Statistical Analysis Plan

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)

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Statistical Analysis Plan

PROTOCOL NUMBER: Narcolepsy-5001

OBSERVATIONAL, MULTICENTRE, CROSS-SECTIONAL STUDY TO DESCRIBE DIAGNOSIS AND TREATMENT PATTERNS IN NARCOLEPSY PATIENTS IN REAL LIFE PRACTICE IN SPAIN

AUTHOR: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V 2.0 for Protocol Narcolepsy-5001.

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1. ABBREVIATIONS

AE:	Adverse Event
ADR:	Adverse Drug Reaction
AHI:	Apnea-hypopnea index
CCI:	Charlson Comorbidity Index
CRF:	Case Report Form
CSF:	Cerebrospinal fluid
eCRF:	electronic Case Report Form
EQ-5D:	EuroQol five-dimensions
ENR:	Patients Enrolled Set
ESS:	Epworth Sleepiness Scale
HLA:	Human leucocyte antigen
HRQoL:	Health-related quality of life
MSLT:	Multiple sleep latency test
MVAs:	Motor vehicle accidents
MWT:	Maintenance Wakefulness Test
NMAs:	Near miss accidents
NT1:	Narcolepsy type 1
NT2:	Narcolepsy type 2
PSG:	Polysomnography
PRO:	Patient Recorded Outcomes
REM:	Rapid eye movements
SAF:	Safety Analysis Set
SAP:	Statistical Analysis Plan
SART:	Sustained Attention to Response Task
SD:	Standard Deviation
SSCI:	8-item Stigma Scale for Chronic Illness
SOREMPs:	Sleep-onset REM periods
TSQM-9:	Treatment Satisfaction Questionnaire Medication
WPAI-GH:	Work Productivity and Activity Impairment Questionnaire General

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of management and treatment patterns of narcolepsy in adults' patients in real world practice in Spain. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.0, dated 20th December 2021 and amendments 1 and case report forms (CRFs) version 3.0, dated 19th January 2022.

3. STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective of the study is:

To describe the treatment patterns (pharmacological and non-pharmacological)

- in patients with narcolepsy between different subgroups, including:
  - Patients with and without cataplexy * (*Note: Patients with narcolepsy type 1 and type 2*)

Patients treated and naïve-treatment patients (*Note: not pharmacological treatments*)

** New terminology regarding type of narcolepsy has been consensed:*

- Patients with narcolepsy Type 1 are those patients with cataplexy
- Patients with narcolepsy Type 1 are those patients without cataplexy

This new terminology has been applied in all this document accordingly

3.2 Secondary Objectives

The secondary objectives are:

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

3.3 Exploratory Objectives

The exploratory objectives are:

1. Identify the proportion of patients with narcolepsy (Type 1 and Type 2) diagnosed and managed in public hospitals in Spain.
2. 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).
3. Describe utilization of health care resources associated with narcolepsy patients in Spain, before diagnosis of narcolepsy

4. STUDY DESIGN

4.1 General Description

A multicenter, non-interventional, cross-sectional, study with retrospective medical chart review, conducted in public and private Spanish institutions which 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 16 months to enroll all patients. 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

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.

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).

Considering 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%).

4.2 Schedule of Events

The schedule of events can be found in Section 4.1 of the protocol.

4.3 Changes to Analysis from Protocol

No changes in analysis or definitions included in the final protocol have been considered.

5. PLANNED ANALYSES

5.1 Interim Analysis

No interim analyses are planned for this study.

5.2 Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Real World (RW) Biostatistics following IQVIA SOPs. Final CSR will be performed using IQVIA template.

6. ANALYSIS SETS

6.1 All Subjects Enrolled Set [ENR]

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study and fulfilling all inclusion and none of exclusion criteria.

6.1.1 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 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 first 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.

6.1.2 Exclusion criteria

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

1. Patient with any serious degenerative disease (Alzheimer, Parkinson or epilepsy) or psychiatric condition
2. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

3. Patient participating in a clinical trial (≤12 months*)

*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.

6.2 Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all enrolled patients who received at least one dose of narcolepsy treatments.

If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

7. GENERAL CONSIDERATIONS

Patients will attend a single visit where they will answer study questionnaires and some clinical variables will be collected from clinical records.

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, 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.

Considering the study design, 3 periods of time will be considered:

- **Index Period** will be the period in which patient is diagnosed of narcolepsy.

- **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)

7.1 Windowing Conventions

No visit windowing will be performed for this study.

7.2 Collected Variables and Measures

Only variables included in the CRF will be used in this analysis. To describe real-world management and treatment patterns in narcolepsy patients in Spain, periods of time will be considered.

7.2.1 Primary endpoint

To achieve the primary objective of this study, describe the treatment patterns of narcolepsy, the following endpoints will be collected and analyzed:

- Percentage of use of treatments (pharmacological and non- pharmacological) (yes / no) in the study visit
    - Total narcolepsy population
        - Patients with Type 1 and Type 2 narcolepsy
- Use of different treatments (pharmacological and non-pharmacological) in the study visit
    - Total narcolepsy population
    - Stratified by the different subgroups
        - Patients with Type 1 and Type 2 narcolepsy
        - Patients treated and treatment-naïve patients

- A description of non-pharmacological treatments (since diagnosis): 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; Other

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).

7.2.2 Secondary endpoints

Below is detailed the secondary objectives of this study and all secondary endpoints that will be collected and analyzed to achieve them:

- Describe sociodemographic and clinical characteristics of patients with narcolepsy
    - Sociodemographic and clinical characteristics (general clinical history and narcolepsy characteristics) of patients with narcolepsy collected in the study visit will be presented stratified by treatment-naïve patients and 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 diagnosis processes 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: 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), ESS, PSG, MSLT and HLA haplotypes will be described.

- Time since first symptoms to diagnosis and time from diagnosis to first treatment will be described.

