NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	REGISTRY OF COMPLETE RESPONSES TO SUNITINIB IN SPANISH PATIENTS WITH METASTATIC RENAL CELL CARCINOMA **(ATILA STUDY)**
Protocol Code	**A6181227**
Protocol Version	Version 1.0 of 18th October 2018
Date of the latest Protocol version	18th October 2018
Active substance	Sunitinib Malate
Drug	SUTENT®
Objectives of the registry:	To identify patients with metastatic renal cell carcinoma (mRCC) who obtained complete response (CR) to treatment with sunitinib alone or with sunitinib and a local treatment to eliminate residual disease and achieve CR in the clinician's opinion. The clinical baseline characteristics of these patients and the tumour will be described in order to find predictive factors of response. The aim is to describe the therapeutic strategy adopted in patients who obtained greater clinical benefit in the cases described once the macroscopic lesions have been eradicated in order to draft recommendations to follow once the statistical analysis of the registry is available.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse event monitoring
AEMPS	*Agencia Española de Medicamentos y Productos Sanitarios* (Spanish Agency of Medicines and Medical Devices)
AR	Autonomous Regions
AUC	Area under the curve
Classification of the prognostic group according to Heng.	Heng risk criteria for anti-VEGF targeted therapies; Prognostic Factors for poor Overall Survival: KPS <80 Time from diagnosis to start of treatment <1 year Anaemia Hypercalcaemia Neutrophilia Thrombocytosis 0 Factors: favourable prognosis group 1-2 Factors: intermediate prognostic group ≥3 Factors: poor prognostic group.
Continuous CR	Continuous CR with no changes in the last recorded imaging test

	(CT).
CR	Complete Response
CR + Local treatment	Complete pharmacological response and with local treatment
CR investigator	Complete response: disappearance of all measurable lesions according to investigator's criteria in at least 2 consecutive CT scans
CRF	Case Report Form
CT scan	Computerised axial tomography
CTCAE version 4	Common Terminology Criteria (Common Terminology Criteria for Adverse Events, version 4) of the U.S. Department of Health and Human Services
CVA	Cardiovascular Accident (Stroke)
DMP	Data management plan
DOR	Duration of Response
DOR Duration of Complete Response (CR)	Duration of complete response (CR) to sunitinibSunitinib; date from the first Computerised axial tomography (CT) scan in which CR was detected to the CT scan in which there was disease progression. If CR continues, continuous CR must be indicated.
DP	Disease Progression
ECOG	Eastern Cooperative Oncology Group. Scale to measure the quality of life of oncology patients with scores running from 0 to 5
eCRF	Electronic Case Report Form
EDP	Exposure during pregnancy
FDA	Food & Drug Administration
GCP	Good Clinical Practice

HFS	Hand-Foot Syndrome
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
KPS	Karnofsky Performance Scale. Scale to quantify the general well-being of patients with cancer and activities of daily living
LDH	Lactate Dehydrogenase
mRCC	Metastatic Renal Cell Carcinoma
mTOR	Mammalian Target of Rapamycin
N/L Ratio	Neutrophil/lymphocyte ratio
NIS	Non-interventional study
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PR	Partial Response
Prognostic group according to Motzer (MSKCC)	Prognostic factors for a poor Overall Survival: KPS <80 Time from diagnosis to start of treatment <1 year Anaemia Hypercalcaemia Elevated lactate dehydrogenase (LDH)

	0 Factors: favourable prognosis group 1-2 Factors: intermediate prognostic group ≥3 Factors: poor prognostic group.
RCC	Renal cell carcinoma
RECIST 1.1 CR	Complete response: disappearance of all measurable lesions according to RECIST 1.1 criteria if it is available in the radiological report
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable disease
SRSD	Single reference safety document
Suni CR	Complete response obtained exclusively with systemic treatment with sunitinib
T. to CR	Time to obtaining CR
TKI	Tyrosine kinase inhibitor
TNM	System used to describe the amount of cancer and its spread in a patient's body
TT	Treatment Time
TTF	Time to Treatment Failure

2. PERSONS RESPONSIBLE FOR THE STUDY

Name	Title	Affiliation	Address
Coordinating Investigator: PPD	MD, PhD.	Medical Oncology Department	PPD Spain PPD
Pfizer Manager: PPD	MD	Pfizer Medical Department	Pfizer Madrid. PPD

3. ABSTRACT

Observational, retrospective, multicentre study in spanish patients with metastatic Renal Cell Carcinoma (mRCC) treated with sunitinib as a first-line treatment (treatment with previous cytokine therapy is accepted) according to clinical practice who obtained a complete response (CR) to treatment in one of these 2 situations:

a) Complete response (CR) obtained exclusively with first-line sunitinib treatment (sunitinib CR).

b) Response obtained after a period of time on treatment with sunitinib in which local treatment was also performed (surgery of the residual metastasis/metastases, radiofrequency ablation or radiotherapy) to achieve the total macroscopic disappearance of the disease, according to the opinion of the physician responsible for the patient (CR + local treatment).

This is a retrospective registry of spanish patient cases, from the drug marketing in 2007 to 30th October 2018.

Since the Summary of Product Characteristics for sunitinib does not provide indications to be followed in patients with complete remission of the disease, there is an open debate on whether they should continue with the treatment for life, with the toxicity that this entails, or by contrast, whether sunitinib should be considered permanently discontinued after a certain time period (also under discussion).

Cases have been reported in which, after a treatment period with the patient in complete remission, it was decided to discontinue the treatment and patients continue being disease free for years. Could we talk about a cure in these cases? What would the definition of CR be?

- **Primary study objectives:**

To describe complete responses in daily clinical practice in Spain between 2007 and 30 October 2018, such as the documented disappearance of all lesions of advanced renal cell carcinoma according to the investigator's criteria in at least 2 consecutive CT (Computerised axial tomography) scans.

To look for associations between CR from a clinical point of view and the baseline characteristics of both the patient and the tumour, such as:

- Demographic data (age at the start of treatment)
- Previous nephrectomy
- Classification of the risk group according to Motzer and/or Heng criteria and the association between each prognostic variable, such as: baseline patient status, time from nephrectomy to systemic treatment start, presence of anaemia, corrected calcium, LDH (lactate dehydrogenase) levels, neutrophil levels and platelet levels.
- Tumour data: histology, Fuhrman grade, presence of tumour necrosis and number and location of metastases (organs involved).

