Post-Authorisation Safety Study Protocol

OZAWADE

Study code: P21-02

Title	A multi-center, observational prospective post-authorization safety study to compare the cardiovascular risks and long-term safety of OZAWADE® in patients with obstructive sleep apnoea treated or not by primary therapy and exposed or not to OZAWADE® when used in routine medical practice.
Protocol version identifier	3.0
Date of last version of protocol	23NOV2023
EU PAS register number	Still has to be registered
Active substance	N07XX11, pitolisant (chlorhydrate)
Medicinal product	OZAWADE® 4,5 mg, film-coated tablet OZAWADE® 18 mg, film-coated tablet
Product reference	OZAWADE® 4,5 mg, film-coated tablet: EU/1/21/1546/001 OZAWADE® 18 mg, film-coated tablet: EU/1/21/1546/002
Procedure number	EMEA/H/C/0005117
Marketing authorisation holder(s)	Bioprojet Pharma 9 rue Rameau 75002 Paris Phone: +[redacted] www.bioprojet.com
Joint PASS	No
Research questions and objectives	**Primary objective** The primary objective of this study is to demonstrate that OZAWADE® supplementation in obstructive sleep apnoea (OSA) patients does not increase the incidence of cardiovascular events (CVE) compared with OZAWADE® unexposed patients (non-inferiority) and to evaluate the long-term safety of OZAWADE® when used as per SmPC in patients with OSA.

	Secondary objective(s) *Safety* • To evaluate the time to cardiovascular events of interest in OSA patients exposed to OZAWADE® as per SmPC compared with OZAWADE®-unexposed OSA patients. • To evaluate the time to adverse drug reaction (serious and non-serious) in OSA patients exposed to OZAWADE® as per SmPC compared with OZAWADE® unexposed OSA patients. **Exploratory objective(s)** *Effectiveness* • To evaluate the effectiveness of OZAWADE® through the Epworth Sleepiness Scale (ESS) when used as per SmPC in patients with OSA. • To evaluate the effectiveness of OZAWADE® through the Maintenance of wakefulness test (MWT) when used as per SmPC in patients with OSA. • To evaluate the effectiveness of OZAWADE® through the Multiple Sleep Latency Test (MSLT) when used as per SmPC in patients with OSA. • To evaluate the effectiveness of OZAWADE® through the Fatigue Severity Scale (FSS) when used as per SmPC in patients with OSA. *Adherence* • To evaluate the adherence to OZAWADE® when used as per SmPC in patients with OSA. • To evaluate the adherence to continuous positive airway pressure (CPAP) / mandibular advancement devices (MAD), between the group of patients exposed to OZAWADE® and the group of patients not exposed to OZAWADE®. *Other* • To evaluate the reduction of car/traffic accidents.
Country(-ies) of study	4 countries: France, Italy, Germany and possibly Netherlands, Belgium or Spain
Author	[redacted] Study Medical Director Bioprojet Pharma Tel: +[redacted] E-mail address: [redacted]

This protocol was drafted according to Good Epidemiological Practices

Confidential information

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Bioprojet Pharma 9 rue Rameau 75002 Paris France Phone: +[redacted] www.bioprojet.com
MAH contact person	[redacted] Regulatory Affairs Director Tel: +[redacted] E-mail address:[redacted]

Participation to the study / Confidential agreement

Information contained in this protocol are confidential and are the property of Bioprojet Pharma.

This protocol contains all necessary details to conduct the study. Each participating physician should ensure strict compliance to the protocol. The participating physician should in no case be a source of protocol modification without having previously obtained Bioprojet Pharma's permission. Respect of the inclusion and exclusion criteria should be documented by the participating physician [or the Designee] on the data collection questionnaire. Participating physicians should take all possible measures to complete the study within the allocated time.

Access to all information provided by Bioprojet Pharma may be given to all involved collaborators under the supervision and responsibility of the participating physician. People taking note of this information should be informed of their confidential nature; they must respect confidentiality without restrictions.

The contents of this protocol cannot be used for other non-interventional study or clinical study and will not be disclosed to any other person or entity without prior written authorization of Bioprojet Pharma. The commitment does not apply to the disclosure required by law or governmental regulation; nevertheless, Bioprojet Pharma should be informed prior to such disclosure.

Bioprojet Pharma may terminate the study at any time, this discontinuation may be motivated or not.

Additional information that could be added to this protocol are also confidential and the property of Bioprojet Pharma; they must remain confidential as the content of this protocol.