- To evaluate and describe clinician assessments (effectiveness) of the used narcolepsy treatments in the study period:

  - Percentage of treatments 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.

- 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 the 12 months before study visit 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 prior to study visit 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. The monetary cost will not be calculated.

  - 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?

- 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
    - EQ VAS
- To assess the perception of stigma in patients with narcolepsy in Spain:
  - To know the level of stigmatization of patients with narcolepsy the score in the SSCI-8 will be described.
- 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 (AE) reported

7.2.3 Exploratory endpoints

- 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 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 (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 before diagnosis will be described.
- Describe utilization of health care resources associated with narcolepsy patients in Spain, before diagnosis of narcolepsy
    - Description (quantity and type) of healthcare resources associated with narcolepsy patients 12 months before being diagnosed for this condition.

7.2.4 Other analysis

Different general linear models (GLM) for the continuous healthcare resources (number of visits, number of tests, number of hospitalizations,… the 12 months before study visit) will be estimated using continuous and/or categorical variables, with a p-value<0.1 at univariate level. Predictors such as age, gender, time since diagnosis, type of narcolepsy will be evaluated. According to the distribution of the dependent variable, logistic regression models will be considered according to the use or non-use of the resource.

In the same way, three models will be carried out to evaluate the predictive factors of QoL (EQ VAS), stigma (SSCI-8 score) and satisfaction (TSQM-9 global satisfaction score).

All those tables presented in section 18 of this document and that are stratified by type of narcolepsy will be analyzed in addition to type of narcolepsy by type of center (public or private). These tables will be included in an annex to the statistical report.

7.3 Software Version

All analyses will be conducted using SAS Enterprise Guide 7.15 or higher.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Tests and Confidence Intervals

A two-sided 95% confidence interval will be considered as a default (alpha= 5%). To analyze statistically significant differences between qualitative variables included as the secondary objective sociodemographic and clinical characteristics of patients with narcolepsy (gender and ethnicity), Chi-Square test, while for quantitative variables included in the same objective (such as age) t-test or Mann-Whitney non-parametric test according to the distribution of data.

8.2 Adjustments for Covariates and Factors to be Included in Analyses

No covariates and factor will be used in the analyses.

8.3 Missing data

Given the real-world nature and retrospective part of the study and the descriptive purposes of most of the objectives included, study variables will not be imputed.

Missing values and drop-outs will be counted in all description of variables, but no imputation will be considered in this study.

8.4 Examination of Subgroups

The variables description (primary, secondary, and exploratory) will be divided by groups. The following subgroups will be assessed:

- Type of narcolepsy
  - Type 1 (NT1)
  - Type 2 (NT2)

- Previous treatment (secondary objective 1)
  - Treated
  - Untreated (naïve): Patients who have not received any pharmacological treatment from diagnosis to study visit.

8.5 Derived variables

Some variables will be calculated to be analyzed:

- Patients untreated (naïve): Percentage of patients with narcolepsy who are not with any pharmacological treatment from diagnosis to study visit.
- Patients treated: Percentage of patients with narcolepsy whose are with any pharmacological treatment.

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition, withdrawals, and protocol violations (as defined in section 6.3), including inclusion and exclusion criteria will be presented for all enrolled patients.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for all subjects enrolled (ENR).

The following demographic and other baseline characteristics will be reported for this study:

- Age at the time of the visit

- Gender
- Ethnicity
- Educational level ongoing or completed level of education
- Occupational status and occupation
- Civil status
- Living conditions
- Height at treatment start (or last available before treatment initiation)
- Weight at treatment start (or last available before treatment initiation)
- BMI
- Blood pressure
- Smoking status
- Alcohol intake
- Exercise status
- Family history of narcolepsy in first or second-degree relatives

12. MEDICAL HISTORY

Medical History information will be presented for the ENR. This information will be collected from the CRF corresponding sections.

13. CONCOMITANT ILLNESSES

Concomitant illnesses will be presented for the ENR.

Comorbidities and other narcolepsy-associated disorders reported during the study period will be collected from comorbidities section and other narcolepsy associated disorders and concomitant treatment experienced by the patient during the study period page of the CRF.

14. MEDICATIONS

Medications will be presented for the ENR. It will include all treatments received the 12 months before the diagnosis of narcolepsy and also 12 months before study visit.

There will be six groups of medications according to the study groups:

- Stimulants
- Wakefulness-promoting agents
- Sodium Oxybate
- Antidepressants
- Benzodiazepines
- Other psychotropic agents

15. PATIENT REPORTED OUTCOMES (PRO)

At the study visit, patients several PROS will completed:

- Work Productivity and Activity Impairment Questionnaire General (WPAI-GH)
- EQ-5D Questionnaire
- Stigma Scale for Chronic Illness 8-item version (SSCI-8)
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)

15.1 WPAI-GH

Work Productivity and Activity Impairment Questionnaire General (WPAI-GH) will be used to estimated indirect health resources used. It will be obtained for:

- Absenteeism (work time missed): Q2/(Q2+Q4) x100
- Presenteeism (impairment at work / reduced on-the-job effectiveness): Q5/10 x100

- Work productivity loss (overall work impairment / absenteeism plus presenteeism): Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)] x100
- Activity Impairment / disability: Q6/10 x100

Information will be described as mean and standard deviation, median and interquartile range, minimum and maximum values. Valid and missing values will be also included.

15.2 EQ-5D

Quality of Life (QoL) will be assess using EQ-5D questionary. The information will be described according to the following dimensions:

- Mobility
- Self-Care
- Usual activities
- Pain / Discomfort
- Anxiety / Depression

Information will be described as number and percentage of patients with problems in each dimension. Valid and missing values will be also included.

15.3 SSCI-8

Regarding Stigma Scale for Chronic Illness 8-item version (SSCI-8), data will be described as mean and standard deviation, median and interquartile range, minimum and maximum values. Valid and missing values will be also included. SSCI-8 raw score will be calculated summing individual items. Stigma prevalence will be calculated (total score>8). It will be describing a frequency and percentage.

