ NA

At Sunitinib initiation, medical history of hypertension? ☐ Yes ☐ No

At Sunitinib initiation was patient receiving an antihypertensive treatment? ☐ Yes ☐ No

Therapy with Sunitinib in first line

Therapy started with Sunitinib on _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Dose at initiation : ☐ 50 mg/day, 4 weeks, then paused for 2 weeks

☐ other: _____

Therapy discontinuation on _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Efficacy

What was the best response with Sunitinib (according to RECIST criteria (v1.1)?

☐ CR (Complete Remission) Date _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

☐ PR (Partial Remission) Date _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

☐ SD (Stable Disease)

☐ PD (Progressive Disease)

☐ NA (Not Assessable) Reason: _____

ADONIS CRF **Subject ID:**

Changes in dosage and schedule

Was Sunitinib dosage or schedule changed during Sunitinib course? ☐ Yes ☐ No

If yes please specify changes :

Date	Change of dosage	If yes, new dosage (mg/day)	Change of schedule	If yes, new schedule
__ / __ / _____ (DD/MM/YYYY)	☐ Yes ☐ No	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ 75 ☐ Other: __	☐ Yes ☐ No	_____ _____
__ / __ / _____ (DD/MM/YYYY)	☐ Yes ☐ No	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ 75 ☐ Other: __	☐ Yes ☐ No	_____ _____

(new lines can be added if more than 2 changes occurred)

Was Sunitinib temporarily interrupted during the course? ☐ Yes ☐ No

If yes please specify interruptions :

First day of interruption	Duration in days	If yes, reason
__ / __ / _____ (DD/MM/YYYY)	__	☐ Adverse events ☐ Radiotherapy ☐ Surgery ☐ Other _____
__ / __ / _____ (DD/MM/YYYY)	__	Adverse events ☐ Radiotherapy ☐ Surgery ☐ Other _____

(new lines can be added if more than 2 interruptions occurred)

Reason for discontinuation of SUNITINIB ☐ Yes ☐ No

☐ Progression, Date __ / __ / _____ (DD/MM/YYYY)

☐ Intolerance Date __ / __ / _____ (DD/MM/YYYY)

Please specify the symptom which you considered decisive

(main reason) _____

☐ Other

Please observe the definitions and AE and serious AE reporting requirements in the protocol.

ADONIS CRF **Subject ID:**

Has the patient experienced adverse events related to Sunitinib during the treatment course?

☐ Yes ☐ No

If yes please report the adverse events in the following table and asses the grade using the CTCAE V4.03
(this version is reachable via le lien)

Adverse event description	Starting date	Grade (CTCAE V4.03)
_____	___/___/_____ (DD/MM/YYYY)	☐ 1 ☐ 2 ☐ 3 ☐ 4
_____	___/___/_____ (DD/MM/YYYY)	☐ 1 ☐ 2 ☐ 3 ☐ 4

(new lines can be added if more than AR have occurred)

Please completed an AE form per AE reported in the table (AE form is attached in annex 2)

(The eCRF, automatically completes any section when data are already available ; the pre-completed sections are still editable /An AE form per AE is completed

The safety requirement as described in the protocol are reminded via a click)

ADONIS CRF

4.2. AXITINIB Follow-up VISIT

Axitinib follow-up visit Date _|_| / _|_| / 20_|_| (DD/MM/YYYY) Patient identifier _|_|

Please check that the patient has completed the QoL questionnaire before coming at the visit

If not, please ask him to complete the questionnaire, preferentially prior to the visit

Tumor assessment according to RECIST criteria (V1.1)

Was tumor assessment done since last visit? ☐ **Yes** ☐ **No**

Date of the assessment _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Imaging procedure *(multiple selections possible)*

☐ CT ☐ Chest X-ray ☐ MRI ☐ Ultrasound ☐ Bone scan

Response to therapy :

☐ CR (Complete Remission)

☐ PR (Partial Remission)

☐ SD (Stable Disease)

☐ PD (Progressive Disease)