- **<u>Secondary objectives</u>:**
  - **To establish recommendations** to be followed **in patients who obtain CR to sunitinib treatment** based on the case recording and the adopted therapeutic strategy that obtained the greatest clinical benefit.
  - To define **the median time on treatment with sunitinib until lesion complete remission is reached in the patient responsible physician opinion.**
  - To define **the median duration of CR.**

- **The time elapsed from the confirmation of CR to disease stabilisation/progression or treatment change due to unacceptable toxicity or death from any cause** will be collected.
- **The dose and treatment regimens used will be recorded**. In the case of treatment dose changes (increase or reduction), the reason (toxicity, efficacy, decision taken after lesion elimination or upon request of the patient) will be specified.
- **Description of local treatment techniques** if they were used and at what time they were applied. In the case of a pathology report on the resected part, the percentage of necrosis and histology will be recorded, as well as the surgical complications in the case that they arose.
- **Sunitinib treatment safety profile:** the adverse effects presented by the higher grade patients and whether the treatment had to be discontinued at any time due to toxicity will be recorded. Pfizer will be notified of the toxicities required in the section on reporting adverse effects.
- In cases of systemic treatment discontinuation after a treatment period with CR maintenance, the reason for the decision and patient participation in this decision (if the patient was consulted, if it was at his/her request or the investigator's decision).
- **Pharmacological group by mechanism of action used in patients on second-line treatment after disease progression:** another TKI, treatment with a drug that acts on the immune system, an mTOR (mammalian target of rapamycin)

- **Exploratory analysis:** baseline neutrophil-lymphocyte ratio and its progression during treatment in laboratory tests available at the follow-up visits that will be attributed to imaging tests (CT scans).

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STUDY TITLE:

REGISTRY OF COMPLETE RESPONSES TO SUNITINIB IN SPANISH PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (ATILA STUDY)

PROTOCOL CODE: A6181227

COORDINATING INVESTIGATOR:

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

PPD **MD, PhD**
PPD

STUDY SITES:

It is initially considered optimal to include patients in the Medical Oncology Departments of approximately fifty Spanish sites (see "investigators list").

IEC ASSESSING THE STUDY

This protocol has been evaluated in the PPD , Spain.

PRIMARY STUDY OBJECTIVES:

To describe complete responses in daily clinical practice in Spain between June 2007 - 30 October 2018, such as: the documented disappearance of all lesions of metastatic renal cell carcinoma according to the investigator's criteria in at least 2 consecutive CT scans.

To look for associations between CR from a macroscopic point of view and the baseline characteristics of both the patient and the tumour, such as:

- Demographic data (age at the start of treatment)
- Previous nephrectomy
- Classification of the risk group according to Motzer and/or Heng criteria and the association between each prognostic variable, such as: baseline patient status, time from nephrectomy to systemic treatment start, presence of anaemia, corrected calcium, LDH (Lactate Dehydrogenase) levels, neutrophil levels and platelet levels.
- Tumour data: histology, Fuhrman grade, presence of tumour necrosis and number and location of metastases (organs involved).

DESIGN

Post-authorisation, observational, retrospective, multicentre study.

STUDY CONDITION

Advanced/metastatic renal cell carcinoma

STUDY POPULATION AND TOTAL NUMBER OF SUBJECTS

Patients over 18 year-old with advanced carcinoma with a renal cell component who have received sunitinib as a first-line treatment according to drug indication and who have achieved CR according to the responsible medical team criteria, will be included.

During the study recruitment period, the participating sites may include all patients who fulfil the inclusion criteria and none of the exclusion criteria of the protocol.

Since this is an observational and exploratory study, no hypotheses have been established and the number of included subjects will not be pre-determined, although a sample of close to 90 cases is estimated in around 50 Spanish sites.

The beginning of sunitinib treatment will have been performed before the patient's enrolment in this registry. Therefore, the therapeutic decision will only depend on the responsible doctor's clinical judgement.

SCHEDULE

It is planned to start the administrative procedures of the study with the central IEC and the AEMPS in October 2018, with the first sites expected to be opened in November-December 2018.

Patient recruitment will be for a maximum of 12 months from the opening of the first participating site.

Patients will not be monitored after inclusion in the study.

The end of the registry is expected to be when all data of the included patients have been collected and analysed, it is estimated for the year 2019.

FUNDING SOURCE

Pfizer España, as sponsor, shall fund the study. This funding includes all research materials, the cost of the recording and surveillance processes of the Committee and healthcare authorities, the design and management of the database, the cost of the statistical analysis of the information and the generated reports and the fees of the professionals involved in the data collection and analysis.

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

4. AMENDMENTS AND UPDATES

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

5. MILESTONES

In order to obtain sufficient information to carry out the data analysis, the work plan is as follows: once the study is approved by the competent authorities and the contracts signed at each site, each hospital will be opened and the investigator can start recording the required data in the case report form (CRF).

The person appointed by the sponsor to monitor the study may request a face-to-face or remote visit from the site for the review of the data reported in the CRF at any time.

The site undertakes to fill in the data in the CRFs, and to resolve any discrepancies that may arise ("queries"), without interfering with the study-planned schedule.

The study sponsor will regularly inform the investigators involved in the study on its status by sending electronic monitoring reports.

The administrative procedures for the study with the central IEC and the AEMPS are expected to start in October 2018, so the following schedule is being considered:

Milestone	**Expected date**
Expected date of approval by the central IEC	November 2018
Start of data collection *Expected date of opening of the first site and start of study recruitment*	December 2018
End of data collection	July 2019
Final Results Report	September 2019

6. STUDY RATIONALE

Complete response (CR) to a tyrosine kinase inhibitor (TKI) is reached infrequently in clinical trials for the treatment of metastatic renal cell carcinoma, where the classic description of CR contemplates only pharmacological treatment and this response is evaluated either by the study investigator or by a centralised radiological committee (most common situation).

Since the eradication of all measurable lesions will be reached in a small percentage of patients, the Summary of Product Characteristics for sunitinib does not provide guidelines regarding the therapeutic strategy to be followed in these cases, i.e. continuing the treatment and at which dose or to discontinue it definitively.

The objective of this registry is to shed light on this matter, reviewing what was done in these patients in order to draft useful recommendations for the clinician who faces this dilemma.

