Clinical Study Protocol

NCT Number: NCT04667338

Title: Observational, Multicentre, Cross-sectional Study to Describe Diagnosis and Treatment Patterns in Narcolepsy Patients in Real Life Practice in Spain

Study Number: TAK-994-5001 (Narcolepsy-5001)

Document Version and Date: 1.0 (02 September 2020)

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Non-Interventional Study Protocol

Title: Observational, multicentre, cross-sectional study to describe diagnosis and treatment patterns in narcolepsy patients in real life practice in Spain.

Short title: SOMNUS

Study ID: TAK-994-5001

Sponsor: Takeda Farmacéutica España S.A.
C/ Paseo de la Castellana 95. Planta 22
28046 - Madrid
Phone: +34 917904330

Study phase: Medical Affairs, Post-Approval Company Sponsored (Observational)

Date of final version of the protocol: 2 September 2020

1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	Iberia Contact
Serious adverse event and pregnancy reporting	[redacted] Takeda Farmacéutica España S.A. Edif. Torre Europa, planta 22 Pº Castellana, 95. 28046- Madrid (Spain) Tel: [redacted] Email: farmacovigilancia@takeda.com
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	[redacted] Takeda Farmacéutica España S.A. Edif. Torre Europa, planta 22 Pº Castellana, 95 28046- Madrid (Spain) Email: [redacted] [redacted] Takeda Farmacéutica España S.A. Edif. Torre Europa, planta 22 Pº Castellana, 95 28046- Madrid (Spain) Email: [redacted] Dr. [redacted], [redacted] Email: [redacted] Dr. [redacted] [redacted] Email: [redacted]

Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted] Takeda Farmacéutica España S.A. Edif. Torre Europa, planta 22 Pº Castellana, 95 28046- Madrid (Spain) Email: [redacted] [redacted] Takeda Farmacéutica España S.A. Edif. Torre Europa, planta 22 Pº Castellana, 95 28046- Madrid (Spain) Email: [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

[redacted] Fecha

Departamento médico, OBU
Takeda Farmacéutica España, S.A

Dr. [redacted] Fecha

[redacted] Fecha

Departamento médico
Takeda Farmacéutica España, S.A

Dr. [redacted] Fecha

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

<Investigator Name (print or type)>

<Investigator's Title>

<Location of Facility (City, State/Provence)>

<Location of Facility (Country)>

STUDY SUMMARY

Name of Sponsor(s): Takeda Farmacéutica España S.A.	**Compound/Product:** Not Applicable
Title of Protocol: Observational, multicenter, cross-sectional study to describe diagnosis and treatment patterns in narcolepsy patients in real life practice in Spain. SOMNUS Study	
Study Number: TAK-994-5001	**Phase**: Non-Interventional
Study Design: Observational, multicenter, cross-sectional study with retrospective medical chart review, conducted in public and private Spanish sleep clinics.	
Primary Objectives: The primary objective is to describe real-world management and treatment patterns in narcolepsy patients in Spain: ▪ To describe the treatment patterns of narcolepsy, including in patients with and without cataplexy (NT1 and NT2)	
Secondary Objectives: • Describe sociodemographic and clinical characteristics of patients with narcolepsy (including a description of these characteristics in both treated and treatment-naïve patients) • To describe which specialists are involved in diagnosis of patients with narcolepsy • To describe diagnosis processes used in real-world as described in patients' medical records • To evaluate and describe real-life effectiveness (treatment outcomes) of the currently used narcolepsy treatments in the study period • To estimate utilization of health care resources associated with narcolepsy patients in Spain, in terms of treatment, number of visits, hospitalization, and additional resources • To estimate indirect costs associated with narcolepsy patients in Spain, using the Work Productivity and Activity Impairment Questionnaire General (WPAI-GH) • To describe the health-related quality of life (HRQoL) of patients with narcolepsy in Spain using the EQ-5D questionnaire. • To assess the perception of stigma of patients with narcolepsy in Spain using the 8-item Stigma Scale for Chronic Illness (SSCI-8). • To describe treatment satisfaction of patients with narcolepsy in Spain using the Treatment Satisfaction Questionnaire for Medication (TSQM-9) • To describe the burden of illness in terms of associated comorbidities and associated disorders • To describe adverse reaction associated to narcolepsy treatments	
Exploratory Objectives: • Identify the proportion of patients with narcolepsy (with and without cataplexy) diagnosed and managed in public hospitals in Spain	

- Evaluate and describe the diagnosis and treatment management of patients with narcolepsy up to one year before diagnosis through medical chart review.
- Describe utilization of health care resources associated with narcolepsy patients in Spain, before and after diagnosis of narcolepsy
- In the patients treated for narcolepsy within the 1st year after diagnosis of narcolepsy; describe the differences in utilization of healthcare resources before and after treatment initiation

Subject Population:

Adult patients with confirmed diagnosis of narcolepsy (both type I and type II) defined by the International Classification of Sleep Disorders, Third Edition (ICDS-3)

Sample Size:	**Study Sites:**
Approximately 196 patients will be included in the study: 137 type 1 and 59 type 2 narcolepsy patients.	15 sites are estimated to participate (10 public and 5 private) with expertise in the management of patients with narcolepsy

Duration of Study:

Overall Study Duration: 24 months (since site selection to final report)
Enrolment period: 8 months
Treatment / Follow-up: One Study Visit (1 day)

Criteria for Inclusion:

- Patient aged **≥18 years** at the time of study inclusion
- Patient with confirmed diagnosis of narcolepsy between 2014 to 2019 defined by the International Classification of Sleep Disorders, Third Edition (ICDS-3)
- Patient with **at least 1-year follow-up with data available** at the participating site **after initial narcolepsy diagnosis** and before study inclusion.
- Patients with data available at the participant site at least **1-year before narcolepsy diagnosis**
- Patient capable to **fulfill** the study questionnaires.
- In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
- The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.

Criteria for Exclusion:

- Patient with any serious degenerative disease (Alzheimer, Parkinson or epilepsy) or psychiatric condition
- Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.
- Patient participating in a clinical trial (≤12 months)

Endpoints/Outcomes and Measures

The primary objective is to describe real-world management and treatment patterns of narcolepsy patients in Spain:

- Treatments (pharmacological and non-pharmacological) to be described and stratified by following groups:
  - Patients with and without cataplexy

- Patients treated and naïve patients

Secondary endpoints for this study are:

- Sociodemographic and clinical characteristics of narcoleptic patients collected in the study.
- Specialists involved in diagnosis of patients with narcolepsy
  - Type of specialists who diagnoses narcolepsy patients in Spain
- Diagnosis processes used in real-world as described in patients' medical records
  - Different procedures or tests for the diagnosis of narcolepsy will be described: Clinical history, ESS, PSG, MSLT, types of HLA
  - Diagnosis processes for patients with narcolepsy in terms of time since first symptoms to diagnosis, time from diagnosis to first treatment to will be described.
- Effectiveness (treatment outcomes) of the currently used narcolepsy treatments in the study period
  - Pharmacological treatments and interventions since diagnosis will be described: type and doses, dose adjustments and reason to modification, drug switching
  - Clinician assessment associated with each treatment received for narcolepsy will be described, stratifying by treatment used: if use of different scales: no/yes, specify Sustained Attention to Response Task (SART), Maintenance of Wakefulness Test (MWT), the Epworth Sleepiness Scale (ESS) and cataplexy scales(1).
  - Non-pharmacological treatment outcomes will be described: Take short naps; Maintain a regular sleep schedule; Avoid caffeine or alcohol before bed; Avoid smoking, especially at night; Exercise daily; Avoid large, heavy meals right before bedtime; Relax before bed.
- Costs associated with direct and indirect healthcare resource use by narcolepsy patients in Spain:
  - Direct medical healthcare resources used by patients with narcolepsy in the 12 months after diagnosis of narcolepsy. Healthcare resources such as outpatient visits, tests performed, previous narcolepsy treatment, complication associated to narcolepsy, hospitalizations, and emergency room/department visits will be presented in terms of:
    - percentage of patients using each healthcare resource
    - resources used per patient/year (for each specific resource)
  - Indirect health resources will be described through
    - the scores obtained in the Productivity loss, Absenteeism, Presenteeism, Disability (WPAI questionnaire) score at study visit.
    - Ad-hoc questions related to occupational accidents
- Health-related quality of life (HRQoL) of patients with narcolepsy in Spain:
  - Description of the scores obtained in the EQ-5D Questionnaire.
- Perception of stigma in patients with narcolepsy in Spain:
  - Describe the level of stigmatization in patients with narcolepsy in the Stigma Scale chronic illnesses (SSCI-8)
- Treatment satisfaction of patients with narcolepsy in Spain:
  - Description of the score obtained in the Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Burden of illness in terms of associated comorbidities and associated disorders since diagnosis:
  - Description (%) of comorbidities and other concomitant disorders will be described.