Approval

A multi-center, observational prospective post-authorization safety study to compare the cardiovascular risks and long-term safety of OZAWADE® in patients with obstructive sleep apnoea treated or not by primary therapy and exposed or not to OZAWADE® when used in routine medical practice

Protocol N° P21-02

Version 3.0

Dated 23 NOV 2023

For the Sponsor

[redacted] Signature: Date:
Head of Global Pharmacovigilance, QPPV

P/O [redacted] Head of clinical Development

[redacted] Signature: Date:
Study Medical Director

[redacted] Signature: Date:
Head of Clinical Development

[redacted] Signature: Date:
Responsible Pharmacist

Scientific Committee/Advisory Board

Prof Jean-Louis PEPIN, M.D. Signature: Date:
Professor of Clinical Physiology
CHU Grenoble Alpes
Boulevard de la Chantourne - CS10217
38043 Grenoble CEDEX 9
France

Scientific Committee member and International Study Coordinator

[redacted]

Signature:

Date:

[redacted]

Scientific Committee member

1. Table of contents

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2. List of abbreviations

Abbreviations, specific or unusual terms and units used in this study protocol are listed in the Table below:

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHI	Apnoea-Hypopnea Index
ALc	Alcohol Consumption
ARD	Absolute Risk Difference
BDI	Beck Depression Inventory
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
ClinRO(s)	Clinician Reported Outcome(s)
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRO	Contract Research Organisation
CRA	Clinical Research Assistant
CV	Cardiovascular
CVE	Cardiovascular Events
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDS	Excessive Daytime Sleepiness
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
FSS	Fatigue Severity Scale
FU	Follow-Up
GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practices
HDL	High Density Lipoproteins
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
IRB	Institutional Review Boards
LDL	Low Density Lipoproteins
MACE	Major Adverse Cardiovascular Events
MAD	Mandibular Advancement Devices
MedDRA	Medical Dictionary for Regulatory Activities
MMAS-8	Morisky Medication Adherence Scale 8-item
MSLT	Multiple Sleep Latency Test

MWT	Maintenance of wakefulness test
NIM	Non-Inferiority Margin
OSA	Obstructive Sleep Apnoea
PASS	Post-Authorization Safety Study
PI	Package Insert
PT	Preferred Term
PRO(s)	Patient Reported Outcome(s)
RMP	Risk Management Plan
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMH	Smoking Habits
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SS	Special Situation

3. Responsible parties

3.1. Marketing Authorization Holder

Bioprojet Pharma
9 rue Rameau
75002 Paris
France
E-mail address: [redacted]

MAH Representative

[redacted]
Regulatory Affairs Director
Bioprojet Pharma
9 rue Rameau
75002 Paris
France
Tel: +[redacted]
E-mail address: [redacted]

3.2. Contract Research Organization

[redacted]
[redacted]
[redacted]
France

3.3. Scientific Committee/Advisory Board

Prof Jean-Louis PEPIN, M.D.
Professor of Clinical Physiology
CHU Grenoble Alpes
Boulevard de la Chantourne - CS10217
38043 Grenoble CEDEX 9
France
E-mail address: [redacted]

[redacted]
[redacted]
[redacted]
[redacted]
Email address: [redacted]

3.4. Principal Investigator / International Study Coordinator

Prof Jean-Louis PEPIN, M.D.
Professor of Clinical Physiology
CHU Grenoble Alpes
Boulevard de la Chantourne - CS10217
38043 Grenoble CEDEX 9
France
E-mail address: [redacted]

3.5. Other Investigators

The list of all participating physicians is available upon request as a stand-alone document.

4. Abstract

Title

A multi-center, observational prospective post-authorization safety study to compare the cardiovascular risk and long-term safety of OZAWADE® in patients with obstructive sleep apnoea treated or not by primary therapy and exposed or not to OZAWADE® when used in routine medical practice.

Background and Rationale

Background

Obstructive Sleep Apnoea (OSA) is a highly prevalent chronic disease affecting nearly 1 billion people aged 30–69 years worldwide [1]. Continuous positive airway pressure (CPAP) is the gold-standard first-line treatment for patients with symptomatic OSA. However, a substantial proportion of CPAP-treated OSA patients continue to experience Excessive daytime sleepiness (EDS) despite optimized CPAP therapy.

Pitolisant is a selective histamine H3 inverse agonist/antagonist for treating patients with narcolepsy and has also showed efficacy in OSA patients treated or not with CPAP. Under the trade name OZAWADE®, it has been authorized for use in the EU on July 22, 2021, in adult patients with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated OSA primary therapy, such as CPAP and Mandibular Advancement Devices (MAD).