- **Data from phase III clinical trials**

In the sunitinib pivotal clinical trial (Motzer *et al.*, 2007), in the intermediate analysis and according to RECIST criteria, no patient reached CR to treatment by central radiological committee while there was one patient with CR in the opinion of the investigators, which accounted for less than 1% of the subjects who participated in the clinical trial. However, in the final analysis published 2 years later (Motzer *et al.,* 2009), 11 patients (3%) in the sunitinib arm achieved CR to treatment in the opinion of the investigator.

In the sorafenib clinical trial, TARGET study (Escudier *et al.*, 2007) , there was no patient with CR by the independent committee in the intermediate analysis, while one CR case (<1%) was described by investigator.

In the phase III trial of pazopanib versus placebo (Sternberg *et al.,* 2010), there was one patient in the intermediate analysis who achieved CR to treatment with pazopanib (<1%) by the independent radiological committee

In the COMPARZ study (Motzer *et al.*, 2013), according to an independent radiological committee, 3 patients achieved CR to treatment with sunitinib versus 1 patient in the pazopanib treatment arm.

- **Data from expanded-access programmes:**

In the sunitinib expanded-access programme (Gore *et al.*, 2015) where the tumour response rate was evaluated by the investigators, 1% of patients achieved CR to treatment as best response.

In the sorafenib expanded-access programme in the USA and Canada (Stadler *et al.*, 2010) less than 1% of patients achieved CR to treatment with sorafenib in the investigator's opinion.

- **Retrospective data on real-world studies:**

However, in real life this figure may be higher than in a clinical trial setting because the definition of CR is laxer, follow-up of patients is greater and, therefore, the opportunity to reach CR is more feasible, as there are late responders to treatment.

In daily clinical practice, the CT scan is used to assess tumour response, while in clinical trials other additional examinations may be performed, such as a bone scan or brain scans that may reveal metastases that otherwise may not be accounted for.

In the pool analysis of 3 prospective studies published by Castellano (Castellano *et al.*, 2017), 6.1% of patients achieved complete response in the investigators' opinion.

In the **retrospective Spanish SULONG study,** in which 97 patients who had had a PFS to sunitinib greater than 22 months were selected, the percentage of patients who achieved CR reached 21% with a median CR of 33 months (Puente *et al.*, 2017).

In a retrospective series from the hospital Gustave Roussy, Dr Albiges analysed 64 patients who obtained CR to TKIs with the drug only (36 cases) or with the combination of local treatment (28 cases); surgery, radiotherapy or radiofrequency ablation (Albiges *et al.*, 2012).

The definition of CR according to RECIST 1.1 criteria was the disappearance of all known target lesions, the disappearance of all non-target lesions and the absence of new lesions.
CR had to be confirmed with two consecutive CT scans performed with at least 4 weeks between them. Confirmation from the oncologist and radiologist was required at each site.

The treatment received was sunitinib in 59 patients and sorafenib in the remaining 5. The dose and regimen used for sunitinib was 50 mg in a 4/2 regimen and sorafenib at 800 mg/24 hours.

Most of the patients had a favourable (22 cases) or intermediate (39 cases) prognosis. However, 3 patients were classified as having a poor prognosis.

Almost all the patients displayed clear cell histology (60 out of 64 patients) and all had been nephrectomised.

There were 26 patients who had a single metastatic location versus 23 who had 2 affected organs and 15 patients who had 3 or more locations.

The median time to eliminate all lesions from the beginning of TKI treatment exclusively was 12.6 months, with a range of 2 to 28 months.
The median time from CR to relapse was 7.9 months.

In the case of subjects in whom remission of lesions was achieved with TKI plus local treatment, 18.5 months were needed (range of 5-45 months).

The median time from CR to relapse was 8.2 months.

The decision taken regarding whether or not to discontinue the treatment was as follows:

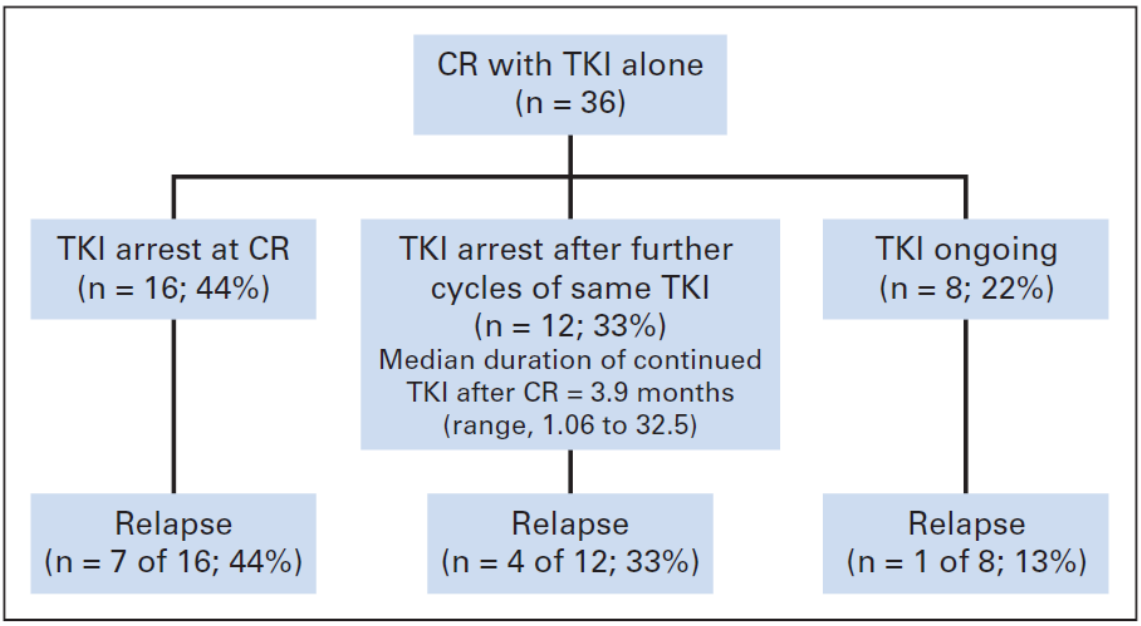

Fig 2. Outcome of patients who achieved complete remission (CR) with a tyrosine kinase inhibitor (TKI) alone.

The conclusion of the author was that CR can be obtained in all the prognostic groups and with metastasis in any location.