15.4 TSQM-9

Treatment Satisfaction Questionnaire for Medication (TSQM-9) domains will be described, including convenience, effectiveness, and global satisfaction.

EFFECTIVENESS ([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100
If one item is missing ([(Sum(Item 1? + Item 2? + Item 3?)) – 2] divided by 12) * 100

CONVENIENCE ([(Item 4 + Item 5 + Item 6) – 3] divided by 18) * 100
If one item is missing ([(Sum(Item 4? + Item 5? + Item 6?)) – 2] divided by 12) * 100

GLOBAL SATISFACTION ([(Item 7 + Item8 + Item 9) – 3] divided by 14) * 100
If either Item 7 or 8 is missing ([((Item7? + Item8? + Item 9)) – 2] divided by 10) * 100
If Item 9 is missing ([((Item7 + Item9)) – 2] divided by 8) * 100

Data will be reported as mean and standard deviation, median and interquartile range, minimum and maximum values. Valid and missing values will be also included.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). A description of AEs (related and not related to Takeda product) will be done, according to SOC and PT.

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18. APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Total column will include description of total evaluable sample (ENR). Main analysis will be presented stratified by subgroups group according to objectives.

18.1 Inclusion-exclusion criteria

Table 1. Patients' validation criteria

PATIENT INCLUSION CRITERIA, n (%)	**Total**
1. Patient aged **≥18 years** at the time of study inclusion	
2. Patient with confirmed diagnosis of narcolepsy 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	
PATIENT EXCLUSION CRITERIA, n (%)	
1.Patient with any serious degenerative disease (Alzheimer, Parkinson or epilepsy) or psychiatric condition	
2.Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study	
3.Patient participating in a clinical trial (≤12 months)	
Total patients enrolled (ENR)	
Narcolepsy Type 1 (NT1)	
Narcolepsy Type 2 (NT2)	
Not Classified*	

*These patients will be excluded from the analysis. If there are enough cases, the characteristics of these patients will be described separately.

18.2 Demographic and baseline characteristics

Table 2. Patients' sociodemographic and baseline characteristics

		NT1	NT2	Total	p-value
Age at the time of the visit, years	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Gender, n (%)	Male				
	Female				
	Valid N				
	N missing				
Ethnicity, n (%)	Caucasian				
	Hispanic				
	African				
	Asian / Oriental				
	Other				
	Valid N				
	N missing				
Educational level ongoing or completed level of education, n (%)	Without studies				
	Primary Studies				
	Secondary Studies				
	University Studies				
	Other Superior Studies				
	Valid N				
	N missing				
Occupational status and occupation, n (%)	Student				
	Employed				
	Self-employed				
	Employed but on sick leave due to the study disease				

		NT1	NT2	Total	p-value
	Permanent incapacity to work due to the study disease				
	Permanent incapacity to work due to other reasons				
	Unemployed				
	Retired				
	Domestic work				
	Other				
	Valid N				
	N missing				
Civil status, n (%)	Married/with partner				
	Divorced/separated				
	Unmarried				
	Widow/er				
	Valid N				
	N missing				
Living conditions, n (%)	Alone				
	Wife/Husband and /or sons				
	Family Caregivers				
	Other Caregivers				
	Valid N				
	N missing				

Table 3. Patients' physical examination at study visit

		NT1	NT2	Total	p-value
Height at treatment start or last available before treatment initiation, cm	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Weight at treatment start or last available before treatment initiation, kg	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				

		NT1	NT2	Total	p-value
	Valid N				
	N missing				
BMI, kg/m^2	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Blood pressure (systolic), mmHg	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Blood pressure (diastolic), mmHg	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Smoking status, n(%)	Current Smoker				
	Ex-Smoker				
	Non-Smoker				
	Valid N				
	N missing				
Alcohol intake, n(%)	Never				
	Once or less per month				
	2-4 times per month				
	2-3 times per week				
	4 or more times per week				
	Valid N				
	N missing				
Exercise status, n(%)	Never				
	Regular (1 - 3times/week)				
	Frequently (4 - 7 times /week)				

		NT1	NT2	Total	p-value
	Always (7 or more times/week)				
	Valid N				
	N missing				
Family history of narcolepsy in first- or second-degree relatives, n (%)	No				
	Yes				
	First-degree relatives				
	Second-degree relatives				
	Valid N				
	N missing				

18.3 Diagnosis of narcolepsy

Table 4. Specialists involved in diagnosis of patients with narcolepsy (secondary objective 2)

	NT1	NT2	Total	p-value
General Practitioner, n (%)				
Specialist, n (%)				
Specialist 1				
Specialist 2				
Specialist 3				
Specialist….				
Valid N				
N missing				

Table 5. Time since first symptoms to diagnosis, time from diagnosis to first treatment and symptoms at diagnosis (secondary objective 3)

		NT1	NT2	Total	p-value
	Mean (SD)				

		NT1	NT2	Total	p-value
Time since first symptoms to diagnosis	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Another disease related to narcolepsy of psychiatric disorders prior to diagnosis of narcolepsy, n (%)	No				
	Yes				
	Type 1				
	Type 2				
	…				
	Specialist 1				
	Specialist 2				
	…				
	Valid N				
	N missing				
Time from diagnosis to first pharmacological treatment	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Time from diagnosis to study visit	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Symptoms at diagnosis, n (%)	None				
	Excessive daytime sleepiness (EDS)				
	Cataplexy				
	Hallucinations upon awakening or going to sleep				
	Sleep paralysis				
	Disturbed night-time sleep				
	Others				

		NT1	NT2	Total	p-value
	Valid N				
	N missing				
Number of cataplexy attacks per week before diagnosis	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 6. Procedures or tests for the diagnosis of narcolepsy (secondary objective 3)