Rationale

The Risk Management Plan for OZAWADE® identifies some potential risks and missing information about safety. One of the potential risks concerns cardiovascular (CV) events including QT-interval prolongation and the missing information refers to the long-term safety of OSA patient treated with OZAWADE® according to the SmPC.

The Sponsor has agreed with the EMA to conduct a Post-Authorization Safety Study (PASS) as part of the Risk Management Plan (RMP) for OZAWADE®.

Research Question and Objectives

Primary objective

The primary objective of this study is to demonstrate that OZAWADE® supplementation in obstructive sleep apnoea (OSA) patients does not increase the incidence of cardiovascular events (CVE) compared with OZAWADE® unexposed patients (non-inferiority) and to evaluate the long-term safety of OZAWADE® when used as per SmPC in patients with OSA.

Secondary objective(s)

Safety

- To evaluate the time to cardiovascular events of interest in OSA patients exposed to OZAWADE® as per SmPC compared with OZAWADE® unexposed OSA patients.
- To evaluate the time to adverse drug reaction (serious and non-serious) in OSA patients exposed to OZAWADE® as per SmPC compared with OZAWADE® unexposed OSA patients.

Exploratory objective(s)

Effectiveness

- To evaluate the effectiveness of OZAWADE® through the Epworth Sleepiness Scale (ESS) when used as per SmPC in patients with OSA.
- To evaluate the effectiveness of OZAWADE® through the Maintenance of wakefulness test (MWT) when used as per SmPC in patients with OSA.
- To evaluate the effectiveness of OZAWADE® through the Multiple Sleep Latency Test (MSLT) when used as per SmPC in patients with OSA.
- To evaluate the effectiveness of OZAWADE® through the Fatigue Severity Scale (FSS) when used as per SmPC in patients with OSA.

Adherence

- To evaluate the adherence to OZAWADE® when used as per SmPC in patients with OSA.
- To evaluate the adherence to continuous positive airway pressure (CPAP) / mandibular advancement devices (MAD), between the group of patients exposed to OZAWADE® and the group of patients not exposed to OZAWADE®.

Other

- To evaluate the reduction of car/traffic accidents.

Study Design

This is a prospective, observational, multi-center, open-label, long term, cohort study (OZAWADE® exposed and OZAWADE® unexposed) designed to collect data on the long-term safety of OZAWADE® treatment. This study will be conducted in patients with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated OSA primary therapy. The study will be conducted by physicians specialized in sleep management such as sleep specialists, pulmonologists, cardiologists, otorhinolaryngologist and neurologists.

Primary, secondary, and exploratory endpoints

Primary endpoint

The primary endpoint will be the occurrence of at least one cardiovascular event (CVE) or one serious drug related adverse event during the five years of follow up for each participating patient.

Secondary endpoints

The following secondary endpoints will separately investigate each type of event globally appraised by the primary endpoint:

- Time to CVE occurrence and CVE distribution in time according to classification MACE and non-MACE
- Time to Adverse Drug Reaction (ADR)
- Time to Serious Adverse Drug Reaction (SADR)
- Beck Depression Inventory global score at each collection time

Exploratory endpoints

Effectiveness

Change from patient inclusion date to the end of study as evaluated with:

- Epworth Sleepiness Scale (ESS) global score
- Maintenance of wakefulness test (MWT) mean sleep latency
- Multiple Sleep Latency Test (MSLT) mean sleep latency
- Fatigue Severity Scale (FSS) global score

Adherence

- Rate of patients compliant with their OZAWADE® treatment (according to the 8-item Morisky Score) at each visit.
- Rate of patients compliant with their primary therapy (according to the mean number of hours of use per night during the last three months) at each visit.

Other

Incidence of car accidents at driving (comparison of answers to the questionnaire "assessment of sleeping at driving" between inclusion and yearly evaluation)

Study Procedures

During the 2-year enrolment phase, 502 patients are planned to be recruited in four to five countries where OZAWADE® is on the market (*i.e.*, France, Germany, Italy and possibly Netherlands, Belgium or Spain), in approximately 8 to 15 centers per country. In each center, participating physicians will enrol all eligible patients consecutively according to a systematic sampling technique (*i.e.,* in chronological order of their arrival at the consultation) irrespective of the treatment decision (i.e. patients prescribed and not prescribed OZAWADE®) until the recruitment target is reached globally in both groups or until the end of the enrolment period. Patients will be followed-up up to 5 years (follow-up visit at six months and then once a year).