☐ NA (Not Assessable) Reason: _____

Clinical parameters

Blood pressure measurement

☐ Yes ☐ No If yes, please specify date: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Please specify levels; if several measurements have been done, please specify levels for every measurement

		Systolic (mmHg)	Diastolic (mmHg)
Measurement 1	☐ Not done	_|_|_	_|_|_
Measurement 2	☐ Not done	_|_|_	_|_|_
Measurement 3	☐ Not done	_|_|_	_|_|_

Changes in the antihypertensive treatment since last visit: ☐ Yes ☐ No

If yes, Date _|_| / _|_| / _|_|_|_| (DD/MM/YYYY

If yes, changes in the antihypertensive treatment were

☐ dose increase
☐ dose reduction
☐ changes of drugs
☐ additional antihypertensive therapy

If changes of drugs, please update the concomitant treatment table *(the table of concomitant treatment is displayed and the investigator can update the table if appropriate)*

Eastern Cooperative Oncology Group (ECOG) available ☐ Yes ☐ No

ADONIS CRF

If yes, ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Laboratory test results

New lab test results ☐ Yes ☐ No (the CRF displays the date of lab test results at the last visit)

if yes date of the last lab test results _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

For the following parameters, please complete the table

LABORATORY PARAMETERS	LEVEL OBTAINED	LEVEL*	UNIT	OTHER UNIT, IF APPLICABLE
Hemoglobin	☐ Yes ☐ No		g/dL	
Calcium	☐ Yes ☐ No		mmol/L	
Albumin	☐ Yes ☐ No		g/L	
LDH	☐ Yes ☐ No		U/L	
Platelets	☐ Yes ☐ No		10^9/L	
Neutrophils	☐ Yes ☐ No		%	

For other biological parameters, please: indicate any abnormal findings

LABORATORY PARAMETERS	LEVEL OBTAINED	LEVEL*	UNIT	OTHER UNIT, IF APPLICABLE
Creatinine	☐ Yes		mg/dL	
ALT (GPT)	☐ Yes		U/L	
AST (GOT)	☐ Yes		U/L	
Alkaline phosphatase	☐ Yes		U/L	
Total bilirubin	☐ Yes		mg/dL	
TSH	☐ Yes		mU/L	
fT3	☐ Yes		pmol/L	
fT4	☐ Yes		pmol/L	
Hematocrit	☐ Yes		%	
Phosphate	☐ Yes		mmol/L	
Glucose	☐ Yes		mmol/L	
Lymphocytes	☐ Yes		%	
Leucocytes	☐ Yes		10^9/L	
Sodium	☐ Yes		mmol/L	
Potassium	☐ Yes		mmol/L	
Magnesium	☐ Yes		mmol/L	
Cholesterol	☐ Yes		mmol/L	
Triglycerides	☐ Yes		mmol/L	

ADONIS CRF

Axitinib therapy

Current Axitinib dosage

(the CRF displays the dosage scheduled at the previous visit)

Has the Axitinib dosage or schedule been changed since the last documented visit (including during this visit)?

☐ Yes ☐ No

If yes please specify changes :

Date	Dose reduction		Dose titration up	
___ / ___ / _____ (DD/MM/YYYY)	☐ Yes ☐ No	new dosage ☐ 7 mg/2x/day ☐ 5 mg/2x/day ☐ 3mg/2x/day ☐ 2mg/2x/day ☐ Other: ___mg/2x/day	☐ Yes ☐ No	new dosage ☐ 10 mg/2x/day ☐ 7 mg/2x/day ☐ 5 mg/2x/day ☐ 3mg/2x/day ☐ Other: ___mg/2x/day
	Reason for dose reduction ☐ Intolerance ☐ Other, _____		Reason for dose titration up ☐ Good tolerance ☐ Inefficacity ☐ Other, _____	

(new lines can be added if more changes have occurred)

Has Axitinib been temporarily interrupted since last visit? ☐ Yes ☐ No

If yes please specify interruptions :

First day of interruption	Duration in days	If yes, new schedule
___ / ___ / _____ (DD/MM/YYYY)	___	☐ Adverse events ☐ Radiotherapy ☐ Surgery ☐ Other _____