In the registry-based retrospective analysis of the kidney cancer Czech cooperative group (Buchler *et al.*, 2016) (RENIS registry), which covers 95% of patients treated outside clinical

trials, out of 2,803 patients, 100 cases of CR were identified as the best response (3.6% of the total) obtained exclusively with TKI as a first-line treatment:

- 84 patients treated with sunitinib
- 4 patients treated with pazopanib
- 9 patients treated with sorafenib
- 3 patients treated with bevacizumab + Interferon alpha

96% of patients had been nephrectomised and the same percentage of tumours displayed clear cell histology.
Regarding the MSKCC classification of the prognostic group, 47% of patients had a good prognosis, while 51% had been classified as having an intermediate prognosis and 2% had a poor prognosis.

The response assessment was performed by RECIST 1.1 criteria and an image was only necessary to confirm CR.

The median for achieving CR was 10.1 months and the number of patients with CR increased linearly up to approximately 20 months after beginning treatment with the anti-angiogenic drug.

The patients had a median PFS of 3.8 years (45.6 months) and OS had not been reached in this cohort. The five-year survival rate was 80%.

The decision on whether or not to continue the treatment after the lesions disappeared was shared by the clinician and the patient.
The patients who achieved CR very soon (before 10 months) were more likely to continue with the treatment, while for those in whom the lesions were eliminated later, it was decided to discontinue the treatment in a higher proportion.

Of the total cohort, 65 patients discontinued therapy in the absence of documented relapse. The reasons included medical or patient decision in 57 cases and 8 due to toxicity. Another 18 patients stopped treatment due to disease progression at the cut-off time, while 17 patients were still on first-line treatment, despite all the lesions having disappeared.

A second PFS was also defined as the time elapsed from obtaining CR to relapse of the disease or death from any cause; PFS from CR was reached at 2.3 years (27.6 months).

Of the 30 patients who discontinued treatment after achieving CR, 14 had progressed at the data cut-off point, of which 12 received a second-line treatment, including 4 subjects who were re-treated with the same drug. The median PFS of this second line was 14.5 months.

The authors' conclusions were that patients who achieved CR to a TKI had an excellent long-term prognosis, with very prolonged PFS and OS.
No association was found between overall survival and progression-free survival after obtaining CR and the baseline prognostic group according to MSKCC.
There were no significant differences in survival between patients who decided to continue treatment after removal of the lesions and those who discontinued it.

In the editorial of the journal *European Urology*, Dr Alimohamed and Dr Sridhar (Alimohamed and Sridhar, 2016) emphasised the importance of maintaining a balance between efficacy and toxicity in cases where it was decided to continue treatment with TKIs after total eradication of lesions. The patient's point of view is important. Discontinuing the treatment can generate anxiety in some people.
On the other hand, continuing treatment once CR has been achieved can promote resistance to it.

Confirmation of the disappearance of lesions from a radiological point of view does not exclude the presence of viable tumour cells.

- **Baseline characteristics associated with CR:**

Factors such as age do not seem to influence the impact of the TKI on the tumour.
In a **study by the Czech cooperative group** of metastatic renal cell carcinoma published by **Poprach** in 2016, where 1,315 patients treated with sunitinib divided into two groups were retrospectively evaluated: 1,016 patients under 70 year-old versus 299 patients over 70 year-old, the percentage of patients <70 year-old who achieved CR was 5.1% versus 4.1% in those >70 year-old, with the elderly nephrectomised patients in a smaller proportion and with a longer interval between the diagnosis of metastatic disease and the beginning of systemic treatment, as well as starting at a lower dose (Buchler *et al.*, 2015).

In the **SULONG study**, favourable baseline blood values and a longer time from nephrectomy to the onset of distant metastases were correlated with longer PFS (Puente *et al.*, 2017).

- **Data from phase III clinical trials with drugs that act on the immune system alone or in combination with an anti-angiogenic agent.**

Before the introduction of targeted drugs, in the era of cytokines with interferon alpha or Interleukin 2, although the benefit of treatment for most patients was less than that obtained today, a group of patients achieved CR to treatment that was also long-lasting. This occurred in 5-8% of the patients treated (Fisher, Rosenberg and Fyfe, 2000; McDermott *et al.*, 2005).

More recently, in the second generation of drugs that act on the immune system alone or in combination with a tyrosine kinase inhibitor (TKI), a significant percentage of complete responses have been obtained.

In the CheckMate 214 study (Motzer, Tannir, *et al.*, 2018), a phase III clinical trial of 1,096 patients with naive renal cell carcinoma of intermediate or poor prognosis and clear cell histology, in which there was a prospective examination of overall survival and response rate of the combination of ipilimumab (T4 cytotoxic anti-lymphatic antibody, CTLA4, at 1 mg/kg), + nivolumab (PD-1 inhibitor antibody at 3 mg/kg) I.V. over 4 doses every 3 weeks (induction phase) followed by nivolumab as monotherapy every two weeks (maintenance phase) versus sunitinib as monotherapy at 50 mg in a 4/2 regimen, 9% of patients in the experimental arm (40 cases) versus 1% (5 cases) in the sunitinib arm obtained CR by a centralised radiological committee.
By investigator, in the combination arm, 11% of the patients achieved CR while 1% obtained CR in the control arm.
The assessment of the CT scans/MRIs took place every 6 weeks after the 2 weeks of rest from the sunitinib cycle.

However, when the anti-tumour activity is evaluated according to programmed death-ligand 1 (PD-L1) expression level in the tumour sample examined at a central laboratory and with the evaluation of the images by an independent radiological committee in the intermediate and poor prognosis patients, the percentage of complete responses in the ipilimumab + nivolumab group decreases to 7% in patients who do not express at least 1% of this biomarker, remaining at 1% for patients treated with sunitinib.

In the positive PD-1 group, CR was achieved in 16% of patients and was maintained in 1% of patients in the sunitinib arm (Motzer, Tannir, *et al.,* 2018).

In the CheckMate 214 study, 26% of the mean or poor prognosis patients expressed PD-1 in tumours in ≥1%, while 74% of the patients expressed it in less than 1% (see table below)

Table S3. Antitumor Activity by PD-L1 Expression Level in Intermediate/Poor-risk Patients.

	PD-L1 <1%		PD-L1 ≥1%	
Outcome	**Nivolumab + Ipilimumab N=284**	**Sunitinib N=278**	**Nivolumab + Ipilimumab N=100**	**Sunitinib N=114**
Objective response rate,* % (95% CI)	37 (32–43)	28 (23–34)	58 (48–68)	22 (15–31)
	P=0.0252†		P<0.001†	
Best overall response,* %				
Complete response	7	1	16	1
Partial response	30	27	42	21
Stable disease	36	47	19	40
Progressive disease	20	13	14	25
NA	7	12	9	13

* IRRC-assessed.
† Exploratory analyses.