Statistical Considerations:

Management and treatment patterns of patients with narcolepsy in Spain will be described in terms of patient´s characteristics and medications or drugs collected in the study period.

The descriptive analysis will include number of patients with valid/missing observations, mean, standard deviation (SD), median, 25 and 75 percentiles (P25 and P75, respectively), minimum and maximum for continuous variables.

All data will be analysed at global and different subgroups.

Sample Size Justification:

The main objective of this study is to describe treatment patterns of narcolepsy patients in Spain.

Since it is an exploratory analysis, the sample size (N) will be calculated based on statistical criteria, using the criterion of maximum indetermination, when the percentage is expected to be around 50%.

A sample of 196 evaluable patients is sufficient to estimate a population percentage of 50%, with a 95% confidence interval of ± 7 percentage units. With this sample size, the continuous variables will be estimated with an accuracy of ±0.071 standard deviations (SD).

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List of Abbreviations and Definition of Terms

AE:	Adverse Event
ADR:	Adverse Drug Reaction
CA:	Competent Authority
CCI:	Charlson Comorbidity Index
CCSI:	Core Company Safety Information
CRF:	Case Report Form
CRO:	Contract Research Organisation
CSF:	Cerebrospinal fluid
CV:	Curriculum Vitae
eCRF:	electronic Case Report Form
DNS:	Disrupted nighttime sleep
EDS:	Excessive daytime sleepiness
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
HLA:	Human leucocyte antigen
HRQoL:	Health-related quality of life
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
ICSD-3:	International Classification of Sleep Disorders
IRB:	Institutional Review Board
MSLT:	Mean sleep latency
NREM:	non-REM
NT1:	Narcolepsy type 1
NT2:	Narcolepsy type 2
PSG:	Polysomnography
PSUR:	Periodic Safety Update Report
REM:	Rapid eye movement
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SOREMPs:	Multiple sleep-onset REM periods
SPC:	Summary of Product Characteristics

2 Introduction

Narcolepsy, a rare chronic primary sleep disorder, for which no cure has been identified. Global prevalence of narcolepsy is 25–50 cases per 100,000 individuals(2) and affects 4.7 of 10.000 (0.047%) individuals in the European general population(3). Its prevalence is low, mainly because the long diagnostic delay (with approximately 50% of patients waiting 6 to 10.5 years to receive an accurate diagnosis) what could cause an underestimation of its prevalence(4, 5).

The typical onset of narcolepsy is during adolescence and early adulthood and it´s symptomatology is characterized by consensus on the five core symptoms: excessive daytime sleepiness (EDS) with symptoms of rapid eye movement (REM), with/without cataplexy ((muscle weakness), sleep paralysis, sleep-related (hypnagogic and hypnopompic) hallucinations, and disrupted nighttime sleep (DNS) with excessive daytime sleepiness and cataplexy being the most common symptom(6).

The establishment of hypocretin deficiency as the cause of narcolepsy made necessary to modify and redefine the terminology used to define the two subtypes of narcolepsy in the 3rd Edition of the International Classification of Sleep Disorders (ICSD-3):

- *Narcolepsy type 1 (NT1)*, the most frequent type, caused by a loss of the hypothalamic hypocretin-producing neurons, and cataplexy as its distinctive symptom. It has a tight association with the human leucocyte antigen (HLA) DQB1*0602 allele and therefore an immune-mediated aetiopathogeny is hypothesized.
- *Narcolepsy type 2 (NT2)* in which EDS is associated with reduced mean sleep latency (MSLT) and multiple sleep-onset REM periods (SOREMPs) in the MSLT, but cataplexy is absent and levels of hypocretin 1 are normal.

But, although hypocretin deficiency is the hallmark of narcolepsy type 1, the relative unavailability of hypocretin assays to date has a result the continuation of the identification of cataplexy to establish a narcolepsy type 1 diagnosis.

Narcolepsy symptoms can often be confused and mimicked by other sleep disorders or overlap with psychiatric symptomology, what difficult the correct diagnosis. As well as the absence of easily measurable biomarkers. This indicates that more specific diagnostic procedures should be incorporated (detailed presenting history, assessment of sleep-wake cycles and sleep deprivation, subjective (sleep diary) and objective testing (polysomnography (PSG), actigraphy, MSLT including drug-testing of urine, human leukocyte antigen (HLA) typing and lumbar puncture to measure CSF hypocretin-1 (orexin) levels)(7).

Currently there is no cure for narcolepsy so current treatments for narcolepsy are based on symptomatic management, basically of sleepiness and cataplexy. Patients with narcolepsy require not only pharmacological treatment (actually there are three main pharmacological drugs for narcolepsy treatment: stimulant for EDS, antidepressants for cataplexy and sodium oxybate for symptoms), but mainly behavioral modifications such as a regular night-time sleep schedule, avoiding sleep deprivation, short scheduled naps, diet, work and school accommodations, and sometimes, psychotherapy(8). It has been described that medication in combination with lifestyle changes helps returns approximately 80% of patients with narcolepsy back to near normal functioning.

Recent advances in the understanding of the neurobiological basis of narcolepsy have led to the investigation of novel treatment options(9). Current recommended therapies for narcolepsy act on several neurotransmitters but do not target the cause of the disorder, just aim to manage selective symptoms with inconsistent efficacy, leaving

others untreated(10). And medications are prescribed based on, mainly, the following symptom: EDS and sleep attacks; disturbed nighttime sleep, and; cataplexy, hypnagogic hallucinations, and sleep paralysis(8, 11).

Measuring the severity of the narcolepsy symptoms and treatment efficacy became a major outcome in management optimization. It´s also known that dose adjustment, switching to another drug, and prescription of multiple medications are often required when managing narcolepsy in the long term(6).

On the other hand, comorbidities live together with narcolepsy, and sometimes is difficult to know where narcolepsy end and comorbidities begin. Treatment of comorbidities is unfortunately often neglected but can be really important for some patients. Attention to comorbidities is important in the comprehensive management of patients with narcolepsy(12).

Although the prevalence of narcolepsy is low, the associated healthcare costs are disproportionately high, with direct medical and pharmacy costs that are twice that of the general population(13). Narcolepsy has no known cure, requires lifelong treatment, diagnosis is delayed, and all increase its economic burden: increased medical costs relative to the general population, an increased risk for work-related or vehicular accidents, and reduced quality of life. Considering the substantial burden of this disease, improvement in a patient's quality of life (QoL) and ability to function in daily work and other activities are critically important(14).

Patients with narcolepsy often present comorbid conditions including cardiometabolic comorbidities (e.g. obesity, type 2 diabetes, sleep apnea, cardiovascular diseases), neuropsychiatric comorbidities (e.g. mood disorders, anxiety, eating disorders and attention-deficit hyperactivity disorder), and other sleep disorders such as restless legs syndrome, periodic leg movements, REM and non-REM (NREM) sleep parasomnias(15-17). Thus, a substantial economic burden, is evidenced by higher healthcare utilization and costs related to the treatment of these comorbidities, inpatient, outpatient, emergency department, and prescription costs(18). It has also been associated with a negative impact on work productivity including increased unemployment, elevated rates of long-term disability, absenteeism, and presenteeism, early retirement, accidents at work, welfare enrollment, general impairment at work, and lower wages(19).

On the other hand, narcolepsy is heavily associated with a substantial adverse impact on mental health and health-related quality of life (HRQoL), including the domains of mood, psychopathology, and other areas such as marital and work problems(20). It´s well described the problems faced by patients with narcolepsy with social stigma, difficulties in obtaining an education and keeping a job, a reduced quality of life and socioeconomic consequences. Besides, the late diagnosis adds to the substantial societal burden, not only at the time of diagnosis and after but also before the diagnosis(18).

Given the limited real-world data available on treatment patterns of care, prevalence and health care resource utilization in patients narcolepsy NT1 and NT2), descriptive data in routine clinical practice would be desirable to improve the knowledge and the management of HR+/Her2-mBC

It´s important to understand the epidemiology of the narcolepsy in Spain, as well as to correctly identify NT1 and NT2 patients and how these patients are being managed in routine clinical practice given the lack of information published in our country.

The current observational study aims to obtain real-world data on the characteristics and current management of NT1 and NT2 patients in a real-world setting.

3 Study Objective(s) and Endpoint(s)/Outcome(s)

3.1 Objective(s)

The study aims to provide a comprehensive overview of the real-world management and treatment patterns of narcolepsy in adults' patients in real world practice in Spain.