(new lines can be added if more than 2 interruptions occurred)

ADONIS CRF

Other treatments

Additional anti-tumor treatment *(e.g. bisphosphonates, others)*

(the previous visit anti-tumor treatment table is displayed)

Has additional anti-tumor treatment been changed since last visit (including during this visit) ? ☐ Yes ☐ No

If yes please update the table :

Medication	Dosage	Starting date	Status
_____ *(trade name)*	_____ / _____ *(dose)* *(unit)*	__ / _ ____ (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :__ / _____ (MM/YYYY)
_____ *(trade name)*	_____ / _____ *(dose)* *(unit)*	__ / _ ____ (MM/YYYY)	❑ Ongoing ❑ Discontinued End date :__ / _____ (MM/YYYY)

(new lines can be added if more than 2 medications are received)

Radiotherapy : ☐ Yes ☐ No

Comedications (other than tumor therapy) : (the previous visit comedication table is displayed)

Have comedications been changed since last visit (including during this visit)? ☐ Yes ☐ No

If yes please update the table :

Drug name	Starting date	Status
_____	__ / _ ____ (MM/YYYY)	☐ Ongoing ☐ Discontinued End date __ / _ ____ (MM/YYYY))
_____	__ / _____ (MM/YYYY)	☐ Ongoing ☐ Discontinued End date __ / _ ____ (MM/YYYY))

(new lines can be added if more than 2 treatment s are received)

ADONIS CRF

Safety

Has the patient experienced adverse events related to Sunitinib during the treatment course?

☐ Yes ☐ No

If yes please report the adverse events in the following table and asses the grade using the CTCAE V4.03 (this version is reachable via ta click)

Adverse event description	Starting date	Grade (CTCAE V4.03)
_____	___/___/_____ (DD/MM/YYYY)	☐ 1 ☐ 2 ☐ 3 ☐ 4
_____	___/___/_____ (DD/MM/YYYY)	☐ 1 ☐ 2 ☐ 3 ☐ 4

(new lines can be added if more than AR have occured)

Please completed an AE form per AE reported in the table (AE form is attached in annex 2)

(The eCRF, automatically completes any section when data are already available ; the pre-completed sections are still editable /An AE form per AE is completed / The safety requirement as described in the protocol are reminded via a click)

ADONIS CRF

Actions done at the end of this visit with AXITINIB

☐ Continuation : ***Please completed this same form at the next visit***

☐ Temporary Interruption ***Please update the temporary interruption table***
(the table is displayed to the investigator)

☐ Discontinuation

If discontinuation, reasons of discontinuation (no multiple selections)

☐ Progression Date _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

☐ Intolerability Date _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

main reason _____

☐ Death Date of death _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

Cause ☐ tumor-related ☐ other cause _____

Please observe the definitions and AE and reporting as defined in the protocol

If discontinuation, will the patient start a 3nd line therapy? : ☐ Yes ☐ No

If yes, which drug will the patient receive?

Name of the drug _____

Date of start _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

Dose _|_|_|

Scheduled _____

Please completed the long term follow-up visit every 6 months

Please complete the "Follow-up visit" at each visit until discontinuation of Sunitinib

Follow up visit are not scheduled by the study but are based on routine care visits. They are expected to approximately every 4 weeks

ADONIS CRF **Subject ID:**

5. LONG TERM FOLLOW-UP FORM

Long term follow-up visit Date _|_| / _|_| / 20_|_| (DD/MM/YYYY) **Patient identifier** _|_|

Patient no longer treated with Sunitinib or Axitinib

Eastern Cooperative Oncology Group (ECOG) available

If yes, ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Death ? ☐ Yes ☐ No

If yes, Date of death _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Cause ☐ tumor-related ☐ other cause _____

Please observe the definitions and AE and serious AE reporting as defined in the protocol

Has the patient received any treatment for mRCC since last visit?