Duration of Study

There will be approximately two years of recruitment and five years of follow-up.

Selection of the Patients

Inclusion Criteria

A patient must meet all of the following criteria to be eligible for participation in the study:

1. Patients with OSA, treated or not by primary therapy (e.g., CPAP, MAD).
2. Patients eligible for treatment by OZAWADE® as per SmPC (being prescribed or not with OZAWADE®).
3. Patients naive of treatment with any wake-promoting agent or patients previously treated with wake-promoting agent for less than six months and having discontinued the treatment for at least three months.
4. Patient informed about the study and who either did not oppose to their data collection or who signed the Informed Consent Form when applicable.

Exclusion Criteria

A patient who meets the following criterion is not eligible for participation in the study:

1. Patient participating in a clinical trial.
2. Patient under curatorship or deprived of liberty.

Variables

The data collected will be those data that the investigating centers are used to assess during routine visits, exception made of some Clinician- or Patient- Reported Outcomes (ClinROs, PROs) questionnaires (see below) planned to properly answer to the study objectives. The following assessments have no obligation to be performed and only the available measures and assessments will be collected in the CRF.

Site Selection Questionnaire

To assess potential selection bias of the participating physicians, the country, speciality, age, department and institution type/patient flow will be collected from all physicians contacted during the selection process.

Demographic and Baseline Characteristics

Patient's demographic and baseline characteristics such as the age, gender, socio-professional status, date of OSA diagnosis and relevant medical history will be collected only at study inclusion. Other data (i.e. height and weight, waist circumference, smoking status, current daily alcohol consumption, physical activity, duration of sleep and perceived sleepiness at driving) will be collected both at study inclusion and at each follow-up visits (except for the perceived sleepiness at driving which will not be collected at the 6-month follow-up visit).

Prior and concomitant medications or therapies

- OSA primary therapy: the use of CPAP of alternative therapy (e.g., MAD) will be collected both at study inclusion and at each follow-up visits.
- Prior and concomitant medications: The data on prior medication will be collected only at study inclusion. The data on concomitant medications will be collected both at study inclusion and at each follow-up visits.

Prospective data (collected both at study inclusion and at each follow-up visit)

- Electrocardiogram (ECG) when available, QTcF;
- Blood pressure and heart rate;
- Beck Depression Inventory (BDI), global score (not collected at the 6-month follow-up visit);
- Disease activity:
    - Apnoea-hypopneoa index (AHI);
    - Epworth Sleepiness Scale (ESS), global score;
    - Maintenance of wakefulness test (MWT) or Multiple Sleep Latency Test (MSLT) (not collected at the 6-month follow-up visit), mean sleep latency;
    - Fatigue Severity scale (FSS), global score (not collected at the 6-month follow-up visit).
- Exposure to OZAWADE® (collected at study inclusion and at the follow-up visit if not started at inclusion);

- Adherence to OZAWADE®: through the Morisky Medication Adherence Scale 8-item (MMAS-8) questionnaire;
- Laboratory assessment: cholesterol, glycemia and triglycedemia (not collected at the 6-month follow-up visit).
- Adverse events and special situation: All AEs, SAEs, Adverse Events of Special Interest (AESI) i.e. cardiovascular events and Special Situations (SS) occurring from each patient's enrolment to the end of the study.

  AESIs defined as cardiovascular events based on the following list:

  Major Adverse Cardiovascular Event (MACE)

  - Acute myocardial infarction;
  - Acute coronary syndrome / ischemic heart disease
  - Stroke (ischemic, haemorrhagic);
  - Heart failure;
  - Cardiovascular death.

  Non-Major Adverse Cardiovascular Events (non-MACE)

  - New onset of angina;
  - Unstable angina;
  - Transient ischemic attack;
  - New onset atrial fibrillation;
  - Unscheduled interventional cardiology procedure (stenting, CABG);
  - New onset hypertension > 140/90 mm Hg (with new hypertension treatment or a posology adjustment of hypertension treatment);
  - New onset or worsening of peripheral vascular disease or unscheduled intervention;
  - Stent thrombosis;
  - QT prolongation (calculated with the electrocardiogram Fridericia's corrected QT interval strictly higher than 450 ms).

Patient Non-Inclusion Log

Data (i.e. age, gender, year of OSA diagnosis, reason for non-participation) collected from eligible patients not enrolled in the study will be collected in such log in order to assess potential selection bias.