		NT1	NT2	Total	p-value
Clinical history, n (%)					
Clinical Assessment: Epworth sleepiness scale (ESS), n(%)					
ESS score	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Neurological Assessment, n (%)					
Polysomnogram (PSG), n (%)					
REM sleep latency in nocturnal PSG, n (%)					
Multiple sleep latency test (MSLT), n (%)					
Number of sleep-onset REM periods (SOREMPs)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Mean sleep latency (min)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

		NT1	NT2	Total	p-value
Apnea-hypopnea index (AHI), n (%)					
AHI Index, n (%)	5-14.9				
	15-29.9				
	>30				
	Valid N				
	N missing				
Other procedures, n (%)					
Electroencephalography (EEG					
Electrooculography					
Electromyography					
Recordings of respiratorymovements in your chest and tummy					
Recordings of airflow through your mouth and nose					
Pulse oximetry					
Electrocardiography (ECG)					
Other					
HLA typing, n (%)					
HLA DQB * 0602					
QB1*0304					
Other at diagnosis					
Hypocretin-1 CSF or Orexin, n (%)					
Levels in pg(mL al diagnosis, n (%)	Low (< or =110 pg/mL), which is indicative of type 1 narcolepsy				
	Intermediate (ranges between 111-200 pg/mL)				
	Normal (>200 pg/mL)				
	Valid N				
	N missing				
Levels at study visit, n (%)	Low (< or =110 pg/mL), which is indicative of type 1 narcolepsy				
	Intermediate (ranges between 111-200 pg/mL)				
	Normal (>200 pg/mL)				
	Valid N				
	N missing				

	NT1	NT2	Total	p-value
Valid N				
N missing				

18.4 Comorbidities

Table 7. Most prevalent comorbidities and other concomitant disorders associated with narcolepsy (present during the study period) (secondary objective 10)

		NT1	NT2	Total	p-value
Comorbidities, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type of comorbidities, n (%)	Depression				
	On going at study visit				
	Bipolar disorder				
	Anxiety disorder				
	Generalized anxiety disorder				
	Post-traumatic stress disorder				
	Social anxiety disorder				
	Panic disorder				
	Phobia disorder				
	Obsessive compulsive disorder				
	Diagnosis of attention deficit hyperactivity disorder (ADHD)				
	Obesity				
	Endocrine Disorders				
	Myocardial infarction				
	Urinary Incontinence				
	Congestive heart failure (CHF)				
	Peripheral vascular disease				

		NT1	NT2	Total	p-value
	Cardiovascular accident or transient ischemic attack (TIA)				
	Dementia (This was an exclusion criteria)				
	Chronic obstructive pulmonary disease (COPD)				
	Connective tissue disease				
	Peptic ulcer disease				
	Liver Disease				
	Mild				
	Moderate to severe				
	Diabetes Mellitus				
	None or diet controlled				
	Uncomplicated				
	End-organ damage				
	Hemiplegia				
	Moderate to severe chronic kidney disease (CKD)				
	Solid tumor				
	Localized				
	Metastatic				
	Leukemia				
	Lymphoma				
	AIDS				
	Others				
	Valid N				
	N missing				
Charlson comorbidity index	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 8. Treatment for comorbidities and other concomitant disorders associated with narcolepsy (during the study period)

		NT1	NT2	Total	p-value
Treatment for comorbidities and concomitant disorders, n (%)	Depression				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Bipolar disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Anxiety disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Generalized anxiety disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				

		NT1	NT2	Total	p-value
	Antidepressants				
	Benzodiazepines				
	Other				
	Generalized anxiety disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Panic disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Phobia disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Obsessive compulsive disorder				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				

		NT1	NT2	Total	p-value
	Antidepressants				
	Benzodiazepines				
	Other				
	Diagnosis of attention deficit hyperactivity disorder (ADHD)				
	Stimulants				
	Wakefulness- Promoting Agents				
	Sodium Oxybate				
	Gammahydroxybutyrate (GHB)				
	Antidepressants				
	Benzodiazepines				
	Other				
	Obesity				
	Endocrine Disorders				
	Treatment 1…				
	Myocardial infarction				
	Treatment 1…				
	Urinary Incontinence				
	Treatment 1…				
	Congestive heart failure (CHF)				
	Treatment 1…				
	Peripheral vascular disease				
	Treatment 1…				
	Cardiovascular accident or transient ischemic attack (TIA)				
	Treatment 1…				
	Dementia (exclusion criteria)				
	Treatment 1…				
	Chronic obstructive pulmonary disease (COPD)				
	Treatment 1…				
	Connective tissue disease				
	Treatment 1…				

		NT1	NT2	Total	p-value
	Peptic ulcer disease				
	Treatment 1…				
	Liver Disease				
	Treatment 1…				
	Diabetes Mellitus				
	Treatment 1…				
	Hemiplegia				
	Treatment 1…				
	Moderate to severe chronic kidney disease (CKD)				
	Treatment 1…				
	Solid tumor				
	Treatment 1…				
	Leukemia				
	Treatment 1…				
	Lymphoma				
	Treatment 1…				
	AIDS				
	Treatment 1…				
	Others				
	Treatment 1…				
	Valid N				
	N missing				

Table 9. Most prevalent comorbidities and other concomitant disorders associated with narcolepsy (on going at study visit) (secondary objective 10)

		NT1	NT2	Total	p-value
Comorbidities, n (%)	No				
	Yes				
	Valid N				
	N missing				

		NT1	NT2	Total	p-value
Type of comorbidities, n (%)	Depression				
	Bipolar disorder				
	Anxiety disorder				
	Generalized anxiety disorder				
	Post-traumatic stress disorder				
	Social anxiety disorder				
	Panic disorder				
	Phobia disorder				
	Obsessive compulsive disorder				
	Diagnosis of attention deficit hyperactivity disorder (ADHD)				
	Obesity				
	Endocrine Disorders				
	Myocardial infarction				
	Urinary Incontinence				
	Congestive heart failure (CHF)				
	Peripheral vascular disease				
	Cardiovascular accident or transient ischemic attack TIA				
	Dementia exclusion criteria				
	Chronic obstructive pulmonary disease (COPD)				
	Connective tissue disease				
	Peptic ulcer disease				
	Liver Disease				
	Mild				
	Moderate to sever				
	Diabetes Mellitus				
	None or diet controlled				
	Uncomplicated				
	End-organ damage				
	Hemiplegia				
	Moderate to severe chronic kidney disease (CKD)				