In the IMmotion 151 study (Motzer, Powles, *et al.*, 2018), a phase III study of atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma, 915 patients were included, of whom 362 (39%) in the intention-to-treat (ITT) population expressed PD-L1 receptors in ≥1% of the immune cells that infiltrated the tumour.

In this subgroup of patients, when the tumour response was evaluated by the investigator in the experimental arm of patients treated with atezolizumab + bevacizumab, up to 9% of the total of 178 patients achieved CR, while in the sunitinib arm (184 patients), CR was achieved in 4% of patients expressing PD-L1 ≥1%.
However, in the ITT population, i.e. subjects with or without PD-L1+, the percentage of complete responses was 5% for the atezolizumab + bevacizumab combination and 2% for the sunitinib arm.

When the analysis was performed by an independent radiological committee, CR rates for the PD-L1+ subgroup were 15% for atezolizumab + bevacizumab and 8% for patients treated with sunitinib.
However, for the PD-L1 patients, the percentage of CR in the experimental arm was 8%, while the comparator arm was 6%.

The investigators were blinded to PD-L1 status.

Endpo

PFS and ORR by IRC

	PD-L1+		PD-L1−[a]		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277[b]	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9, 12.5)	7.2 (6.1, 11.1)	11.0 (8.3, 13.3)	8.4 (7.4, 10.1)	9.6 (8.3, 11.5)	8.3 (7.0, 9.7)
Stratified HR (95% CI)	0.93 (0.72, 1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	
Confirmed ORR, % (95% CI)	36% (29, 44)	33% (26, 40)	32% (26, 37)	30% (25, 36)	33% (29, 38)	31% (27, 36)
CR rate	15%	8%	8%	6%	11%	7%

- IRC and investigator assessment of PFS benefit was generally consistent in the ITT population; however, results differed from investigator assessment in patients with PD-L1+ disease
- Investigators, IRC reviewers and the sponsor were blinded to PD-L1 status

[a] PD-L1 negative tumors had a PD-L1 IC IHC expression < 1%. [b] n = 276 for ORR.

In an analysis published by Lolli (Lolli *et al.*, 2016), a retrospective analysis was conducted in 335 patients treated with sunitinib as first-line treatment, this analysis assessed the prognostic and predictive value of the systemic immune-inflammation index (SII), based on the levels of lymphocytes, platelets and neutrophils at the start of treatment and the changes after 6 weeks of treatment.
The patients were stratified into two levels according to these values ($p<0.0001$):
High SII level and low SII level with a cut-off value of 730.
SII values were associated with objective tumour response, PFS and OS.

SII >730 (inflamed tumours):
. PFS 3.6 months
. OS: 13.5 months
SII <730 (Non-inflamed tumours):
. PFS 18.7 months
. OS: 43.6 months

Complete Response Rates				
TKI Pivotal Clinical Trials				
Sunitinib	Motzer 2007	Independent committee	0%	
		By investigator	<1%	
	Motzer 2009	By investigator	3%	
Sorafenib **TARGET** Study	Escudier 2007	Independent committee	0%	
		By investigator	<1%	
Pazopanib	Sternberg 2010	Independent committee	<1%	
Phase III clinical trial				
Comparz	Motzer 2013	Independent committee	3 patients sunitinib	1 patient pazopanib
Expanded-access programmes				
Sunitinib	Gore 2015	By investigator	1%	
Sorafenib	Stadler 2010	By investigator	<1%	
Retrospective real-world studies with sunitinib				
Pool analysis	Castellano 2017	By investigator	6.1%	
SULONG Long-term responders to sunitinib >22 months	Puente 2017	By investigator	21%	
Gustave Roussy	Albiges 2012	By investigator	64 patients	
RENIS Registry	Buchler 2016	By investigator	3.6%	
Clinical trials with immunotherapy alone or combined with a TKI versus sunitinib				

CheckMate 214 Intermediate and poor prognosis	Motzer 2018	Independent committee	9% Ipi Nivo	1% Suni
IMmotion 151 Powles 2018		By investigator PD-L1 ≥1% (39% of the population)	9% Atezo Beva	4% Suni
		In ITT by investigator	5% Atezo Beva	2% Suni
		ITT population in total by independent committee	11% Atezo Beva	7% Suni
		ITT by independent committee PD-L1 +	15% Atezo Beva	8% Suni
		ITT by independent committee PD-L1 -	8% Atezo Beva	6% Suni

7. HYPOTHESIS AND OBJECTIVES

This study is a retrospective registry of cases of CR to treatment with sunitinib in patients with metastatic renal cell carcinoma and has a purely descriptive purpose. Therefore, no previous hypothesis has been established.

7.1. Primary objectives:

To describe complete responses in daily clinical practice in Spain between 2007 and 30 October 2018, such as the documented disappearance of all lesions in the investigator's opinion on at least 2 consecutive CT scans.

To look for associations between CR from a macroscopic point of view and the baseline characteristics of both the patient and the tumour, such as:

- Demographic characteristics (age at the start of treatment)
- Comorbidities: cardiac, renal, endocrine, autoimmune and liver.
- Previous nephrectomy

- Classification of the risk group according to Motzer and/or Heng criteria and the association between each prognostic variable, such as: baseline patient status, time from nephrectomy to systemic treatment start, presence of anaemia, corrected calcium, LDH levels, neutrophil levels and platelet levels.

- Tumour data: histology, Fuhrman grade, presence of tumour necrosis and number and location of metastases (organs involved).

7.2. Secondary objectives:

- **To establish recommendations** to be followed **in patients who obtain CR to sunitinib treatment** based on the case recording and the adopted therapeutic strategy that obtained the greatest clinical benefit.

- To define **the median time on treatment with sunitinib until lesion complete remission is reached in the patient responsible physician opinion.**

- To define **the median duration of CR.**

- **The time elapsed from the confirmation of CR to disease stabilisation/progression or change of treatment due to unacceptable toxicity or death from any cause** will be collected.

- **The dose and treatment regimens used will be recorded**. In the case of changes in the treatment dose (increase or reduction), the reason (toxicity, efficacy, decision taken after lesion elimination or upon request of the patient) will be specified.

- **Description of local treatment techniques** if they were used and at what time they were applied. In the case of a pathology report on the resected part, the percentage of necrosis and histology will be recorded, as well as the surgical complications in the case that they arose.