3.1.1 Primary Objective

The primary objectives of the study are:

- To describe the treatment patterns of narcolepsy between different subgroups, including:
  - Patients with and without cataplexy
  - Patients treated and naïve-treatment patients

3.1.2 Secondary Objective(s)

- To characterize sociodemographic and clinical characteristics of patients with narcolepsy and compare it between treated and untreated patients.
- To describe specialists involved in diagnosis of patients with narcolepsy.
- To describe diagnosis processes used in real-world as described in patients' medical records.
- To evaluate and describe effectiveness (treatment outcomes) of the currently used narcolepsy treatments in the study period.
- To estimate direct costs associated with narcolepsy patients in Spain, in terms of treatment, number of visits, hospitalization, and additional resources in the last 12 months.
- To estimate indirect costs associated with narcolepsy patients in Spain, using the Work Productivity and Activity Impairment Questionnaire General (WPAI-GH).
- To describe the health-related quality of life (HRQoL) of patients with narcolepsy in Spain using the EQ-5D Questionnaire.
- To assess the perception of stigma of patients with narcolepsy in Spain using the 8-item Stigma Scale for Chronic Illness (SSCI-8).
- To describe treatment satisfaction of patients with narcolepsy in Spain using the Treatment Satisfaction Questionnaire Medication (TSQM-9).
- To describe the burden of illness in terms of associated comorbidities and associated disorders in the last 12 months.
- To describe adverse reaction associated to narcolepsy treatments

3.1.3 Exploratory Objective(s)

- Identify the proportion of patients with narcolepsy (with and without cataplexy) diagnosed and managed in public hospitals in Spain.
- Evaluate and describe the diagnosis and treatment management of patients with narcolepsy up to one year before diagnosis (this objective will be assessed through medical chart review).
- Describe utilization of health care resources associated with narcolepsy patients in Spain, before and after diagnosis of narcolepsy
- In the patients treated for narcolepsy within the 1st year after diagnosis of narcolepsy; describe the differences in utilization of healthcare resources before and after treatment initiation

3.2 Endpoint(s)/Outcome(s)

3.2.1 Primary Endpoint

The primary objective is to describe real-world management and treatment patterns of narcolepsy patients in Spain:

- A description of the different treatments (pharmacological and non-pharmacological) will be described and compared between the following groups:
  - Patients with and without cataplexy
  - Patients treated and treatment-naïve patients

3.2.2 Secondary Endpoint(s)

- A description of all sociodemographic and clinical characteristics of patients with narcolepsy collected in the study. The following groups will be compared:
  - Treatment-naïve patients and treated patients
  - To describe specialists involved in diagnosis of patients with narcolepsy
    - A description of specialists who diagnoses narcolepsy patients in Spain
- To describe diagnosis processes used in real-world as described in patients' medical records
  - Clinical History
  - A description of the different procedures or tests for the diagnosis of narcolepsy will be described: clinical history, (absence/presence of cataplexy, number of cataplexy attacks, number of sleep-onset REM periods (SOREMPs),absence/presence of apneas and /or Apnea-hypopnea index (AHI), hipocrexine levels, ESS, PSG, MSLT and types of HLA.
  - Diagnosis processes for patients with narcolepsy in terms of time since first symptoms to diagnosis, time from diagnosis to first treatment to will be described.
- To evaluate and describe clinician assessments (effectiveness) of the currently used narcolepsy treatments in the study period:
  - Pharmacological treatments and interventions since diagnosis will be described: type and doses, dose adjustments and reason to modification, drug switching, adverse events related to treatments
  - The outcomes associated with each treatment received for narcolepsy will be described, stratifying by treatment used: if any scale used for the outcomes and specify: Sustained Attention to Response Task (SART), Maintenance of Wakefulness Test (MWT) and the Epworth Sleepiness Scale (ESS).
  - Non-pharmacological treatment outcomes will be described: Take short naps; Maintain a regular sleep schedule; Avoid caffeine or alcohol before bed; Avoid smoking, especially at night; Exercise daily; Avoid large, heavy meals right before bedtime; Relax before bed.
- To estimate the costs associated with direct and indirect healthcare resource use by narcolepsy patients in Spain:
  - Direct medical healthcare resources used by patients with narcolepsy in the last 12 months before study visit. Healthcare resources such as outpatient visits, tests performed, previous narcolepsy

treatment, complication associated to narcolepsy, hospitalizations, and emergency room/department visits will be presented in terms of:

- percentage of patients using each healthcare resource
- resources used per patient/year (for each specific resource)

- Indirect health resources will be described though:
  - the scores obtained in the Productivity loss, Absenteeism, Presenteeism, Disability (WPAI questionnaire) score at study visit.
  - Ad-hoc questions at study visit related to occupational accidents.

- To describe the health-related quality of life (HRQoL) of patients with narcolepsy in Spain:
  - Description of the scores obtained in the EQ-5D Questionnaire.
- To assess the perception of stigma in patients with narcolepsy in Spain:
  - To know the level of stigmatization of patients with MS the score in the SSCI-8 will be described.
- To describe treatment satisfaction of patients with narcolepsy in Spain:
  - Description of the score obtained in the Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- To describe the burden of illness in terms of associated comorbidities and associated disorders:
  - Description (%) of comorbidities and other concomitant disorders will be described.
- To describe adverse reaction associated to narcolepsy treatments
  - Describe type of adverse events reported

3.2.3 Exploratory Endpoint(s)

- Identify the proportion of patients with narcolepsy (with and without cataplexy) diagnosed and managed in public hospitals in Spain:
  - Description (%) of total number of patients with narcolepsy attended in the participating site according to routine clinical practice with at least 12-months follow up after over total population under the hospital's circumscription.
- Evaluate and describe the diagnosis and treatment management of patients with narcolepsy up to one year before diagnosis assessed through medical chart review.
  - Percentage (%) of treatments received for narcolepsy in the year before narcolepsy diagnosis will be described.
  - Percentage (%) and type of diagnosis received before narcolepsy diagnosis will be described
- Describe utilization of health care resources associated with narcolepsy patients in Spain, before and after diagnosis of narcolepsy
  - Description (quantity and type) of healthcare resources associated with narcolepsy patients before and after being diagnosed for this condition.

- Describe utilization of health care resources associated with narcolepsy patients in Spain, before and after treatment for narcolepsy
    - In those patients that received treatment within the 1st year after diagnosis of narcolepsy: Description (quantity and type) of healthcare resources associated with narcolepsy patients before and after receiving treatment for this condition

4 Study Methods

This study is a 'non-interventional study' as defined in Directive 2001/20/EC and will follow the guidelines for GPP.

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.

4.1 Study Schedule

- Planned Start of Study: November 2020
- Planned collection of first data point: November 2020
- Planned End of Study: September 2021
- Planned collection of the last data point: July 2021
- Planned completion of the Study Report: December 2021

The Start of Study is defined as date of first informed consent signed and the End of study is defined as last information of last subject included in the study is recorded in the database.

The Sponsor will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB for each site and for the complete study, as locally required.

The Sponsor will ensure that results are made publicly available as required by local authorities.

Based on upcoming knowledge, the Sponsor might choose to terminate the study prematurely. In such case study sites, IECs/IRBs and authorities will be informed promptly.

4.2 Study Design

A multicenter, non-interventional, cross-sectional, study with retrospective medical chart review, conducted in public and private Spanish institutions has been designed to describe the management of narcolepsy in adults' patients in real world practice in Spain.

The study will be conducted in a single visit, considering a fieldwork period of approximately 8 months to enroll all patients. This period could be extended if due to causes unrelated to the study (for example, a re-outbreak of COVID-19) the expected sample was not reached during that time.