Data Sources

This is a prospective, observational study, and patient data collected from the participating physicians will be abstracted from medical records and from administration of baseline and follow-up assessments and questionnaires (PROs and ClinROs).

A yearly blinded review of the adverse events and adjudication of the events (major adverse cardiovascular events [MACE] and non-major adverse cardiovascular events [non-MACE]) will be centrally performed by an Independent Committee.

Sample Size

[redacted]

Data Analysis

Population

In this observational study, all included patients are eligible to the analysis.

Statistical Method

The estimates of the main endpoint will be compared among OZAWADE® users and non-users by a generalized Linear Model featuring Poisson regression. In this model we consider a post stratification model based on fixed covariates combined with a random effect attempting a correction on the expected imbalance due to the non-randomized treatment. Cumulative incidence estimate and Cox proportional Hazard regression will be used as secondary analysis.

Milestones

- Ethics submission: Q2/Q3 2024
- Start of data collection: Q3/Q4 2024
- End of data collection: Q4 2030/Q1 2031
- Interim study report: yearly throughout the study
- Final report of study results: Q4 2031

5. Amendments and updates

None.

6. Milestones

The planned study milestones, as per Good Pharmacovigilance Practices definitions, are summarized below.

Table 1. Study Milestones

Study Milestone	**Planned date**
Ethics submission	Q2/Q3 2024
Start of data collection	Q3/Q4 2024
End of data collection	Q4 2030/Q1 2031
Interim study report	Yearly throughout the study
Final report of study results	Q4 2031

7. Rationale and background

7.1. Background

Obstructive Sleep Apnoea (OSA) is a highly prevalent chronic disease affecting nearly 1 billion people aged 30–69 years worldwide [1]. OSA is characterized by repetitive collapses of the upper airway during sleep, resulting in intermittent hypoxia, leading to secondary sympathetic activation, oxidative stress and systemic inflammation [2]. The diagnosis of OSA is based on the apnoea-hypopnoea index (AHI) – that is the number of apnoeas and hypopnoeas per hour of sleep, as determined by standard overnight polysomnography –, and the presence of other symptoms such as daytime sleepiness or fatigue [3, 4]. According to the American Academy of Sleep Medicine, OSA is classified as mild with AHI of 5–15, moderate with AHI of 16–30, and severe with AHI > 30 [3]. The mechanisms of OSA are multifactorial, including obesity, craniofacial changes, alteration in upper airway muscle function, and pharyngeal neuropathy [2]. OSA is recognized as associated with poor health outcomes, including cardiovascular diseases (mainly hypertension), diabetes, cognitive deficits and early mortality [2, 5-8].

Excessive daytime sleepiness (EDS) is a prominent symptom of OSA and is associated with a higher incidence of concentration difficulties, impaired vigilance, depressive symptoms, and increased risk of accidents [9, 10]. This impairment in daily functioning and deterioration in quality of life results in considerable economic and societal burdens. EDS has been reported to affect 12 to 58 % of people with OSA [11-13]. The variations in EDS prevalence could be explained by different factors such as the nature of EDS and the variety of factors impacting its presentation, the overlap with other comorbidities and the existence of various tools for EDS assessment. The Epworth Sleepiness Scale (ESS) is the most commonly used self-administered assessment for EDS [14]. The ESS evaluates the propensity to fall asleep in common real-world situations. A cut-off of > 10 points in the ESS is accepted to indicate EDS [15-17].

Continuous positive airway pressure (CPAP) is the gold-standard first-line treatment for patients with symptomatic OSA. CPAP acts as a pneumatic splint to the upper airway during sleep allowing restoration of upper airway patency and thus normalization of oxygen saturation and sleep quality and architecture. CPAP was shown to improve cognitive function and quality of life and to reduce daytime sleepiness in adherent patients [18, 19]. Adherence is one of the major issues with long-term CPAP therapy. A recent study in France showed that the overall rate of CPAP therapy termination was 48 % at 3 years [20]. Also, a substantial proportion of CPAP-treated OSA patients continue to experience EDS despite optimized CPAP therapy. Residual EDS has been reported to affect 6 to 15 % of CPAP-treated (> 3 hours/night) OSA patients [21, 22]. In these patients, for whom other sleep disorders or psychiatric disorders have been ruled out, pharmacologic therapy with wake-promoting agent, for residual EDS is now recommended [17].

Wake-promoting agents, such as modafinil and, more recently, solriamfetol were shown to significantly improve residual EDS in OSA patients treated with CPAP [23-26]. Yet, the European Medicines Agency (EMA) removed the indication for modafinil (and restricted its use to narcolepsy) because of potential cardiovascular safety concerns observed in trials in OSA patients [27]. Solriamfetol has been approved for the treatment of residual EDS in patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, in 2019 in the USA and in 2020 in Europe.