☐ Yes ☐ No

If yes, please update the following table :

Drug name	Starting date	Status	Reason for discontinuation
_____ Line : ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ other : --- Best response ☐ CR ☐ PR ☐ SD ☐ PD ☐ NA	_|_| / _| _|_|_| (MM/YYYY)	☐ Ongoing ☐ Discontinued End date _|_| / _| _|_|_| (MM/YYYY)	☐ Progressive disease Date : _|_| / _|_| / _|_|_|_| ☐ Intolerance ☐ other _____
_____ Line : ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ other : ---- Best response ☐ CR ☐ PR ☐ SD ☐ PD ☐ NA	_|_| / _|_|_|_| (MM/YYYY)	☐ Ongoing ☐ Discontinued End date _|_| / _| _|_|_| (MM/YYYY)	☐ Progression disease Date : _|_| / _|_| / _|_|_|_| ☐ Intolerance ☐ other _____

(new lines can be added if more than 2 lines are received) (Not Assessable)

Occurrence of adverse events

Has the patient experienced adverse events since last visit? ☐ Yes ☐ No

(The eCRF, automatically completes any section when data are already available ; the pre-completed sections are still editable / An AE form per AE is completed

The safety requirement as described in the protocol are reminded via a click)

ADONIS CRF **Subject ID:**

Please complete this form every 6 months until end of the study

ADONIS CRF **Subject ID:**

6. STUDY DISCONTINUATION

Study Discontinuation

Please complete this form in case of study discontinuation during the study at any time of the study for any reason

Date of study discontinuation : _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Reason for study discontinuation

☐ Subject did not show up again (e.g. moved away), "Lost to follow-up",

☐ Subject was enrolled in another clinical study

☐ Subject's request / withdrawal of subject's consent

☐ Death

☐ Other, please specify : _____

If the patient is alive at study discontinuation:

Date of the last visit with the patient at the site _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

If the patient was treated with Sunitinib / Axitinib* at the previous visit :

Sunitinib /Axitinib* status at the last visit date : ☐ Ongoing ☐ Discontinued

End date _|_| / _| _|_|_| (MM/YYYY)

Reason for discontinuation

☐ Progression disease Date : _|_| / _|_| / _|_|_|_|

☐ Intolerance

☐ other _____

*: name to be selected according to the line of the treatment

In case of death ? ☐ Yes ☐ No

Date of death _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Cause ☐ tumor-related ☐ other cause _____

If the patient was treated with Sunitinib / Axitinib* at the previous visit :

Sunitinib /Axitinib* status at the date of death : ☐ Ongoing ☐ Discontinued

End date _|_| / _| _|_|_| (MM/YYYY)

Reason for discontinuation

☐ Progressive disease Date : _|_| / _|_| / _|_|_|_|

☐ Intolerance

☐ other _____

*: name to be selected according to the line of the treatment

ADONIS CRF

Subject ID:

ANNEX 2: ADVERSE EVENT REPORT FORM

ADONIS CRF

Subject ID:

Non Interventional Study Adverse Event Report Form

AER # (insert when known)	For Pfizer internal use only	
	Local #	Date Reported to Pfizer

PROTOCOL # SUBJECT #

Protocol Title:

☐ Initial Report ☐ Follow Up Report **Country where event occurred:**

Patient Data Date of Birth **Ethnicity:** Asian ☐ Black ☐ Hispanic ☐ Native American ☐ White ☐ Other (specify) Cannot ask per local regulations ☐

☐ Male ☐ Female Weight ☐ lb ☐ kg Height ☐ in ☐ cm

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 additional 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 serious 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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ADONIS CRF

Subject ID:

Non Interventional Study Adverse Event Report Form

AER # (insert when known)									

For Pfizer internal use only	
Local #	Date Reported to Pfizer
	___-_____-___

PROTOCOL # 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 Drug Action Taken During Event(s), specify drug name:	**Last Drug Action Taken During 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 SAE(s)/AE(s):	

ADONIS CRF

Subject ID:

Non Interventional Study Adverse Event Report Form

AER # (*insert when known*)	For Pfizer internal use only	
	Local #	Date Reported to Pfizer
		___-_____-___

PROTOCOL # 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 (or Designee) Awareness Date:** - - DD-MMM-YYYY

Investigator or Designee Signature: _____

ADONIS CRF

Subject ID:

ANNEX 3 : QUALITY OF LIFE QUESTIONNAIRES

1. FKSI-19 QUESTIONNAIRE

NCCN-FACT FKSI-19

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	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GP5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP6	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

Please inform your doctor of any adverse event you have experienced

CCI

ADONIS CRF

Subject ID:

2. RE AND MH DOMAINS OF SF-16 QUESTIONNAIRE

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

In general, would you say your health is: (Please tick one box.)