The patient will be enrolled in one of the two study cohorts according to the type of narcolepsy at the time of the visit and after patient informed consent is obtained:

Cohort A: type 1 narcolepsy patients

Cohort B: type 2 narcolepsy patients

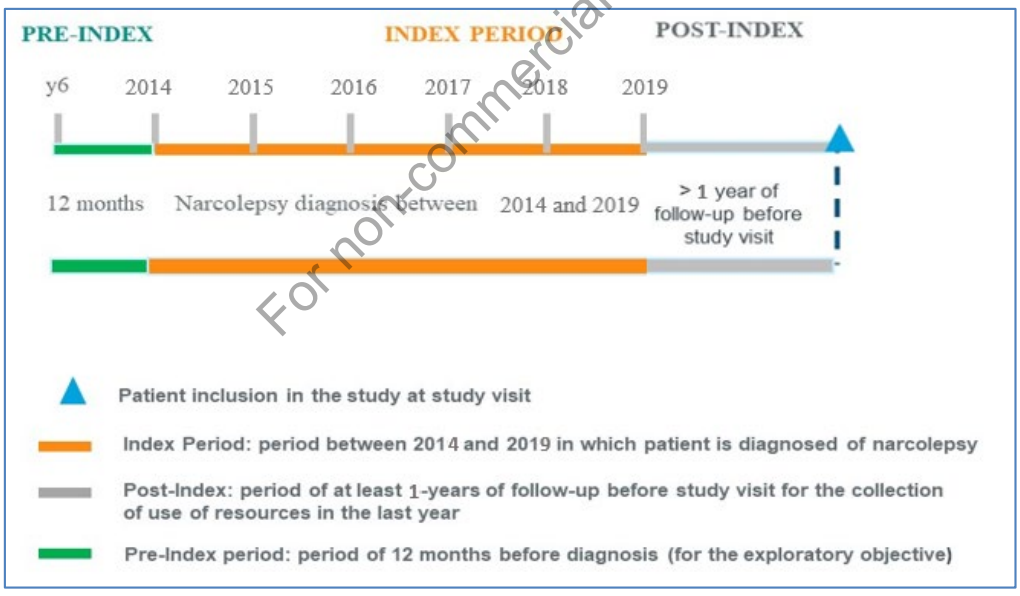
Patients will attend a single visit where they will answer study questionnaires and some clinical variables will be collected from clinical records. In the event of a possible outbreak of COVID-19 that makes it necessary to replace face-to-face visits in the participating centers with telematic visits, both the informed consent and the study questionnaires will be collected remotely so as not to interfere with the development of the present study.

Data will be collected:

- **Retrospective Period:** patient should have at least 1 year of follow-up before narcolepsy diagnosis and must have been diagnosed of narcolepsy between 2014 and 2019, having at least 1 year of follow-up before study visit**.**
- **Study visit**: Clinical and demographic data and PRO will be collected from the patient during the study visit, respectively.

Figure 1 illustrates the 3 study periods and timelines for data collection.

Figure 1. Study Diagram



- **Index Period** will be the period in which patient is diagnosed of narcolepsy, between 2014 and 2019.
- **Post-Index** will be the at least a 1-year period before study visit all patients must have for the collection of use of resources in the last year
- **Pre-Index period** will 12 months before diagnosis (for the exploratory objective)

Data source:

The study variables will be recorded in an electronic case report form (eCRF) specially designed for the study eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice.

Patient Recorded Outcomes (PROs) will be completed by patients in paper/electronic questionnaires and recorded in the corresponding section of eCRF. In the event of a possible outbreak of COVID-19 that makes it necessary to replace face-to-face visits in the participating centers with telematic visits, the study questionnaires will be collected remotely so as not to interfere with the development of the present study.

Variables collected at the time of the study visit will be obtained based on and limited to those available in the medical records of the selected patients and only those according to standard clinical practice.

To identify the proportion of patients with narcolepsy (with and without cataplexy) diagnosed and managed in public and private hospitals in Spain (exploratory objective of prevalence), secondary data will be collected from data included in the hospital (proportion of patients with narcolepsy with and without cataplexy managed at hospital level in the participant centers).

4.3 Selection of Study Population

Target population will be patients with confirmed diagnosis of narcolepsy defined by the International Classification of Sleep Disorders, Third Edition (ICDS-3), up to 7 years before study inclusion.

Patients will be recruited consecutively as they go to the hospital: approximately 10 patients per site will be included.

Patients will be invited to participate in this study during a routine medical visit for any purpose with their physician and the patient will be considered included when he/she agrees to participate in the study by signing the informed consent and if all of the following criteria are met. All included patients will attend a single visit. In the event of a possible outbreak of COVID-19 that makes it necessary to replace face to face visits in the participating centers with telematic visits, the invitation to participate, the obtention of patient's informed consent and the collection of patient's questionnaires will be carried out remotely.

4.3.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to inclusion into the study:

1. Patient aged **≥18 years** at the time of study inclusion
2. Patient with confirmed diagnosis of narcolepsy between 2014 to 2019 defined by the International Classification of Sleep Disorders, Third Edition (ICDS-3)
3. Patient with at least 1-year follow-up with data available at the participating site after initial narcolepsy diagnosis and before study inclusion.
4. Patients with data available at the participant site at least 1-year before narcolepsy diagnosis
5. Patient capable to fulfill the study questionnaires.
6. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
7. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.

4.3.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.
2. Patient participating in a clinical trial (≤12 months*)
3. Patient with any serious degenerative disease (Alzheimer, Parkinson or epilepsy) or psychiatric condition

*Clinical trial participation could be cause of bias regar*ding healthcare resource use data collection.*

Subjects should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available, will not be included in or will be deleted from the database.

4.4 Treatments

Non-interventional treatments/pharmacotherapy are instructed by the study protocol.

4.5 Premature Termination or Suspension of Study or Study Site

4.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- The Data Monitoring Committee or the Sponsor recommends that the study should be suspended or terminated. [if applicable]
- Significant violation of Good Clinical Practice (GCP/GPV) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- The sponsor has the right to close the study with serving a preliminary written notice to investigators and hospitals. The sponsor has the right to unilaterally stop at any time enrolment of patients and/or gathering of data in the study with serving a preliminary written notice thereof on the Investigator indicating the date of stop of enrolment. The sponsor should ensure that notification about premature termination or suspension of the study is submitted to the concerned authorities and IEC.
- The investigator has the right to stop recruitment at any time with serving a preliminary written notice to the Sponsor/responsible CRO.
- In case of premature closure of the site/termination of the study, all completed and also unused (including the unused pages of partially completed CRFs) CRFs and all documentation forms (except documentation that has to remain stored at site) must be returned to the Sponsor, even unused ones. Study material may be destroyed only with permission of the Sponsor.

4.5.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

4.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the Sponsor, an IRB/IEC or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

4.6 Study Plan

Data collection overview:

	Before study visit	Study Visits
Informed consent		X
Inclusion/exclusion criteria		X
Socio-demographics	X	X
General Clinical history	X	X
Narcolepsy characteristics	X	
Treatments: previous and current treatment	X	X
Safety reporting	X	X
Direct healthcare resources used	X	X
Indirect health resources used: WPAI		X
HRQoL: EQ-5D questionnaire		X
Satisfaction: TSQM-9		X
Ad-hoc questionnaire by Physician		X

The following variables will be collected during all the study period:

SOCIODEMOGRAPHIC CHARACTERISTICS AT STUDY VISIT	
▪ Age	Age of the patient at the time of the visit will be recorded
▪ Gender	Man/woman
▪ Ethnicity	Caucasian/Hispanic/African/Asian/Other/Unknown
▪ Education	The ongoing or completed level of education will be recorded: no studies/primary studies, secondary studies, university studies.

▪ Occupational status and occupation	Employed, self-employed, employed but on sick leave due to the study disease, permanent incapacity to work due to the study disease, permanent incapacity to work due to other reasons, student, unemployed, retired, domestic work, other
▪ Civil status:	Married/with partner, divorced/separated, unmarried, widow/er
CLINICAL CHARACTERISTICS AT STUDY VISIT	
▪ Physical examination	Weight, height, BMI and blood pressure
▪ Smoking status	Smoker, ex-smoker, non-smoker, unknown
▪ Alcohol intake	Yes / No
▪ Exercise Status	Never, Regular (1/-3 times/week), Frequently (4-7 times /week)
▪ Family history related to the study disease in first or second-degree relatives	Yes/No and degree: first or second-degree relatives
▪ Charlson Comorbidity Index	Score
▪ Comorbidities and other narcolepsy associated disorders:	Depression, depression, bipolar disorder, anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, panic disorder, phobia disorder, obsessive compulsive disorder, and total diagnosed anxiety
DIAGNOSIS OF NARCOLEPSY	
▪ Date of first symptoms onset	Age at reported onset will be calculate
▪ Specialist responsible for diagnosis	General Practitioner, Specialist: specify
▪ Date of Diagnosis	Date of diagnosis
▪ First symptoms	At diagnosis. Describe: Excessive daytime sleepiness (EDS), cataplexy, hallucinations upon awakening or going to sleep, sleep paralysis, and disturbed night-time sleep Date of first symptoms onset, if known
▪ Type of narcolepsy	NT1 or NT2
▪ Diagnosis procedures	Result and date of performance:

	• Presence/Absence of cataplexy, number of cataplexy attacks • Clinical History • Clinical Assessment: Epworth sleepiness scale (ESS) • Neurological Assessment: polysomnogram (PSG), REM sleep latency in nocturnal PSG • Multiple sleep latency test (MSLT): number of sleep-onset REM periods (SOREMPs) • Apnea-hypopnea index (AHI): > 10, and > 30 • Other procedures: electroencephalography (EEG), electrooculography, electromyography (EMG), recordings of movements in your chest and tummy, recordings of airflow through your mouth and nose, pulse oximetry, electrocardiography (ECG), etc • HLA typing: HLA DQB * 0602, DQB1 *0304, other at diagnosis and date • Hypocretin-1 CSF or Orexin: Date and levels in pg/mL at diagnosis and during the study period: Categories: low (< or =110 pg/mL), which is indicative of type 1 narcolepsy; intermediate (ranges between 111-200 pg/mL); and normal (>200 pg/mL)
▪ Concomitant treatment	For each comorbidity since diagnosis up to study visit when applicable: type of treatment, start date/stop date
TREATMENTS	
▪ Previous Treatments	Pharmacological treatment/s received since diagnosis: Yes, No (% naïve-treatment patients) (active agents will be collected): • type, dose, start/stop date. o Stimulants: Amphetamine salts for excessive daytime sleepiness, Dextroamphetamine (sleep attacks), Methylphenidate, Dexmethylphenidate, Lisdexamfetamine. o Wakefulness-Promoting Agents: Modafinil, Pitolisant and Sunosi for excessive daytime sleepiness, o Sodium Oxybate, Gamma-hydroxybutyrate for EDS and cataplexy for excessive daytime sleepiness, sleep attacks, cataplexy, sleep paralysis, hypnagogic hallucinations, disturbed nocturnal sleep o Antidepressants: TCAs (Clomipramine, Imipramine) for cataplexy, SSRIs (Prozac, Celexa) for sleep paralysis and SNRIs (Effexor, Pristiq) for hypnagogic hallucinations o Benzodiazepines Hypnotics (Rivotril, Ambien) for disturbed nocturnal sleep o Other psychotropic agents • If applicable: Dose/s adjustment/s, reason to modification, start/stop date and drug switching

▪ Treatment at study visit	Current treatment: o Type (as above), doses, start date and dose adjustment o If applicable: Dose adjustment, reason to modification, start date and drug switching
▪ Non-Pharmacological Treatment	At study Visit a brief ad-hoc survey will be completed by patient to collect: Take short naps; Maintain a regular sleep schedule; Avoid caffeine or alcohol before bed; Avoid smoking, especially at night; Exercise daily; Avoid large, heavy meals right before bedtime; Relax before bed.
▪ Safety	Adverse Events since diagnosis to study visit
HEALTHCARE RESOURCES USE	
▪ Direct costs	The first 12 months since diagnosis: • Number of routine monitoring visits (specialists involved, tests conducted, treatment variations) since diagnosis up to study visits • Number of emergency visits (specialists involved, tests/procedures conducted, treatment administered) after diagnosis • Number and duration of hospitalizations • Complications derived from narcolepsy
PROS COMPLETED BY PATIENT AT STUDY VISIT	
- **Indirect costs**	
• ***Work Productivity and Activity Impairment Questionnaire General (WPAI-GH)(21)***: 6-item questionnaire, to be completed during the visit, which assesses how the disease being studied has affected work productivity in the past 7 days. The validated Spanish-language version will be used. This questionnaire is self-administered by the patient.	
- **Health Related Quality of Live**	
• ***EQ-5D Questionnaire (22):*** The EQ-5D is a generic instrument for describing and valuing health. It is based on a descriptive system that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 3 response categories corresponding to no problems, some problems, and extreme problems. The instrument is designed for self-completion, and respondents also rate their overall health on the day of the interview on a 0–100 hash-marked, vertical visual analogue scale (EQ-VAS). The EQ-5D has been widely tested and used in both general population and patient samples and has been translated into over 130 different language versions. • ***Stigma Scale for Chronic Illness 8-item version (SSCI-8)(23):*** 8 items scale developed to assess internalized and experienced stigma across neurological conditions. It uses a 5-point Likert scale ranging from 1 (never) to 5 (always).	
- **Satisfaction**	

<table>
<tr><td colspan="2">

- ***Treatment Satisfaction Questionnaire for Medication (TSQM-9)(24):*** The 14-item treatment satisfaction questionnaire for medication (TSQM-14) was developed and validated as a general measure of satisfaction with treatment. It is a reliable and valid instrument to evaluate patient satisfaction with medication, providing scores on four scales: side effects, efficacy, convenience and overall satisfaction. A naturalist study concluded that the administration of the TSQM-14, which includes the side effects domain, can interfere with regular clinical practice. As a result, a shorter 9-item questionnaire was created, the TSQM-9, derived from the TSQM-14, but without the five items in the side effects domain. The TSQM-9 has been recently validated to evaluate patient satisfaction with any kind of medication in observational naturalistic studies in the cardiovascular area; it is not specific for any disease and/or risk factor and has been used in Spanish of Spain.

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<tr><td colspan="2">***EXPLORATORY INFORMATION***</td></tr>
<tr><td>***Prevalence and incidence***</td><td>

- Total population under the hospital's circumscription

At least 12-months follow up after diagnosis:

- Total of patients with narcolepsy attended in the participating site according to routine clinical practice and type of narcolepsy
- New patients with narcolepsy diagnosed per year (incidence)

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<tr><td>***Treatment management before diagnosis***</td><td>

Up to 12-months before diagnosis

- "narcolepsy-related" medication
- Other medication "non-narcolepsy-related"
- number of patients with at least one prescription in the 12 months pre-index
- Diagnosis pattern prior to the diagnosis of narcolepsy

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<tr><td>***Utilization of health care resources before diagnosis of narcolepsy***</td><td>

The last 12 months before diagnosis of narcolepsy:

- Number of routine monitoring visits (specialists involved, tests conducted, treatment variations) since diagnosis up to study visits
- Number of emergency visits (specialists involved, tests/procedures conducted, treatment administered) after diagnosis
- Number and duration of hospitalizations
- Differences in utilization of healthcare resources before and after diagnosis of narcolepsy
- In the patients treated for narcolepsy within the 1st year after diagnosis of narcolepsy; differences in utilization of healthcare resources before and after treatment initiation

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5 Study Administrative Structure

5.1 Study Sites

The study is planned to be conducted in approximately 15 Spanish sites: 10 public and 15 private institutions with expertise in the management of patients with narcolepsy.

As a pre-study activity, sites will need to answer a site feasibility questionnaire in order to determine that the site has adequate facilities and investigator is qualified and meets the needs of the study, recruitment targets, quality and timelines in compliance with the applicable regulatory requirements.

The Sponsor will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

5.2 Sponsor Personnel

The Sponsor will keep a record of all relevant sponsor personnel. This record will include the Sponsor Coordinating Study Managers, local Study Managers and other medical staff, medical responsible for the study, drug safety responsible for the study.

5.3 Contract Research Organisation (CRO)

The CRO, will be responsible of the following regulatory activities:

- Regulatory activities: preparing, signing and submitting documents required by the applicable local ethics committees, central ethics committees and regulatory authorities and other local regulatory bodies when applicable,
- Study implementation and initiation, study conducting and study close-out
- Data management and project management
- Making payments on Sponsor´s on behalf to institutions, investigators and other staff members related to the conduct of the study
- Statistical analysis, elaboration of Statistical Analysis Plan (SAP)

The CRO will keep a record of all involved CRO personnel.

6 Ethics

This study is an observational study where the existence of the study has no impact on the subject except for collection of informed consent to use of the subject's data.

Patients will complete some questionnaires /PROs and the CRO will ask for the permission of use and will be included as part of the protocol for their evaluation and approval.

In the event of a possible outbreak of COVID-19 that makes it necessary to replace face-to-face visits in the participating centers with telematic visits, both the informed consent and the study questionnaires will be collected remotely so as not to interfere with the development of this study. Once the situation is normalized, the patient will be asked to give consent again, and the doctor must record the date of signing the consent in the patient's record.

6.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and according to Spanish SAS Order/3470/2009 of December 16 of the Ministry of Health and Social Policy which publishes the guidelines on observational post-authorization studies for medicinal products for human use, and the local laws and regulations. Special attention will be paid to data protection law: Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales

The Sponsor and/or the appointed CRO will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

The sponsor is responsible for meeting the International Conference on Harmonisation (ICH) requirement for yearly updates to the IECs/IRBs, if applicable.