- **Sunitinib treatment safety profile:** the adverse effects presented by the higher grade patients and whether the treatment had to be discontinued at any time due to toxicity will be recorded.

- In cases of systemic treatment discontinuation after a treatment period with CR maintenance, the reason for the decision and patient participation in this decision

(if the patient was consulted, if it was at his/her request or the investigator's decision).

- **Pharmacological group by mechanism of action used in patients on second-line treatment after disease progression:** another TKI, treatment with a drug that acts on the immune system.

7.3. Exploratory analysis:

Baseline neutrophil/leukocyte ratio and changes in neutrophil/lymphocyte ratio throughout treatment; after 4-6 weeks, at 3 months, at 6 months, at 9 months, 12 months, and then every 6 months in the laboratory tests available at approximately these dates.

8. METHODS OF INVESTIGATION

The purpose of this study is to describe in the routine practice setting, outside the clinical trial setting, the clinical characteristics of Spanish patients with metastatic renal cell cancer who have been receiving treatment with Sunitinib since it was marketed in 2007 until 30 October 2018, obtaining CR to treatment on their tumour documented with at least 2 imaging tests.

No hypothesis has been pre-specified, and all the study data will be analysed using descriptive statistical techniques.

8.1. Study design

Observational, retrospective, multicentre study in spanish patients with metastatic Renal Cell Carcinoma (mRCC) treated with sunitinib as a first-line treatment (treatment with previous cytokine therapy is accepted) according to clinical practice who obtained a complete response (CR) to treatment in one of these 2 situations:

a) Complete response (CR) obtained exclusively with first-line sunitinib treatment (sunitinib CR).

b) Response obtained after a period of time on treatment with sunitinib in which local treatment was also performed (surgery of the residual metastasis/metastases, radiofrequency ablation or radiotherapy) to achieve the total macroscopic disappearance of the disease, according to the opinion of the physician responsible for the patient (CR + local treatment).

8.2. Scope

The patient population eligible for this study includes any patient with advanced or metastatic renal cell cancer who has been treated with Sunitinib and has achieved CR of the tumour and its metastases at any time during treatment and according to the usual assessment criteria in daily clinical practice, whether it was obtained with sunitinib alone or if a local treatment was needed to eradicate all the lesions: (surgery of the residual metastases, radiofrequency ablation or radiotherapy)

The requirements for inclusion are:

1. These patients must have received Sunitinib as first-line treatment, according to their Summary of Product Characteristics.

2. Data collection: clinical, safety, response in patients with advanced renal cancer.

The study is expected to be conducted in 50 sites throughout Spain to reach the maximum number of patients in the registry.

The collection of cases will start at each hospital after the agreement with the site is signed and all study documentation has been completed and the person appointed by the sponsor delivers training on the procedures and objectives of the protocol.

As many patients at the site who meet the inclusion criteria and none of the exclusion criteria may be included.

This is an observational study designed to reflect routine clinical practice, there will be no interference with the routine daily medical care of patients with renal cancer.

The data collected will correspond to the data normally included in the medical records; demographic variables of the patients (never personal data that could lead to patient identification), age at the time of starting treatment, routine laboratory values required in the diagnosis and control of this condition, patient performance status and clinical status. It is also intended to collect treatment compliance, tolerability and adverse events and effectiveness of treatment.

As this is a retrospective observational study, no additional material or additional examinations not contemplated in regular practice will be required.

A patient who meets the inclusion criteria, who does not meet any exclusion criteria, and who has received treatment with sunitinib prior to participation in the registry will be considered assessable.

No patient follow-up period is established and there are no patient interviews, as there is only one time when the patient's data are reviewed; this will be when the investigator completes his/her CRF.

8.2.1. Inclusion Criteria

Patients must meet all the inclusion criteria described below to be eligible for the study:

1. Patients who are 18 year-old or over who have been treated for metastatic renal cell carcinoma with sunitinib as first-line treatment (treatment with prior cytokine therapy is accepted) between 2007 and 30 October 2018 and who have obtained as a best treatment response the total remission of the disease in the opinion of the doctor in charge from a clinical, radiological and/or macroscopic point of view. This response must have been reached through two possible strategies:

    A) Systemic treatment with sunitinib alone.

    B) Treatment with sunitinib and subsequent local treatment for one or more residual lesions that have not responded to the drug (traditional surgery, radiotherapy, SBRT (*Stereotactic Body Radiation Therapy)*).

2. The duration of CR must have been confirmed with at least 2 consecutive imaging tests, without having a limit in the duration of this response. Although the patient had progressed subsequently, he/she may be included in this registry.

3. Patients from any risk group

4. Tumours of any histology

The doctor responsible for the patient, in the event that he/she continues to attend routine reviews at the hospital, undertakes to send the patient a privacy alert according to the new EU legislation on personal data: regulation 2016/679 of the European parliament.

8.2.2. Exclusion Criteria

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

1. Patients treated with another drug other than Sunitinib.
2. Patients with no radiology reports proving CR.
3. Patients with no record of the dose and regimen received with Sunitinib.
4. Patients who achieved complete remission after 30 October 2018.**Variables**

ECOG	Eastern Cooperative Oncology Group	Risk groups
Age of the patient at the time of diagnosis	Epidemiological data	Years
TNM stage (T describes the size of the tumor and the spread of the cancer to nearby tissue; N describes the spread of the cancer to the nearby lymph nodes and the letter M describes the metastases)	Epidemiological data	Tumor stage
Histology of the tumor	Epidemiological data	Pathological anatomy
Tumor Fuhrman grade	Epidemiological data	Pathological anatomy
KPS	Karrnofsky Performance Status	Risk groups
Previous nephrectomy	Epidemiological data	Surgery
Cardiac, renal, endocrine, autoimmune and hepatic comorbidities.	Epidemiological data	Disease data
Risk group classification	Epidemiological data	Risk groups
Baseline status of the patient	Epidemiological data	Risk groups
Time from nephrectomy to the start of systemic treatment	Epidemiological data	Risk groups
Hemoglobin	Epidemiological data	Risk groups
Calcium correction	Epidemiological data	Risk groups
LDH levels	Epidemiological data	Risk groups
Lymphocytes	Epidemiological data	Risk groups
Platelets	Epidemiological data	Risk groups