Items of Role-Emotional (RE) domains

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

Items of Mental-Health (MH) domains

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6

Please inform your doctor of any adverse event you have experienced

CCI [redacted]

ANNEX 4. PATIENT INFORMATION LETTER AND CONSENT

Pfizer	**NON-INTERVENTIONAL STUDY INFORMED CONSENT DOCUMENT**	Page: 1 of 7
ICD	**Protocol Number:** A4061078	**Version 5.1 Date**: 05 Dec 2014
Language: English	**Center ID:**	**Country:**
ICD Derived From: protocol V12.1 25 April 2014		

CONSENT TO TAKE PART IN A NON-INTERVENTIONAL RESEARCH STUDY

Name of Research Study: **ADONIS**

Protocol Number: **A4061078**

Name of Company Sponsoring the Research Study: **PFIZER**

Name of Principal Investigator (Study Doctor):

Address of Research Site:

Daytime Phone Number:

24-Hour Phone Number:

This consent document gives you important information about the non-interventional research study you have been asked to participate in. A non-interventional study collects information only. Your doctor will manage your care no differently than if you were not part of this study.

Please read this information carefully before deciding to take part. No one can make you take part and you can stop at any time. If you choose to take part in this research study, you will need to sign this consent document and you will receive a copy of the signed document for your records.

This research study is being conducted for Pfizer. Pfizer is sponsoring the study and will be paying the study doctor to conduct the study.

The following sections describe the research study. Before you decide to take part, please take as much time as you need to ask questions to the site staff, with family and friends, or with your personal physician or other healthcare professional. The site staff will fully answer any questions you have before you make a decision.

1. WHAT IS THE PURPOSE OF THE STUDY?

You are being asked to take part in this research study because you have a renal tumor. There is a need to learn more about the use of the treatment you are receiving (Sunitinib or Axitinib) in clinical practice. For this reason, Pfizer is conducting a non-interventional study to collect additional information on the best way to use these drugs and on their side effects.

Pfizer	**NON-INTERVENTIONAL STUDY INFORMED CONSENT DOCUMENT**	Page: 2 of 7
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2. HOW MANY OTHER PEOPLE WILL BE IN THE STUDY AND HOW LONG WILL PARTICIPATION IN THE STUDY LAST FOR?

There will be about 750 people enrolled in this study. This study is being done at about 111 different research sites in up to 13 countries (Austria, Belgium, Denmark, France, Finland, Germany, Greece, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, The Netherlands and UK).

3. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

You will be in this study for up to 5 years.

4. WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you will be asked to sign this consent document. No information will be collected before you have signed this document.

Upon informed consent, when you start treatment with Sunitinib (first line) or Axitinib (second line) at time of inclusion into this study, data from your medical records will be collected when you visit your doctor; from now on into the future for up to 5 years.

If you start a treatment with Axitinib at time of inclusion into this study, data regarding your previous treatment with Sunitinib will also be collected. These data will be those collected by your doctor in the past during routine clinical visits.

If you are no longer treated with Sunitinib or Axitinib during the 5 coming years, your doctor will complete a short form about your treatment every 6 months.

During the whole study period you will be treated in the routine clinical setting, all treatment decisions will follow the general clinical practice and will not be influenced by this study protocol in any way.

Parameters that will be collected from your medical records include personal information (e.g. year of birth, sex), clinical data (disease severity, laboratory test results, disease evolution), and treatment related information (e.g. all adverse events that happened during the observation period, changes in other medications you might take etc.).