6.2 Independent Ethics Committee / Institutional Review Board and Authorities IEC/ IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Subject Information Sheet / Informed Consent Form and questionnaires and Questionnaires

The appointed CRO or the Study Responsible will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results

The Sponsor or the responsible CRO will supply relevant documents for submission to the Independent Ethic Committee for the protocol's review and approval. This protocol, amendments to the protocol, the informed consent form, and other documents required by all applicable laws and regulations, must be submitted to a central IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or the responsible Contract Research Organisation before start of the study. Documented approval from central IECs will be obtained for all participating investigational sites (principle investigators) prior to the study start.

The Sponsor or the appointed CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

6.3 Authorities

The Sponsor or the appointed CRO will send required documents to the competent authority (CA) and/or other national or regional authorities when applicable. The Sponsor or the appointed CRO will keep an updated list of submission and approval dates and a copy of all documents submitted.

6.4 Subject Information and Written Informed Consent

The Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (and if applicable, the parent or legal guardian) can understand, and obtain the subject's (and if applicable, the subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, parent or legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The subject must agree that sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g., to other companies or authorities, that may be located in other countries with potentially different regulations for data.

However, in the event of a recurrence of COVID-19 that requires the replacement of routine face-to-face visits at the health center with telematic visits as part of routine clinical practice, both the invitation to participate in the study and the obtention of consent informed and the completion of the study questionnaires will be done remotely. Once the situation is normalized, the manual signature of the informed consent of each patient who has agreed to participate remotely will be collected.

The subject and subject's parent or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form, it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. One original signed Informed Consent Form must be kept at the study site, and one is provided to the subject and/or subject's parent or legal guardian, as applicable.

For details, see the Subject Information Sheet and Informed Consent Form.

7 Safety Reporting

7.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an Serious Adverse Event (SAE)
- A laboratory test result that requires the subject/patient to receive specific corrective therapy

- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.

- Lack of efficacy of Takeda Product
- Occupational exposure
- Use outside the terms of the marketing authorization, also known as "off-label"
- Use of falsified medicinal product

A SSR should be reported even if there is no associated AE.

Adverse Events not being collected

Information on all adverse events should be collected and recorded from healthcare professionals or consumers in the course of the study unless the protocol provides with a due justification for not collecting certain adverse events. Any reference to adverse events that are not collected should be made using the appropriate level of the MedDRA classification.

The healthcare professional or patient shall be informed of the possibility to report directly to the local Takeda Pharmacovigilance department or national pharmacovigilance reporting system any adverse reactions not being collected as part of the study. These will be treated as spontaneous reports and independent of the study.

7.2 Collection and Recording of Adverse Events, Special Situation Reports and Product Quality Issues

Collection and recording of SAEs, AEs, ADRs SSRs and PQI will commence once the study participant has provided informed consent.

- SAEs, AEs, ADRs, SSRs and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints

  Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

- SAEs, AEs, SSRs and PQIs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints

  Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

- SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s) or research team *(not required for database studies)*

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be forwarded to the relevant Takeda Pharmacovigilance department within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

This is typically achieved by the investigator completing the adverse event report pages of an electric CRF or by submitting an AE Report Form to Takeda.

The Investigator may be contacted by Takeda to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested additional information and will notify Takeda within 1 working day of obtaining the additional information for a fatal or life-threatening SAE, within 4 calendar days for other SAEs, and within 7 calendar days for all other events/issues.

Takeda Contact Information

Spontaneous reports are notified to the local Pharmacovigilance Department in Spain, through the email address farmacovigilancia@takeda.com for Legacy Takeda products and to the email address DrugSafety@Shire.com for Legacy Shire products.

7.3 Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Authorities

- The expedited reporting of AEs and SSRs that are study endpoints to regulatory agencies is not required. Such events should be included in the Clinical Study Report.
- For spontaneously reported events that are not study endpoints, the Sponsor shall notify regulatory agencies in accordance with local regulatory requirements or Sponsor's post-marketing commitments.

8 Data Quality Control and Assurance

8.1 Quality Control

The data will be entered by the investigators themselves and/or authorized personnel directly in the electronic case report form (eCRF). A data management plan (DMP) will be created to describe the method and procedure for each data management step for the study, from electronic Case Report Form (eCRF) design up to final database delivery.

Participating Investigators will be trained before start of data collection on:

- the background and objectives of the study
- study procedures
- safety reporting
- ethical regulations,
- data entering and database in the eCRF

The data quality will be assured by using the following methods of quality review:

- remote monitoring contacts performed by the CRO for the verification of the compliance of the data presented in the CRF with the data of the primary documentation, signature of the Informed Consent - source data verification (SDV) if applicable

- Once the data collection has been completed, the CRO will perform remote close out visits in all the participant sites. The close out visit will remotely confirm any potential remaining queries and review that study documents are in place.

The eCRFs will include programmable edit checks to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. The Edit Checks Specifications (Data Validation Plan (DVP)) is included in the eCRF specification documentation. These checks will be performed once data is entered into the eCRF. Thus the

data entered into the eCRF will be validated within the system and the physician will receive alerts for missing or inconsistent data. In case any changes of already entered data will be required, an audit trail will be available.

The investigator(s)/institution(s) will allow study-related monitoring, audits, independent ethics committee/-review board (IEC/IRB) review, and regulatory inspection(s), providing direct access to source data documents.

8.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

8.3 Inspection by IRB/IEC or Competent Authority

Representatives from IRB/IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact the Sponsor and must make the records available as requested. The Inspector must be reminded up front that consent to access to personal data has not been obtained from the participants in this study.

8.4 Data Management

This study will be performed by the CRO IQVIA with guidance, input, review and approval of Takeda, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analysis.

Data Management will be carried out according to a Data Management Plan (DMP), which must be written and approved before the design of the study database is finalised. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database. If a subject is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and adverse events/reactions (MedDRA) must be followed.

Centres will be selected by sponsor and that will also be part of data analysis. Each investigator will nominate a study investigator for the centre that will collect the study data.

The Study Site will receive data collection tools (CRFs, access to electronic data capture, etc.) from the CRO. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the CRF completion guide.

Patients' data will be collected from the source documents for each patient in the study, consisting of medical records containing demographic data, medical, treatment and diagnostic documentation and laboratory assessments, from the medical charts.

All data will be collected and entered directly into the electronic case report form (eCRF) designed for this study. All participating sites will have access to the data entered regarding the individual site its own enrolled patients. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and

help files. Sites will be responsible for entering extracted patient data into a secure internet-based platform via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the Principal investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required.

8.4.1 Data Collection Tools and Flow

Data entered manually will be collected via electronic case report form (eCRF). Technical support will be provided for all study participants throughout the study. The investigator will be responsible for completion of all the sections of the eCRF and that the entries correspond to his or her professional experience and regular clinical practice. The CRO will be responsible for supervising recruitment in this study through the eCRFs. In the data collection period, standard monthly emails will be sent to the sites during data extraction, to inform about progression, tackle any problems and remind the investigators of their responsibilities in the study.

PRO data will be collected on paper format and the data from the questionnaires will be entered into the eCRF system by the investigator team. Takeda will perform oversight of the data management of this study, including approval of the CRO data management plans and guidance. The CRO will produce eCRF specifications for the study based on the study initiator's templates including quality checking to be performed on the data.

In all cases, the doctor must keep the original documents of each study patient. All the information entered in the eCRF must be traceable to the original documents in the patient's file. Only the study site doctors will keep a patient follow-up sheet, with a list of the patient numbers together with names and dates of birth, to enable their identification. The doctor must also keep the original informed consent form signed by the patient (the patient will be given a signed copy), if required.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 7 and data on serious AE/ADR reactions collected according to section 4 should be signed off separately by a physician who may or may not be involved in the study.

9 Statistical Methods and Determination of Sample Size

9.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses.

Statistical analyses will be performed by IQVIA Information S.A. with SAS® statistical software version 7.15 or higher or R. A Statistical Analysis Plan (SAP) with a detailed description of analyses to be performed and imputation methods to deal with missing data and censoring will be developed. The final SAP will include (mock) table shells to be populated for the clinical study report (CSR). The SAP will be prepared and accepted before the data analysis initiation. The SAP describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised SAP before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

In this non-interventional study, retrospective data from medical charts and data at the study visit will be collected for patients with narcolepsy. Once the study has been completed and all data from the last patient have been recorded, the database will be closed, and statistical analysis will be performed.

For details of the statistical analyses please refer to the Statistical Analysis Plan.

9.2 General considerations

A description of all patients included in the study will be performed. All patients participating in the study who meet the eligibility criteria will be included in the study population. Continuous variables will be described by the number of patients with valid/missing observations, mean, standard deviation (SD), median, 25 and 75 percentiles (P25 and P75, respectively), minimum and maximum. Categorical variables will be described by frequencies and related percentages. A p-value lower than 0.05 will be considered significant. Count variables (healthcare utilization) will be analysed as unadjusted rates.