Neutrophil/lymphocyte index at baseline and after 6 weeks of treatment, at 3 months, at 6 months, at 9 months, at 12 months and then every 6 months	Epidemiological data	Risk groups
Number of metastases	Disease data	Disease data
Number of organs with metastasis	Disease data	Disease data
Median time with treatment before reaching the CR	Treatment data	Disease data
Median duration of the CR	Treatment/disease data	Disease data
Reason why CR ends: progression, tumor stabilization or intolerable toxicity	Disease data	Disease data
Doses and schemes of Sunitinib	Treatment data	Treatment data
Temporary treatment interruptions	Treatment data	Treatment data
Definitive treatment interruption after reaching CR	Treatment data	Treatment data
Active participation of the patient in the decision to definitively interrupt the treatment once the CR has been reached	Patient empowerment	
Time in Sunitinib treatment once the CR has been reached	Treatment data	Treatment data
Local treatment techniques of residual lesions	Treatment data	Treatment data
PA (pathological anatomy) of metastasectomy: histology and degree of necrosis	Disease data	Disease data
Adverse effects related to Sunitinib treatment of the highest degree achieved	Treatment data	Treatment data
Serious side effects (SAEs) during Sunitinib treatment	Treatment data	Treatment data
Pharmacological group of 2nd line treatment after disease	Treatment data	Treatment data

progression after a period of time in CR (TKI, mTOR, Immunotherapy)		
Cause of death	Disease data	Disease data

For this observational study, demographic variables that do not imply personal data with which the patient can be identified will be recorded, medical history including date and stage of the disease at diagnosis and progression, surgical treatment, histology, risk criteria for the disease before of its onset, comorbidities, blood and biochemical hematimetry, history of Sunitinib treatment, associated adverse events, clinical efficacy, dose, date of onset and subsequent treatments, as well as the patient's condition (alive, deceased), and date of last contact.

A full description of the variables, including the definitions, will be detailed in the Statistical Analysis Plan of the study.**Source documents**

The investigator will have full responsibility for the accuracy and authenticity of the clinical and laboratory data included in the CRFs at all times.

The source document of this study will be the patient's medical records in their clinical history, including their surgical records that will be kept at the centre where the study is conducted. All data will be captured in a CRF.

If special problems and/or questions arise or governmental requirements to carry out an inspection, it will be necessary to access, in addition, to the complete file of the study, as long as the right to anonymity of the patients is protected.

The information collected in the CRFs must match the data from the medical records.

8.5. Sample size

Since this is a case registry with descriptive intent, it is not necessary to make a sample size calculation.

It is planned to include around 90 patients according to an initial estimation, but there is no limit of patients to be included as long as they are circumscribed to the period of case collection. There is no predetermined hypothesis with a defined sample.

The period of case collection will be from the approval of the reference Independent Ethics Committee and opening of the centres until July 31, 2019 or the inclusion in the CRF of all localized cases, whichever occurs first.

8.6. Treatment of data

The detailed methodology of the data management software that will be applied in this study will be documented in the Data Management Plan (DMP), which will be designed, archived and maintained by Pfizer. This document will include details about which data (eg adverse events, etc.) will be coded using the drug reference list (The World Health Organization [WHO] Drug Reference List [DRL]), which will use the ATC classification system (The Anatomical Therapeutic Chemical (ATC) classification System), or the dictionary of medical terms MedDRA (Medical dictionary for regulatory activities [MedDRA]). The specific versions of the coding dictionaries used will be documented within the DMP.**Case Report Forms (CRFs)**

As used in this protocol, the term CRF should be understood as referring to a paper form or an electronic data record, or both, according to the method of data collection used in this study.

In this study a paper CRF will be used that must be completed for each patient included. The full original CRFs are the exclusive property of Pfizer and should not be available in any form to third parties, except Pfizer authorized representatives or the corresponding regulatory authorities, without Pfizer's written permission. The investigator will ensure that the CRFs are stored securely in the study centre in paper format and will be secured in a locked room to prevent unauthorized third party access.

The investigator has the final responsibility to collect and report all clinical, safety and laboratory data entered in the CRF and any other data collection form (source documents) and ensure that they are accurate, original, attributable, complete, consistent, legible, current, durable and available when necessary. The CRFs must be signed by the investigator or by an authorized staff member to certify that the data contained in the CRFs are true. Corrections to the entries made in the CRF or the documents of origin must be dated, signed and explained (if necessary) and should not hide the original data.

In most cases, the source documents will be found in the hospital or doctor's history. In these cases, the data collected in the CRFs must match those clinical histories.

In some cases, the CRF can also serve as the source document. In these cases, a document must be available in the investigator's centre and in Pfizer that clearly identifies the data that will be registered in the CRF and for which the CRF will remain as a source document.**Records preservation**

To facilitate evaluations and/or inspections/audits by the regulatory authorities or Pfizer, the investigator undertakes to maintain records, including the identity of all participating patients (sufficient information to link the records, for example, CRF with the hospital records), copies of all CRFs, safety notification forms, source documents, detailed records of treatment disposition and appropriate documentation of relevant correspondence (eg, patient privacy notice, letters,

meeting minutes or reports of telephone calls). Records must be kept by the investigator in accordance with local regulation or as specified in the clinical trial agreement, during the longer period of both. The investigator must ensure that the records are kept safely throughout the conservation period.

If for any reason, the investigator can no longer keep the study records during the stipulated period (eg, retirement or transfer), he/she must notify Pfizer in advance. The study records must be transferred to a delegated person acceptable to Pfizer, as another investigator or other institution, or to an independent third party provided by Pfizer.

The investigator's records must be kept for a minimum of 15 years after the conclusion or interruption of the study, or for longer if required by applicable local regulations.

The investigator must obtain written authorization from Pfizer before disposing of any record, even if the preservation requirements have been met.

8.7. Data analysis

The details of the methodology for the summary and statistical analysis of the data collected in this study will be documented in the Statistical Analysis Plan (SAP), will be archived, and maintained by the sponsor. The SAP can modify the plans originally described in the protocol; any major changes to the definitions of the primary objective of the study or its analysis will be reflected as an amendment to the protocol.

The data will be analysed using descriptive statistics. A statistical summary will be provided including sample size, mean, standard deviation, median and range for continuous variables when applicable; frequency and percentages for categorical variables. Depending on the results of interest, a stratified analysis of the data can be carried out.

Additional exploratory analyses will be developed, such as the neutrophil/lymphocyte index of the patients and additional analyses if required.