If you are treated with Axitinib, your doctor will give you a questionnaire about your quality or life that you will complete by yourself every month. You will be requested to complete it at home every month. You will be given a prestamped envelop to send it.

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Language: English	**Center ID:**	**Country:**
ICD Derived From: protocol V12.1 25 April 2014		

5. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS OF BEING IN THIS STUDY?

Sunitinib or Axitinib may cause some side effects, as described in the information sheet accompanying your prescription. Any negative effects you experience should be reported to your doctor. If you experience a serious adverse event, such as any illness requiring you to be hospitalized, report that to your study doctor immediately or as soon as possible.

Because this is a non-interventional study and you are receiving treatment with Sunitinib or Axitinib as part of your standard medical care, an adverse reaction to Sunitinib or Axitinib would not be considered a research injury.

If you, or your partner, become pregnant during the study, please tell the study doctor immediately. Please also tell the doctor who will be taking care of you/your partner during the pregnancy that you were taking Sunitinib or Axitinib. The study doctor will ask if you/your partner or your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you/your partner agree, this information will be provided to the study sponsor for safety monitoring follow-up.

6. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

This study is for research purposes only. The only alternative is to not take part in this study and continue with your routine care/treatment.

7. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

This study is for research purposes only. There is no direct benefit to you from your participation in the study. Information learned from the study may help other people in the future.

8. IS BEING IN THE STUDY VOLUNTARY?

Yes. Taking part in this study is up to you. You may choose not to take part or you can change your mind and withdraw (drop out) later. There will be no penalty, and you will not lose any benefits you receive now or have a right to receive. Your decision will not affect your access to medical care in the future.

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

There is no additional cost burden to you for being in this study.

Because this study is collecting information only and there is no change to your usual medical care, the sponsor will not pay for any treatments or procedures that you may receive during your participation in this study, including Sunitinib or Axitinib.

10. WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not receive any payment for taking part in this study.

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

Access to Your Medical History

For the purposes of this study, the study team may need access to your medical history, including collecting only necessary information from your past medical records and test results. By signing this consent form you give permission to the study team to contact your other health care providers and obtain access to the necessary health information in their custody.

Keeping Your Health Information Confidential

Your health information will be used for clinical research in the area of renal tumor. Your health information could include physical examination details, as well as the results of any medical, analytical or test procedures. All of your health information will be kept confidential. Your health information will not be disclosed outside the research site, except as required by law and as explained below.

The only people with regular access to your health information in a form that can identify you will be the study team. On occasion, it may become necessary for the following people to visit the research site to talk to the study team and look at study documents:

- representatives from the study sponsor, and its group companies and authorised service providers/representatives
- the ethics committee or institutional review board that approved the study
- the government agency or agencies overseeing the study (e.g. Medicines Regulatory Agencies in this country or other countries, such as the FDA).

These persons may view materials that may identify you to make sure the study is conducted properly and that you and other people taking part in the study are safe.

Use and Disclosure of Your Coded Health Information

Pfizer	**NON-INTERVENTIONAL STUDY INFORMED CONSENT DOCUMENT**	**Page:** 4 of 7
ICD	**Protocol Number:** A4061078	**Version 5.1 Date**: 05 Dec 2014
Language: English	**Center ID:**	**Country:**
ICD Derived From: protocol V12.1 25 April 2014		

Everyone involved in the study, including the study sponsor and study team, recognize the importance and their legal obligations regarding protecting your privacy and wellbeing. For that reason, the study team will take steps to protect your privacy and will identify you on any study-related documents only with a code. This allows your health information to be used, processed and disclosed without you being identified. Only the study team will have access to the key to the code (the key enables the study team to identify individuals). Any report or publication generated as a result of this study will not identify you in any way.

By participating in this study, you agree that your coded health information may be used by the following entities and agencies:

- the study team;
- the representatives from the study sponsor, and its group companies and authorised service providers/representatives;
- the ethics committee or institutional review board that approved this study; and
- domestic and foreign regulatory agencies

in order to:

(a) conduct this study;

(b) confirm the accuracy of the research data;

(c) monitor that the study is carried out in accordance with good clinical practices and the law;

(d) seek approval from regulatory authorities to market the studied Sunitinib or Axitinib;

(e) to comply with legal and regulatory requirements; and

(f) conduct further related research (as discussed below in the section entitled Future Research).