Questionnaire scores provided by patients will be described using the descriptive measures described above, and according to the manual users of each questionnaire.

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning, i.e. all data listed in section 4.

Descriptive analyses will be conducted to describe the sociodemographic and health characteristics of the total sample and the narcolepsy and sub study groups. Bivariate analyses (chi-square tests for categorical variables and t-tests for continuous variables) will be conducted to assess whether patients with narcolepsy diagnosis with or without cataplexy differed significantly on any sociodemographic or health characteristic variables. Finally, percentage of patients with cataplexy will be presented.

9.2.1 Evaluable patients

All patients fulfilling all inclusion and none of exclusion criteria, giving their informed consent and completing main eCRF data will be considered as evaluable patients.

9.2.2 Primary Endpoint

- Describe treatment patterns in narcolepsy patients in Spain. The following subgroups will be analyzed:
    - Total narcolepsy population
        - Patients with and without cataplexy (Type 1 and Type 2)
        - Narcolepsy patients Type 1 and Type 2 previously treated and naïve-treatment patients

The percentage of use of treatments (yes / no) and the use of different treatments (pharmacological and non-pharmacological) in the study visit will be described in global and stratified by the different subgroups describe above: type of narcolepsy and if previously treated. Also, a description of percentage of use of each type of treatment in the study visit will be stratified by type of hospital (public or private centers).

9.2.3 Secondary Endpoint(s)

- Describe sociodemographic and clinical characteristics of patients with narcolepsy (both treated and untreated patients)

  Sociodemographic and clinical characteristics (general clinical history and narcolepsy characteristics) of patients with narcolepsy collected in the study visit will be presented stratified by the use of treatments in

the study visit (untreated or treated patients). Comparisons between groups will be performed using a Chi-Square test for categorical variables and t-test or non-parametric test for continuous variables.

- To describe specialists involved in diagnosis of patients with narcolepsy

  The percentage of different specialists who diagnosed narcolepsy will be presented

- To describe outcome measures used in real-world as described in patients' medical records

  The percentage of the different procedures or tests for the diagnosis of narcolepsy will be described: ESS, PSG, MSLT, absence/presence of cataplexy, number of cataplexy attacks, number of sleep-onset REM periods (SOREMPs), absence/presence of apneas and /or Apnea-hypopnea index (AHI), hypocretin levels etc, used for narcolepsy diagnosis will be described.

  Time since first symptoms to diagnosis and time from diagnosis to first treatment will be described, also the percentage of patients who had each type of procedure performed at diagnosis (ESS, PSG, MSLT, PSG, other).

- To evaluate and describe clinician assessments (effectiveness) of the used narcolepsy treatments in the study period since diagnosis:
  - Percentage of pharmacological treatments and interventions received in relation with the presence of most typical symptoms will be presented: excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. Symptomatology will be stratified by current treatment used for narcolepsy.
  - Percentage of pharmacological treatments at each line
  - Percentage of patients in which information on scales used to measure treatment outcomes is available: ESS , MWT and SART at the study visit will be described and the relation with the treatment received.
  - A description of non-pharmacological treatments: Take short naps; Maintain a regular sleep schedule; Avoid caffeine or alcohol before bed; Avoid smoking, especially at night; Exercise daily; Avoid large, heavy meals right before bedtime; Relax before bed

- To estimate direct and indirect healthcare resources utilization use by narcolepsy patients in Spain, based on measures of healthcare resource utilization, and on reported work productivity loss in terms:
  - Direct medical healthcare resources used by patients with narcolepsy will be described in terms of percentage of patients who used each direct healthcare resource in the las 12 months including previous treatments for narcolepsy, outpatient visits, clinical tests, emergency room/department visits, hospitalizations and complication associated to narcolepsy . Also, it will be described the number of each type of direct resources used by patient/year (assuming as zero when patients did not used it). To compute total cost, the following direct cost components will be summed for fees for visits to doctors, laboratory tests and imaging tests, outpatient visits, emergency room visits, inpatient stays, rehabilitation stays, and drug treatments related to MS. Unitary costs for health care resources will be retrieved from different databases.
  - Indirect health resources in the last 7 days will be described through the WPAI questionnaire scores obtained for:

1. Absenteeism (work time missed).
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment / disability .

- Indirect health care due to occupational accidents motor vehicle accidents (MVAs) and near miss accidents (NMAs) will also be described, through the answer of the two following questions: Have you had a motor vehicle accident at work during the last years?", "Have you had a near-miss driving accident during the last year?
- Costs will be calculated considering the healthcare resource use and will be described in the final report. Unitary costs for direct resources will be obtained from E-SALUD database (http://esalud.oblikue.com/). If necessary, costs will be updated using Consumer Price Index published by INE. And unitary costs for treatments for narcolepsy will be obtained from BOTPLUS–Consejo General de Colegios Oficiales de Farmacéuticos (https://botplusweb.portalfarma.com/), considering active drug, posology and duration of the prescription. Costs will be reported at annual basis and calculated at patient-level according to the resources used obtaining the following cost drivers for descriptive purposes:
    - Annual cost of treatment received
    - Annual cost of routine monitoring visits (specialists and GPs)
    - Annual cost of conducted tests
    - Annual cost of emergency rooms visits
    - Annual cost of hospitalizations
    - Annual cost of complications derived from narcolepsy

- To describe the Health-Related Quality of Life (HRQoL) of patients with narcolepsy in Spain:
    - The EQ-5D scores of patients with narcolepsy in Spain will be described according to the following dimensions
        - Mobility
        - Self-Care
        - Usual activities
        - Pain / Discomfort
        - Anxiety / Depression
- To describe treatment satisfaction of patients with narcolepsy in Spain
    - TSQM-9 domains will be described, including convenience, effectiveness and global satisfaction.
- To describe burden of illness in terms of associated comorbidities and associated disorders
    - Percentages (%) of most prevalent comorbidities and other concomitant disorders associated with narcolepsy will be described.
    - Charlson Comorbidity Index(25) (CCI), score is a method to estimate 10-year mortality based on a score from a range of 12 comorbidities, the comorbidity score ranges from 0 to a maximum of 24 points.

- To describe adverse reaction associated to narcolepsy treatments
    - Describe type of adverse events reported

9.2.4 Exploratory Endpoint(s)

- Identify the proportion of patients with narcolepsy (with and without cataplexy) diagnosed and managed in public hospitals in Spain
    - The percentage of total number of patients with narcolepsy attended in the participating site according to routine clinical practice with at least 12-months follow up after over total population under the hospital's circumscription
    - New patients diagnosed with narcolepsy in the last year in the participating sites
- Evaluate and describe the diagnosis and treatment management of patients with narcolepsy up to one year before diagnosis (if this information is not available in the medical charts, this objective will be assessed through a patient survey).
    - Description (%) treatments received for narcolepsy in the last year will be described.
- Describe utilization of health care resources associated with narcolepsy patients in Spain, before and after diagnosis of narcolepsy
    - Description (quantity and type) of healthcare resources associated with narcolepsy patients before and after being diagnosed for this condition.
- Describe utilization of health care resources associated with narcolepsy patients in Spain, before and after treatment for narcolepsy
    - In those patients that received treatment within the 1st year after diagnosis of narcolepsy: Description (quantity and type) of healthcare resources associated with narcolepsy patients before and after receiving treatment for this condition

ADRs reported in the study as well as ADRs reported directly to authorities and to Takeda International Drug Safety according to Section 7 and not captured in the study database will be extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR).

9.3 Interim Analyses

No interim analyses are planned for this study.

9.4 Determination of Sample Size

The main objective of this study is to describe treatment patterns of narcolepsy patients in Spain.

Since it is an exploratory analysis, the sample size (N) will be calculated based on statistical criteria, using the criterion of maximum indetermination, when the percentage is expected to be around 50%.

A sample of 196 evaluable patients is sufficient to estimate a population percentage of 50%, with a 95% confidence interval of ± 7 percentage units. In this way, the continuous variables will be estimated with an accuracy of 0.14 standard deviations (SD).

Taking into account that around 20% of patients will not have any evaluable data or will be not considered evaluable for the study purposes, the number of patients with narcolepsy to be included will be **approximately 245 patients:** 172 patients with type 1 narcolepsy and 73 patients with type 2 narcolepsy (a relation of 70%-30%).

10 Reports

The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

11 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor aims to have the results of this study published.

The Sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

Takeda may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the below essential documents in the Study Site File:

- Written agreement between the Sponsor and the participating site.
- The study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible
- Subject Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required), including the original signed Forms
- The list of participating subjects
- Written IEC / IRB approval / vote according to local regulations
- Authority approval according to local regulations
- The completed CRFs
- The progress reports

After final database lock the Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 5 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

13 References

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14 APPENDICES

Appendix 1: Case Report Form

Appendix 2: Study Investigator Agreement

Appendix 3: Ethics Committee Approval

Appendix 4: Patient Information Sheet

Appendix 5: Informed Consent Form

Appendix 6: Economic Details

Appendix 7: Productivity loss, Absenteeism, Presenteeism, Disability (WPAI questionnaire).

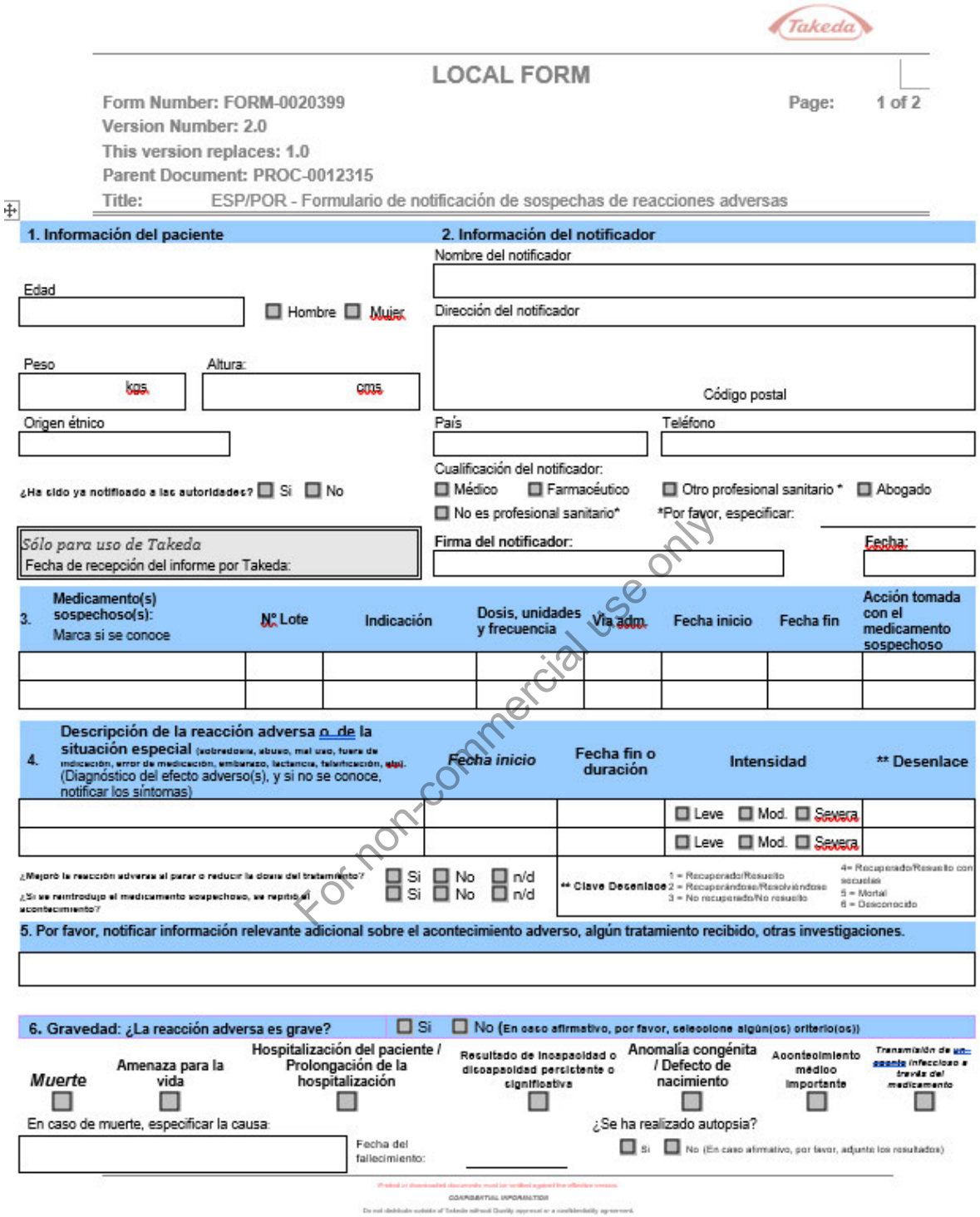
Appendix 8: EQ-5D questionnaire.

Appendix 9: Stigma Scale chronic illnesses (SSCI-8)

Appendix 10: Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Extracted from Supplemental materials for: Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. Blood. 2015;2068–74.

Appendix 11: Takeda AE Report Form



LOCAL FORM

Form Number: FORM-0020399 Page: 1 of 2
Version Number: 2.0
This version replaces: 1.0
Parent Document: PROC-0012315
Title: ESP/POR - Formulario de notificación de sospechas de reacciones adversas

1. Información del paciente

Edad

☐ Hombre ☐ Mujer

Peso kgs

Altura: cms

Origen étnico

¿Ha sido ya notificado a las autoridades? ☐ Si ☐ No

Sólo para uso de Takeda
Fecha de recepción del informe por Takeda:

2. Información del notificador

Nombre del notificador

Dirección del notificador

Código postal

País

Teléfono

Cualificación del notificador:
☐ Médico ☐ Farmacéutico ☐ Otro profesional sanitario * ☐ Abogado
☐ No es profesional sanitario* *Por favor, especificar:

Firma del notificador:

Fecha:

3. Medicamento(s) sospechoso(s): Marca si se conoce	Nº Lote	Indicación	Dosis, unidades y frecuencia	Vía adm.	Fecha inicio	Fecha fin	Acción tomada con el medicamento sospechoso

4. Descripción de la reacción adversa o de la situación especial (sobredosis, abuso, mal uso, fuera de indicación, error de medicación, embarazo, lactancia, falsificación, etc). (Diagnóstico del efecto adverso(s), y si no se conoce, notificar los síntomas)	Fecha inicio	Fecha fin o duración	Intensidad	** Desenlace
			☐ Leve ☐ Mod. ☐ Severa	
			☐ Leve ☐ Mod. ☐ Severa	

¿Mejoró la reacción adversa al parar o reducir la dosis del tratamiento? ☐ Si ☐ No ☐ n/d
¿Si se reintrodujo el medicamento sospechoso, se repitió el acontecimiento? ☐ Si ☐ No ☐ n/d

** Clave Desenlace: 1 = Recuperado/Resuelto; 2 = Recuperándose/Resolviéndose; 3 = No recuperado/No resuelto; 4= Recuperado/Resuelto con secuelas; 5 = Mortal; 6 = Desconocido

5. Por favor, notificar información relevante adicional sobre el acontecimiento adverso, algún tratamiento recibido, otras investigaciones.

6. Gravedad: ¿La reacción adversa es grave? ☐ Si ☐ No (En caso afirmativo, por favor, seleccione algún(os) criterio(os))

Muerte	Amenaza para la vida	Hospitalización del paciente / Prolongación de la hospitalización	Resultado de incapacidad o discapacidad persistente o significativa	Anomalía congénita / Defecto de nacimiento	Acontecimiento médico importante	Transmisión de agente infeccioso a través del medicamento
☐	☐	☐	☐	☐	☐	☐

En caso de muerte, especificar la causa:

Fecha del fallecimiento:

¿Se ha realizado autopsia? ☐ Si ☐ No (En caso afirmativo, por favor, adjunte los resultados)

CONFIDENTIAL INFORMATION

LOCAL FORM

Form Number: FORM-0020399 Page: 2 of 2
Version Number: 2.0
This version replaces: 1.0
Parent Document: PROC-0012315
Title: ESP/POR - Formulario de notificación de sospechas de reacciones adversas

7. Causalidad: ¿Considera la reacción adversa relacionada con el medicamento sospechoso? ☐ Si ☐ No

8. Historia Médica relevante / Enfermedades concomitantes.

- Por favor, también incluya anteriores reacciones adversas a medicamentos, alergias, factores ambientales, abuso de alcohol y(o) drogas

9. Medicación concomitante (Excluir el tratamiento del acontecimiento)	**Indicación**	**Dosis diaria**	**Vía adm.**	**Fecha inicio**	**Fecha fin**

Por favor, complete este formulario y envíelo antes de 24 horas, al Departamento de Farmacovigilancia de Takeda Farmacéutica España SA: correo electrónico farmacovigilancia@Takeda.com , Fax: 91 857 48 08