8.8. Quality control

This is a post-authorization study, and the procedures will be the same as those followed in the usual clinical practice by the investigator for the review of the patient's medical records. No interview or additional testing will be carried out on patients at the time of their inclusion in the study.

However, investigators are responsible to ensure the compliance with the protocol and Good Clinical Practices (GCP).

The study centres may be subject to face-to-face or distance monitoring by the person designated by the sponsor and to a review by the IEC and/or quality audits carried out by the appropriate regulatory authorities and the sponsor of the study.

During the conduct of the present study, Pfizer (or its delegate) will monitor the activities of data collection by the centres and may also conduct monitoring visits to ensure the proper conduct of the study.

During the visits in the centres, monitors will be able to review the source documents to confirm that the data registered in the CRF is correct. All information recorded in the CRF for this study must be consistent with the patient's source documentation (the medical record).

Data included in the database and some integrated data from third parties (if applicable), will be verified/validated as documented in the components of the DMP, which will be prepared, stored, and maintained by the sponsor. After carrying out these activities, the investigator will be required to sign the CRF.

8.9. Research methods limitations

Due to the low incidence of patients with advanced kidney cancer treated with Sunitinib with the required response characteristics, it is difficult to estimate the number of patients that can be collected in the entire study.

As this is a retrospective study it is possible that some data of the patients are not available. This will be reflected in the CRF.

8.10. Other aspects

For the inclusion of patients in the study, the investigator should review the inclusion/exclusion criteria

The request for informed consent is not required in the case of not conducting an interview with the patient and to ensure the process of data dissociation in such a way that in the information that is handled from the clinical history there is no personal data, such and as stated in order SAS/3470/2009 of December 16 on observational post-authorization studies.

These are patients who in some cases have already died and in others contact has been lost. Some patients may continue with routine visits for follow-up. In these cases, the investigator agrees to send the patient a privacy notice.

With the data available in the clinical history, the requested information will be recorded in the CRF in order to analyze the study variables.

9. PROTECTION OF STUDY SUBJECTS

The study will be carried out according to daily clinical practice, as described in the protocol, the standards of good clinical practice, the international conference on harmonization and the requirements and applicable local laws (order SAS/3470/2009 of December 16). The sponsor undertakes to follow the legislation in force regarding the post-authorization study and the commitments that result from it.

9.1. Patient information and consent

All parties will comply with all applicable laws, including laws related to the implementation of organizational and technical measures to ensure the protection of patient's personal data. Such measures will include the omission of patient names or other directly identifiable information in reports, publications or other media, except when required by current laws.

Personal data will be kept in the study centre in paper format and will be in a closed room to ensure access to only authorized study personnel. The study centre will apply the appropriate technical and organizational measures to ensure that personal data can be recovered in the event of a disaster.

In case of a possible breach in the personal data security, the study centre will be responsible for determining if a personal data security breach has actually occurred and, in such case, to notify the incident as required by law.

To protect the rights and freedoms of natural persons with respect to the processing of personal data, when the study data is compiled for transfer to Pfizer and other authorized parties, patient names will be deleted and replaced by a unique numeric code specific based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this unique code specific to the patient.

The investigators centre will keep a confidential list of patients who have participated in the study, linking the numerical code of each patient with their real identity. In case of transfer of the data, Pfizer will maintain high standards of confidentiality and protection of the personal data of patients in accordance with the clinical study agreement and the applicable privacy laws.

9.2. Patient consent

9.3. Withdrawal of patients

9.4. Independent Ethics Committee (IEC)

The coordinator/investigator is responsible for obtaining the prospective approval of the study protocol, the protocol amendments and other relevant documents, as applicable, of the IEC. All correspondence with the IEC must be kept in the Investigator Files. Copies of IEC approvals must be sent to Pfizer.

9.5. Ethical aspects of the study

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

In no case will the investigator's decision be interfered with regarding the most appropriate treatment for the patient.

It is a non-interventional study, therefore decisions to indicate treatment and inclusion in the study should be independent and always based on daily clinical practice.

10. HANDLING AND COMMUNICATION OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires a manual review of unstructured patient data; the term unstructured data refers to literal medical data, including descriptions based on texts and visual representations of medical information, such as medical records, images of doctor's notes,

neurological images, radiographs, or narrative fields of a database. The reviewer must report the adverse events (AE) explicitly attributable to any Pfizer medication that appear in the revised information (defined according to the study population and the study period specified in the protocol). Explicit attribution should not be deducted by a temporal relationship between the administration of the drug and an AE, but should be based on a definitive causality statement by a healthcare professional, linking the administration of the drug to the AE.

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

All serious and non-serious AEs with explicit attribution to any Pfizer product that appears in the revised information must be recorded in the CRF and notified within 24 hours of its knowledge to the Department of Drug Safety of Pfizer using the NIS AEM Report Form.

Situations involving exposure to a drug, including exposure during pregnancy, exposure during lactation, medication error, overdose, incorrect use of the drug, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product, should be reported to the Pfizer Medication Safety Department within 24 hours of your knowledge through the NIS AEM Report Form.

In the case of these safety events with explicit attribution or associated with the use, respectively, of a Pfizer product, the data reflected in the clinical record will constitute all known information regarding these adverse events. There will be no follow-up of these related adverse events.

All research staff will have to complete the mandatory training in: "Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)" and any additional training from Your Reporting Responsibilities that is considered relevant. This training will be provided to the research staff before the start of the study. All training modules include a "Confirmation of Training Certificate" (which must be signed by the person who has received the training) as a record of the training, and must be kept in a retrievable format. Copies of all signed training certificates will be delivered to Pfizer.

The training must be completed annually using the most recent version of: "Your Reporting Responsibilities".

10.1. Single reference safety document

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

The SRSD must be used by the investigator as a guide for the prescription, as well as evaluation of any event with the safety of the patients in relation to the received drug.

11. DISSEMINATION OF RESULTS

The registry results will be published in appropriate scientific forums after the preparation of the final report.

INCIDENT COMMUNICATION

In the event that a competent authority anywhere in the world imposes a prohibition or restriction (eg, temporary suspension), or if the investigator is aware of any new information that could influence the evaluation of the benefits and risks of a Pfizer product, you must inform Pfizer immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures adopted by him to protect the patients of the study from any danger, and any protocol violation of which he or she knows.

12. REFERENCES

13. TABLES LISTING

14. GRAPHICS LISTING

15. ANNEX 1. LISTING OF INDEPENDENT DOCUMENTS