		NT1	NT2	Total	p-value
	Solid tumor				
	Localized				
	Metastatic				
	Leukemia				
	Lymphoma				
	AIDS				
	Others				
	Valid N				
	N missing				
Charlson comorbidity index	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

18.5 Treatment patterns

Table 10. Type of previous pharmacological treatment (treatments received in the 12 months prior to diagnosis) according to type of narcolepsy (exploratory objective 2)

		NT1	NT2	Total	p-value
Treatment, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type of treatment, n (%)	Stimulants				
	Wakefulness-Promoting Agents				
	Modafinil				
	Pitolisant				
	Solriamfetol				
	Other				
	Sodium Oxybate				

		NT1	NT2	Total	p-value
	Antidepressants				
	Benzodiazepines				
	Other psychotropic agents				
	Valid N				
	N missing				

Table 11. Type of pharmacological treatment (1st treatment after diagnosis) according to type of narcolepsy (primary objective)

		NT1	NT2	Total	p-value
1st Treatment, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type of treatment, n (%)	Stimulants - monotherapy				
	Wakefulness-Promoting Agents - monotherapy				
	Modafinil				
	Pitolisant				
	Solriamfetol				
	Other				
	Sodium Oxybate - monotherapy				
	Antidepressants - monotherapy				
	Benzodiazepines - monotherapy				
	Other psychotropic agents - monotherapy				
	Combinations (all combination to be described)				
	Valid N				
	N missing				
Duration (in months) of first treatment	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				

		NT1	NT2	Total	p-value
	N missing				

Table 12. Type of pharmacological treatment (since diagnosis up to study visit) according to type of narcolepsy (primary objective)

		NT1	NT2	Total	p-value
Treatment, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type of treatment, n (%)	Stimulants				
	Wakefulness-Promoting Agents				
	Modafinil				
	Pitolisant				
	Solriamfetol				
	Other				
	Sodium Oxybate				
	Antidepressants				
	Benzodiazepines				
	Other psychotropic agents				
	Combinations (modafenil, pitolisant, sodium Oxybate, solriamfetol)*				
	Valid N				
	N missing				

* how these treatments combined with other treatments, independently of the line of treatment

Table 13. Type of non-pharmacological treatment since diagnosis according to type of narcolepsy (primary objective)

		NT1	NT2	Total	p-value
	No				

		NT1	NT2	Total	p-value
Non-pharmacological treatment, n (%)	Yes				
	Valid N				
	N missing				
Type, n (%)	Take short naps				
	Maintain a regular sleep schedule				
	Avoid caffeine or alcohol before bedtime				
	Avoid smoking, especially at night				
	Exercise daily				
	Avoid large, heavy meals right before bedtime				
	Other				
	Valid N				
	N missing				

Table 14. Type of non-pharmacological treatment since diagnosis according to treated or untreated patients (primary objective)

		Naïve	Treated	Total	p-value
Non-pharmacological treatment, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type, n (%)	Take short naps				
	Maintain a regular sleep schedule				
	Avoid caffeine or alcohol before bedtime				
	Avoid smoking, especially at night				
	Exercise daily				
	Avoid large, heavy meals right before bedtime				
	Other				
	Valid N				
	N missing				

Table 15. Type of pharmacological treatment (at study visit) according to type of narcolepsy (primary objective)

		NT1	NT2	Total	p-value
Treatment, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type of treatment, n (%)	Stimulants				
	Wakefulness-Promoting Agents				
	Modafinil				
	Pitolisant				
	Solriamfetol				
	Other				
	Sodium Oxybate				
	Antidepressants				
	Benzodiazepines				
	Combinations (all combinations to be described)				
	Other psychotropic agents				
	Valid N				
	N missing				

Table 16. Clinician assessment (effectiveness) of the used narcolepsy treatments in the study period since diagnosis (secondary objective 4)

		Stimulants	Wakefulness-Promoting Agents	Modafinil	Pitolisant	Solriamfetol	Sodium oxybate	Antidepressants	Benzodiazepines
NT1 (total)									
Effectiveness of treatment by Clinician Assessment, n (%)	None								
	Assessment with scales								
	SART								
	MWT								
	ESS								

		Stimulants	Wakefulness-Promoting Agents	Modafinil	Pitolisant	Solriamfetol	Sodium oxybate	Antidepressants	Benzodiazepines
	Cataplexy scales								
	Other assessments								
	Other 1								
	Other 2								
	Valid N*								
	N missing								
SART value	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
MWT minutes	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
ESS score	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
Cataplexy scale score	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
NT2									

		Stimulants	Wakefulness-Promoting Agents	Modafinil	Pitolisant	Solriamfetol	Sodium oxybate	Antidepressants	Benzodiazepines
Effectiveness of treatment by Clinician Assessment, n (%)	None								
	Assessment with scales								
	SART								
	MWT								
	ESS								
	Cataplexy scales								
	Other assessments								
	Other 1								
	Other 2								
	Valid N*								
	N missing								
SART value	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
MWT minutes	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
ESS score	Mean (SD)								
	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								
	Mean (SD)								

		Stimulants	Wakefulness-Promoting Agents	Modafinil	Pitolisant	Solriamfetol	Sodium oxybate	Antidepressants	Benzodiazepines
Cataplexy scale score	Median (Q1-Q3)								
	Min-Max								
	Valid N*								
	N missing								