Pitolisant is a selective histamine H3 inverse agonist/antagonist. Double-blinded placebo-controlled phase III trials demonstrated pitolisant strong wake-promoting effects and safety profile in patients with narcolepsy [28-30]. Pitolisant, under the trade name of Wakix®, has been authorized for use in the EU in this indication, in adults and children, on March 31, 2016 and in the USA in adults, in 2019. Efficacy of pitolisant was also demonstrated during double-blinded placebo-controlled phase III trials in OSA patients treated or not with

CPAP. In OSA patients with residual EDS, refusing or non-adherent to CPAP, pitolisant significantly reduced self-reported daytime sleepiness and fatigue, and improved patient-reported outcomes and physician disease severity assessment after 12 weeks of treatment [31]. Pitolisant, used as adjunct to CPAP therapy for OSA with residual EDS despite good CPAP adherence, also significantly reduced subjective and objective sleepiness and improved participant-reported outcomes and physician-reported disease severity after 12 weeks [32]. In two dedicated QT studies, supra-therapeutic doses of pitolisant (6-12-times the therapeutic dose, that is 108 mg to 216 mg) produced mild to moderate prolongation of QTc interval (10-13 ms). As reported in the OZAWADE® SmPC, patients with cardiac disease, hypertension, at risk of major adverse cardiovascular events (MACE), co-medicated with other QT-prolonging medicinal products or known to increase the risk of repolarization disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and AUC ratio or patients with severe renal or moderate hepatic impairment should be carefully monitored [33].

Clinical studies have not raised any safety concerns and confirmed in OSA patients the favourable safety profile of pitolisant as reported in patients with narcolepsy. Pitolisant, under the trade name OZAWADE®, has been authorized for use in the EU on July 22, 2021, to improve wakefulness and reduce EDS in adult patients with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated OSA primary therapy, such as CPAP.

7.2. Rationale

The Risk Management Plan for OZAWADE® identifies some potential risks and missing information about safety. One of the potential risks concerns cardiovascular (CV) events including QT-interval prolongation and the missing information refers to the long-term safety of OSA patient treated with OZAWADE®, according to the SmPC.

The Sponsor has agreed with the EMA to conduct a Post-Authorization Safety Study (PASS) as part of the Risk Management Plan (RMP) for OZAWADE®.

8. Research question and objectives

8.1. Primary objective

The primary objective of this study is to demonstrate that OZAWADE® supplementation in obstructive sleep apnoea (OSA) patients does not increase the incidence of cardiovascular events (CVE) compared with OZAWADE® unexposed patients (non-inferiority) and to evaluate the long-term safety of OZAWADE® when used as per SmPC in patients with OSA.

8.2. Secondary objective(s)

Safety

- To evaluate the time to cardiovascular events of interest in OSA patients exposed to OZAWADE® as per SmPC compared with OZAWADE® unexposed OSA patients.
- To evaluate the time to adverse drug reaction (serious and non-serious) in OSA patients exposed to OZAWADE® as per SmPC compared with OZAWADE® unexposed OSA patients.

8.3. Exploratory objective(s)

Effectiveness

- To evaluate the effectiveness of OZAWADE® through the Epworth Sleepiness Scale (ESS) when used as per SmPC in patients with OSA.
- To evaluate the effectiveness of OZAWADE® through the Maintenance of wakefulness test (MWT) when used as per SmPC in patients with OSA.
- To evaluate the effectiveness of OZAWADE® through the Multiple Sleep Latency Test (MSLT) when used as per SmPC in patients with OSA.
- To evaluate the effectiveness of OZAWADE® through the Fatigue Severity Scale (FSS) when used as per SmPC in patients with OSA.

Adherence

- To evaluate the adherence to OZAWADE® when used as per SmPC in patients with OSA.
- To evaluate the adherence to continuous positive airway pressure (CPAP) / mandibular advancement devices (MAD), between the group of patients exposed to OZAWADE® and the group of patients not exposed to OZAWADE®.

Other

- To evaluate the reduction of car/traffic accidents.