Some of the entities that will have access to your coded health information may be based in countries other than your own, including the United States and other countries whose data protection and privacy laws may be less strict than those in your own country of residence. However, the study sponsor and institution will take appropriate steps regarding protection of the data. The sponsor has enrolled in the EU-US Safe Harbor program and abides by its requirements when handling your information. More information about Safe Harbor can be located on the US Department of Commerce website at: http://www.export.gov/safeharbor.

Future Research

As noted above, your health information may be used for further related research. By signing this consent form you agree to the use of your health information for future research into the area of renal tumor.

Withdrawal from the Study

If you wish to withdraw from the study, you should tell your 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 (via your doctor) may be used in order to re-establish contact with you and check whether you wish to carry on with the study.

If you do withdraw from the study, no new information about you will be collected by the study team, although information that has already been collected may continue to be used, processed and shared as described above. In addition, during and after your participation in the study your study doctor will be required to report to the sponsor information related to any serious adverse effect that you may experience due to your participation in the study. If you have any questions or concerns about this, we recommend that you ask your study doctor for advice.

Retention of Research Data

Any retained research data will be kept for a period of 15 years.

Your Right to Access Research Data

You have a general right to access your health information and, where it is shown to be incorrect, request its correction. Any request seeking access or changes to any information should be directed to your study doctor.

12. WHERE CAN I FIND ADDITIONAL INFORMATION ABOUT THIS RESEARCH STUDY OR THE RESEARCH RESULTS?

A description of this study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. It may be many years; however, before research results are posted. The ClinicalTrials.gov Web site is in English only. If you need assistance understanding the content on this Web site, please ask your study doctor.

Results of the study will be presented at scientific conferences and published in scientific journals. After the study ends and if you wish so, you will be informed about the study results.

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13. WHO SHOULD I CONTACT ABOUT MY RIGHTS OR IF I HAVE QUESTIONS?

Before you sign this document, you should ask questions about anything that you do not understand. The site staff will answer questions before, during, and after the study. If you do not think your question was fully answered or do not understand the answer, please continue to ask until you are satisfied.

If you have any concerns or complaints about this study or how it is being run, please discuss your concerns with the site staff. The phone numbers to reach the site staff are on the first page of this document. If you do not feel comfortable discussing your complaint with the site staff, please contact the Principal Investigator listed below.

Principal investigator name : _____

Phone number : _____

E-mail address : _____

If you have any questions about your rights as a research participant, or you would like to obtain information or offer input, or you wish to speak with someone **not** directly involved with the study, you should contact:

Provide name, phone number and address of any of the following: (1) Institutional Review Board/Independent Ethics Committee (IRB/IEC); (2) Patient rights advocate; (3) Institutional contact; and/or, (4) Bioethicist.

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CONSENT FORM : ***AGREEMENT TO PARTICIPATE***

Your Consent	Please tick the box
1. I confirm I have read and understand the information sheet dated *<enter date of information sheet>* for the above study and have had the opportunity to ask questions. I have been given enough time and opportunity to ask about the details of the study and to decide whether or not to participate in the study	☐
2. I understand that my participation is voluntary and that I am free to withdraw without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that others working on the study sponsor's behalf, ethics committees or institutional review boards, and regulatory agencies and bodies will need my permission to look at my health records in respect of the current study and any further research, and I agree to this access.	☐
4. I consent to the collection, processing, reporting and transfer of my health information within and outside my country of residence for healthcare and/or medical research purposes as described in the information sheet.	☐
5. I agree not to restrict the use of any data or results, which arise from this study.	☐
6. I agree to take part in the above study.	☐

I do not give up any of my legal rights by signing this consent document.
I have been told that I will receive a signed and dated copy of this document.

_____
Printed name of study participant

_____ _____
Signature of study participant Date of signature

PERSON OBTAINING CONSENT

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____
Signature of the Person Conducting the Consent Discussion Date of signature