*N valid correspond to total of treatments

18.6 Direct and indirect healthcare resources utilization

18.6.1 Healthcare resources in the last 12 months prior to study visit

Table 17. Direct medical healthcare resources used by patients – treatments in the last year prior to study visit (secondary objective 5)

		NT1	NT2	Total	p-value
Treatment, n (%)	No				
	Yes				
	Valid N				
	N missing				
Type of treatment, n (%)	Stimulants				
	Wakefulness-Promoting Agents				
	Modafinil				
	Pitolisant				
	Solriamfetol				
	Other				
	Sodium Oxybate				
	Antidepressants				
	Benzodiazepines				
	Other psychotropic agents				
	Valid N				
	N missing				

Table 18. Direct medical healthcare resources used by patients - Outpatients visits in the last year (secondary objective 5)

		NT1	NT2	Total	p-value
Routine monitoring visits, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of routine monitoring visits	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Specialists involved, n (%)	General Practitioner				
	Specialist				
	Neurologist				
	Neurophysiologist				
	Psychiatris				
	Other				
	Other 1				
	…				
	Valid N				
	N missing				
Number of visits to General Practitioner	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to Neurologist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

		NT1	NT2	Total	p-value
Number of visits to Neurophysiologist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to Psychiatrist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to other specialist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 19. Direct medical healthcare resources used by patients – Tests conducted in the last year (secondary objective 5)

		NT1	NT2	Total	p-value
Tests, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of tests	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Tests conducted, n (%)	Clinical history				
	Presence of cataplexy				
	Neurological Assessment				

		NT1	NT2	Total	p-value
	Clinical Assessment				
	Determination of Hypocretin-1 CSF or Orexin				
	Apnea-hypopnea index (AHI)				
	Number of sleep-onset REM periods (SOREMPs)				
	Epworth Sleepiness Scale (ESS) score				
	PSG				
	MSLT				
	Laboratory				
	Other				
	Other 1				
	…				
	Valid N				
	N missing				
Number of clinical histories	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Presence of cataplexy	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Neurological Assessment	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Clinical Assessment	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				

		NT1	NT2	Total	p-value
	Valid N				
	N missing				
Number of determinations of Hypocretin-1 CSF or Orexin	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Apnea-hypopnea index (AHI)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of sleep-onset REM periods (SOREMPs)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Epworth Sleepiness Scale (ESS)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of PSG	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of MSLT	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

		NT1	NT2	Total	p-value
Number of laboratories	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Other	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 20. Direct medical healthcare resources used by patients – Emergency visits in the last year (secondary objective 5)

		NT1	NT2	Total	p-value
Emergency visits, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of emergency visits	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 21. Direct medical healthcare resources used by patients – Hospitalizations in the last year (secondary objective 5)

		NT1	NT2	Total	p-value
Hospitalizations, n (%)	No				
	Yes				
	Valid N				

		NT1	NT2	Total	p-value
	N missing				
Total number of hospitalizations	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Hospitalizations' duration (days)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 22. Direct medical healthcare resources used by patients – complications derived from narcolepsy in the last year (secondary objective 5)

		NT1	NT2	Total	p-value
Complications, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of complications	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Type of complications, n (%)	Obesity				
	Interference with intimate relationships				
	Fertility				
	Physical harm: Attending to psychiatrist				
	Work problems				
	Others				
	Other 1…				

		NT1	NT2	Total	p-value
	Valid N				
	N missing				

Table 23. Indirect health resources - WPAI questionnaire scores (secondary objective 6)

		NT1	NT2	Total	p-value
Absenteeism	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Presenteeism	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Work productivity loss	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Activity Impairment / disability	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 24. Indirect health care – Ad-hoc questionnaire (secondary objective 6)

		NT1	NT2	Total	p-value
Days off work (sick leave) in the last year due to narcolepsy, n (%)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				

		NT1	NT2	Total	p-value
	Valid N (1)				
	N missing				
Narcolepsy has influenced/affected the fact that you do not work, n (%)	No				
	Yes				
	Valid N (2)				
	N missing				
Due to narcolepsy your level of work productivity is or has been lower, n (%)	No				
	Yes				
	Valid N (1)				
	N missing				
Narcolepsy has affected you or may have affected your lack of professional promotion, n (%)	No				
	Yes				
	Valid N (1)				
	N missing				
Near miss accidents, n (%)	No				
	Yes				
	Related with symptoms				
	Due to medications				
	Other				
	Required ambulance presence				
	Required ER Visit				
	Required Hospital Admission				
	Valid N				
	N missing				
Motor vehicle accidents, n (%)	No				
	Yes				
	Related with symptoms				
	Due to medications				
	Other				
	Required ambulance presence				
	Required ER Visit				
	Required Hospital Admission				

		NT1	NT2	Total	p-value
	Valid N				
	N missing				
Work-related accident, n (%)	No				
	Yes				
	Related with symptoms				
	Due to medications				
	Other				
	Required ambulance presence				
	Required ER Visit				
	Required Hospital Admission				
	Valid N				
	N missing				

(1) Patients who have worked

(2) Patients who have not worked in the last year

18.6.2 Healthcare resources before diagnosis of narcolepsy

Table 25. Utilization of health care resources associated with narcolepsy before diagnosis – outpatients visits (exploratory objective 3)

		NT1	NT2	Total	p-value
Routine monitoring visits, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of routine monitoring visits	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Specialists involved, n (%)	Total				

		NT1	NT2	Total	p-value
	General Practitioner				
	Specialist				
	Neurologist				
	Neurophysiologist				
	Psychiatrist				
	Other				
	Other 1				
	…				
	Valid N				
	N missing				
Number of visits to General Practitioner	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to Neurologist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to Neurophysiologist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to Psychiatrist	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of visits to other specialist	Mean (SD)				
	Median (Q1-Q3)				

		NT1	NT2	Total	p-value
	Min-Max				
	Valid N				
	N missing				

Table 26. Utilization of health care resources associated with narcolepsy before diagnosis – Tests conducted (exploratory objective 3)