9. Research methods

9.1. Study design

9.1.1. Overall Design of the Study

This is a prospective, observational, multi-center, open-label, long term, cohort study (OZAWADE® exposed and OZAWADE® unexposed) designed to collect data on the long-term safety of OZAWADE® treatment. This study will be conducted in OSA patients with EDS whose EDS has not been satisfactorily treated by, or who have not tolerated OSA primary therapy. The study will be conducted by physicians specialized in sleep management such as sleep specialists, pulmonologists, cardiologists, otorhinolaryngologist and neurologists.

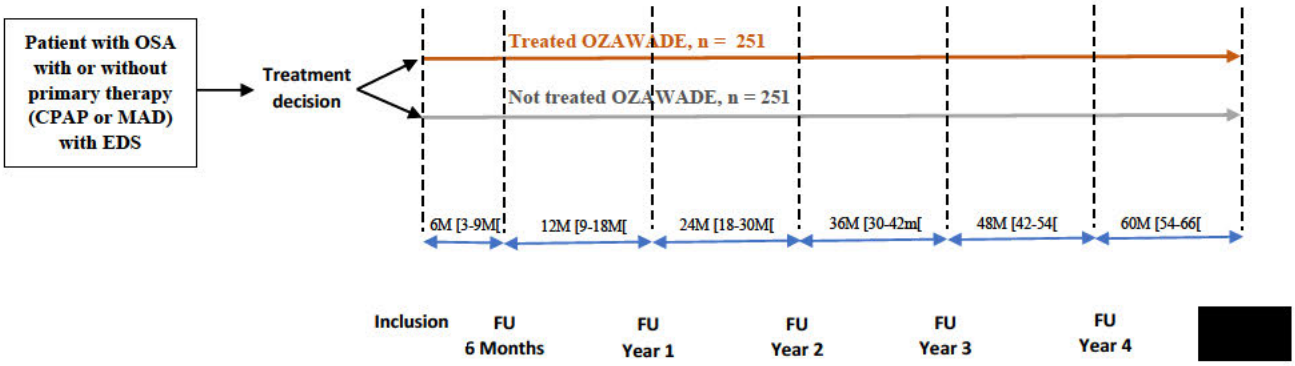
As an observational study, the assignment of the patient to a particular therapeutic strategy should be decided within the current clinical practice and the decision to prescribe OZAWADE® should necessarily precede and be independent of the decision to enrol the patient into the study. OZAWADE® should be prescribed and used based on the routine clinical practice as well as on the individual situation of each patient, according to the approved SmPC.

During the 2-year enrolment phase, 502 patients are planned to be recruited in four to five countries where OZAWADE® is on the market (*i.e.*, France, Germany, Italy and possibly Netherlands, Belgium or Spain), in approximately 8 to 15 centers per country.

Once eligible patients are enrolled, baseline data should be collected. Data collected in the CRF will correspond to data collected in routine practice in the investigating centers.

Patients will be followed-up up to five years, during which time they should be assessed by their treating participating physicians at 6, 12, 24, 36, 48 and 60 months, to follow routine care schedule.

Study visits, procedure and evaluations are summarized in the study flow (**Figure 1**) and schedule of assessments below (**Table 2**).



CPAP: Continuous Positive Airway Pressure; EDS: Excessive Daytime Sleepiness; FU: Follow-up; MAD: Mandibular Advancement Device; OSA: Obstructive Sleep Apnoea.

Figure 1: Study Flow.

Table 2. Schedule of Assessments

Procedures[1] /Visits		Inclusion	FU 6 Months	FU Year 1	FU Year 2	FU Year 3	FU Year 4	FU Year 5	End of study
Visit window			6M [3-9M[	12M [9-18M[	24M [18-30M[	36M [30-42M[	48M [42-54M[	60M [54-66M[	
Patient interview	Demography: age, gender	X							
	Profession / Socio-economic status	X							
	Height[2], weight	X	X	X	X	X	X	X	X
	Waist circumference	X	X	X	X	X	X	X	X
	Smoking status[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
	Alcohol consumption	X	X	X	X	X	X	X	X
	Physical activity	X	X	X	X	X	X	X	X
	Relevant medical history	X							
Medical examination	Prior medications (last three months)	X							
	Relevant concomitant medications	X	X	X	X	X	X	X	X
	Physical examination	X		X	X	X	X	X	X
	All Adverse Events including adverse events of special interest[4]		X	X	X	X	X	X	X
	Blood pressure, heart rate	X	X	X	X	X	X	X	X
	Biological assessment of less than 12 months (cholesterol, glycemia and triglycedemia)	X		X	X	X	X	X	X
	ECG brought by the patient when available (QT measure)[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]