		NT1	NT2	Total	p-value
Tests, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of tests	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Tests conducted, n (%)	Clinical history				
	Presence of cataplexy				
	Neurological Assessment				
	Clinical Assessment				
	Determination of Hypocretin-1 CSF or Orexin				
	Apnea-hypopnea index (AHI)				
	Number of sleep-onset REM periods (SOREMPs)				
	ESS				
	PSG				
	MSLT				
	Laboratory				
	Other				
	Other 1				
	…				
	Valid N				

		NT1	NT2	Total	p-value
	N missing				
Number of clinical histories	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Presence of cataplexy	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Neurological Assessment	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Clinical Assessment	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Determination of Hypocretin-1 CSF or Orexin	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Apnea-hypopnea index (AHI)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
	Mean (SD)				

		NT1	NT2	Total	p-value
Number of Number of sleep-onset REM periods (SOREMPs)	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of ESS	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of PSG	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of MSLT	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of laboratories	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Number of Other	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 27. Utilization of health care resources associated with narcolepsy before diagnosis – Emergency visits (exploratory objective 3)

		NT1	NT2	Total	p-value
Emergency visits, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of emergency visits	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 28. Utilization of health care resources associated with narcolepsy before diagnosis – Hospitalizations (exploratory objective 3)

		NT1	NT2	Total	p-value
Hospitalizations, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of Hospitalizations	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Hospitalizations durations (days)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

Table 29. Utilization of health care resources associated with narcolepsy before diagnosis – complications derived from narcolepsy (exploratory objective 3)

		NT1	NT2	Total	p-value
Complications, n (%)	No				
	Yes				
	Valid N				
	N missing				
Total number of complications	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Type of complications, n (%)	Obesity				
	Interference with intimate relationships				
	Fertility				
	Physical harm: Attending to psychiatrist				
	Work problems				
	Others				
	Other 1…				
	Valid N				
	N missing				

18.7 Patient Reported Outcomes (PRO)

18.7.1 Health-Related Quality of Life (HRQoL)

Table 30. EQ-5D Questionnaire (secondary objective 7)

		NT1	NT2	Total	p-value
Mobility, n (%)	I have no problems in walking about				
	I have slight problems in walking about				
	I have moderate problems in walking about				
	I have severe problems in walking about				
	I am unable to walk about				
	Valid N				

		NT1	NT2	Total	p-value
	N missing				
Self-Care, n (%)	I have no problems washing or dressing myself				
	I have slight problems washing or dressing myself				
	I have moderate problems washing or dressing myself				
	I have severe problems washing or dressing myself				
	I am unable to wash or dress myself				
	Valid N				
	N missing				
Usual activities, n (%)	I have no problems doing my usual activities				
	I have slight problems doing my usual activities				
	I have moderate problems doing my usual activities				
	I have severe problems doing my usual activities				
	I am unable to do my usual activities				
	Valid N				
	N missing				
Pain / Discomfort, n (%)	I have no pain or discomfort				
	I have slight pain or discomfort				
	I have moderate pain or discomfort				
	I have severe pain or discomfort				
	I have extreme pain or discomfort				
	Valid N				
	N missing				
Anxiety / Depression, n (%)	I am not anxious or depressed				
	I am slightly anxious or depressed				
	I am moderately anxious or depressed				
	I am severely anxious or depressed				
	I am extremely anxious or depressed				
	Valid N				
	N missing				
EQ VAS (0-100)	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				

		NT1	NT2	Total	p-value
	Valid N				
	N missing				

18.7.2 Perception of stigma

Table 31. Description of SSCI score (secondary objective 8)

		NT1	NT2	Total	p-value
SSCI-8 score	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
SSCI-8 (categorical), n (%)	= 8 points				
	> 8 points				
	Valid N				
	N missing				

18.7.3 Treatment satisfaction

Table 32. Description of TSQM-9 domains score (secondary objective 9)

		NT1	NT2	Total	p-value
Effectiveness	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Convenience	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				

		NT1	NT2	Total	p-value
	N missing				
Global satisfaction	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				

18.8 Factors related to healthcare resources utilization, quality of life, stigma and satisfaction

Table 33. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to healthcare resources utilization - number of routine monitoring visits in the last year

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					
…					

* variables with p<0.1 in the univariate

Table 34. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to healthcare resources utilization - number of tests conducted in the last year

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					
…					

* variables with p<0.1 in the univariate

Table 35. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to healthcare resources utilization - number of emergency visits in the last year

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					
…					

* variables with p<0.1 in the univariate

Table 36. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to healthcare resources utilization - number of hospitalizations in the last year

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					
…					

Table 37. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to healthcare resources utilization – number of complications in the last year

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					
…					

Table 38. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to QoL – EQ VAS

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Age					
Gender					
…					

Table 39. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to stigma – SSCI-8 score

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					
…					

Table 40. Multivariate linear regression analysis of the sociodemographic and clinical characteristics related to stigma – TSQM-9 global satisfaction score

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
Intercept	-				
Age					
Gender					

Variable	Univariate	Multivariate*			
	Pr>|t|	Estimate	Standard error	t-value	Pr>|t|
…					

18.9 Proportion of patients with narcolepsy diagnosed and managed in public hospitals

Table 41. Patients with narcolepsy (with and without cataplexy) diagnosed and managed in public hospitals (exploratory objective 1)

Only public hospitals		Total	Type 1	Type 2
Total population under the hospital's circumscription	Mean (SD)		-	-
	Median (Q1-Q3)		-	-
	Min-Max		-	-
	Valid N		-	-
	N missing		-	-
Total of patients with narcolepsy attended in the participating site according to routine clinical practice and type of narcolepsy	Mean (SD)			
	Median (Q1-Q3)			
	Min-Max			
	Valid N			
	N missing			
Proportion of patients with narcolepsy	(%)			
New patients with narcolepsy diagnosed per year	Mean (SD)			
	Median (Q1-Q3)			
	Min-Max			
	Valid N			
	N missing			
Proportion of new patients with narcolepsy	(%)			

18.10 Sociodemographic and clinical characteristics of patients with narcolepsy according to treated and untreated patients.

Following tables will be analyzed considering the type of narcolepsy (NT1 and NT2)

Table 42. Sociodemographic and clinical characteristics of patients with narcolepsy stratified by treated and untreated patients (secondary objective 1)

		Untreated (naïve)	Treated	Total	p-value
Age at the time of the visit, years	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Gender, n (%)	Male				
	Female				
	Valid N				
	N missing				
Ethnicity, n (%)	Caucasian				
	Hispanic				
	African				
	Asian / Oriental				
	Other				
	Valid N				
	N missing				
Educational level ongoing or completed level of education, n (%)	Without studies				
	Primary Studies				
	Secondary Studies				
	University Studies				
	Other Superior Studies				
	Valid N				
	N missing				
Occupational status and occupation, n (%)	Student				
	Employed				

		Untreated (naïve)	Treated	Total	p-value
	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				
	Unemployed				
	Retired				
	Domestic work				
	Other				
	Valid N				
	N missing				
Civil status, n (%)	Married/with partner				
	Divorced/separated				
	Unmarried				
	Widow/er				
	Valid N				
	N missing				
Living conditions, n (%)	Alone				
	Wife/Husband and /or sons				
	Family Caregivers				
	Other Caregivers				
	Valid N				
	N missing				

Table 43. Patients' physical examination at study visit stratified by treated and untreated patients (secondary objective 1)

		Untreated (naïve)	Treated	Total	p-value
	Mean (SD)				
	Median (Q1-Q3)				

		Untreated (naïve)	Treated	Total	p-value
Height at treatment start or last available before treatment initiation, cm	Min-Max				
	Valid N				
	N missing				
Weight at treatment start or last available before treatment initiation, kg	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
BMI, kg/m^2	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Blood pressure (systolic), mmHg	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Blood pressure (diastolic), mmHg	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Smoking status, n(%)	Current Smoker				
	Ex-Smoker				
	Non-Smoker				
	Valid N				
	N missing				
Alcohol intake, n(%)	Never				
	Once or less per month				
	2-4 times per month				

		Untreated (naïve)	Treated	Total	p-value
	2-3 times per week				
	4 or more times per week				
	Valid N				
	N missing				
Exercise status, n(%)	Never				
	Regular (1 - 3times/week)				
	Frequently (4 - 7 times /week)				
	Always (7 or more times/week)				
	Valid N				
	N missing				
Family history of narcolepsy in first- or second-degree relatives, n (%)	No				
	Yes				
	First-degree relatives				
	Second-degree relatives				
	Valid N				
	N missing				

18.11 Adverse drug reaction associated to narcolepsy treatments

Table 44. Adverse events (AE) associated to narcolepsy treatments (secondary objective 11)

		Adverse event related to a Takeda product		
		No	Yes	Total
Adverse event, n (%)	No			
	Yes			
	Valid N			
	N missing			
Type of AE*	SOC1			
	PT1			

		Adverse event related to a Takeda product		
		No	Yes	Total
	…			
	SOC2			
	PT1			
	…			
	Valid N			
	N missing			

*MedDRA codification

19. ANNEX

All those tables presented in section 18 of this document and that are stratified by type of narcolepsy will be analyzed in addition to type of narcolepsy by type of center (public or private). These tables will be included in an annex to the statistical.

The following two tables are shown as an example:

Table 45. Patients' sociodemographic and baseline characteristics by type of center (NT1)

		NT1		Total	p-value
		Public	Private		
Age at the time of the visit, years	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Gender, n (%)	Male				
	Female				
	Valid N				
	N missing				
Ethnicity, n (%)	Caucasian				

		NT1		Total	p-value
		Public	Private		
	Hispanic				
	African				
	Asian / Oriental				
	Other				
	Valid N				
	N missing				
Educational level ongoing or completed level of education, n (%)	Without studies				
	Primary Studies				
	Secondary Studies				
	University Studies				
	Other Superior Studies				
	No available				
	Valid N				
	N missing				
Occupational status and occupation, n (%)	Student				
	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				
	Unemployed				
	Retired				
	Domestic work				
	Other				
	Valid N				
	N missing				
Civil status, n (%)	Married/with partner				
	Divorced/separated				
	Unmarried				
	Widow/er				

		NT1		Total	p-value
		Public	Private		
	Valid N				
	N missing				
Living conditions, n (%)	Alone				
	Wife/Husband and /or sons				
	Family Caregivers				
	Other Caregivers				
	Valid N				
	N missing				

Table 46. Patients' sociodemographic and baseline characteristics by type of center (NT2)

		NT2		Total	p-value
		Public	Private		
Age at the time of the visit, years	Mean (SD)				
	Median (Q1-Q3)				
	Min-Max				
	Valid N				
	N missing				
Gender, n (%)	Male				
	Female				
	Valid N				
	N missing				
Ethnicity, n (%)	Caucasian				
	Hispanic				
	African				
	Asian / Oriental				
	Other				
	Valid N				
	N missing				
	Without studies				

		NT2		Total	p-value
		Public	Private		
Educational level ongoing or completed level of education, n (%)	Primary Studies				
	Secondary Studies				
	University Studies				
	Other Superior Studies				
	No available				
	Valid N				
	N missing				
Occupational status and occupation, n (%)	Student				
	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				
	Unemployed				
	Retired				
	Domestic work				
	Other				
	Valid N				
	N missing				
Civil status, n (%)	Married/with partner				
	Divorced/separated				
	Unmarried				
	Widow/er				
	Valid N				
	N missing				
Living conditions, n (%)	Alone				
	Wife/Husband and /or sons				
	Family Caregivers				
	Other Caregivers				
	Valid N				

		NT2		Total	p-value
		Public	Private		
	N missing				