Procedures /Visits		Inclusion	FU 6 Months	FU Year 1	FU Year 2	FU Year 3	FU Year 4	FU Year 5	End of study
Visit window			6M [3-9M[	12M [9-18M[	24M [18-30M[	36M [30-42m[	48M [42-54[	60M [54-66[	
OSA and sleep history	OSA and sleep history, duration of sleep	X	X[7]	X	X	X	X	X	X
	Apnoea-hypopnea index (AHI) At diagnosis of OSA At follow-up visits (with or without CPAP)[8]	X	X	X	X	X	X	X	X
	Epworth Sleepiness Scale (ESS)	X	X	X	X	X	X	X	X
	CPAP or alternative (e.g., MAD) and adherence[9]	X	X	X	X	X	X	X	X
	Maintenance of wakefulness test (MWT) or Multiple Sleep Latency Test (MSLT)	X		X	X	X	X	X	X
	Beck Depression Inventory	X		X	X	X	X	X	X
	Fatigue Severity scale	X		X	X	X	X	X	X
	Assessment of perceived sleepiness at driving	X		X	X	X	X	X	X
OZAWADE® use	Prescription (when applicable)	X							
	Adherence with the Morisky Medication Adherence Scale 8-item (MMAS-8)		X	X	X	X	X	X	X

1. Data collected in the CRF will correspond to data collected in routine practice in the investigating centers.
2. Height at inclusion visit only.
3. Smoking status: in pack-year.
4. Adverse events of special interest include the following cardiovascular events: acute myocardial infarction, new onset of angina, unstable angina, stroke (ischemic, haemorrhagic), transient ischemic attack, new onset atrial fibrillation, unscheduled interventional cardiology procedure (stenting, CABG), new onset hypertension (with new hypertension treatment or a posology adjustment of hypertension treatment), new onset or worsening of peripheral vascular disease or unscheduled intervention, stent thrombosis, heart failure, QT prolongation and cardiovascular death.
5. ECG when available.
6. Last test available at the time of the visit.
7. Duration of sleep.
8. Although the data will be limited for patients not using primary therapy, the data can be systematically collected from CPAP softwares in those under CPAP during the follow-up visits.
9. CPAP or alternative primary treatment adherence will be reported as the mean number of hours of use per night.

9.1.2. Primary, secondary and exploratory endpoints

9.1.2.1. *Primary endpoint*

The primary endpoint will be the occurrence of at least one cardiovascular event (CVE) or one serious drug related adverse event during the five years of follow up for each participating patient.

9.1.2.2. *Secondary endpoints*

The following secondary endpoints will separately investigate each type of event globally appraised by the primary endpoint:

- Time to CVE occurrence and CVE distribution in time according to classification MACE and non-MACE (See section 9.3.10)
- Time to Adverse Drug Reaction (ADR)
- Time to Serious Adverse Drug Reaction (SADR)
- Beck Depression Inventory global score at each collection time

9.1.2.3. *Exploratory endpoints*

Effectiveness

Change from patient inclusion date to the end of study as evaluated with:

- Epworth Sleepiness Scale (ESS) global score
- Maintenance of wakefulness test (MWT) mean sleep latency
- Multiple Sleep Latency Test (MSLT) mean sleep latency
- Fatigue Severity Scale (FSS) global score

Adherence

- Rate of patients compliant with their OZAWADE® treatment (according to the 8-item Morisky Score) at each visit.
- Rate of patients compliant with their primary therapy (according to the mean number of hours of use per night during the last three months) at each visit.

Other

Incidence of car accidents at driving (comparison of answers to the questionnaire “assessment of sleeping at driving” between inclusion and yearly evaluation)

9.1.3. Patient discontinuation and study termination

The patients are free to withdraw from the study at any time without prejudice to their drug prescriptions or therapeutic management. In this case, their data will be collected up to the time of withdrawal, with no additional information collected thereafter. The patients have also the right to oppose to the use of their personal data for the purpose of the study without prejudice to future medical care by the participating physician. However, in this case and in the case of withdrawal, any adverse events (AE) will still be

collected/reported and followed-up until resolved or stabilised or until the patient died or is lost to follow-up.

Missing evaluations at one or several time points is not a criterion for patient withdrawal.

A patient may be withdrawn from the study prior to completion in case of patient consent withdrawal and physician's or Sponsor's decision and/or safety reason. If the patient withdraws or is withdrawn, the reason will be collected in the eCRF.

All patients discontinuing OZAWADE® will be maintained in the study until completion of the follow-up period.

The participating physicians may interrupt their participation to the study at any time and will immediately inform Bioprojet Pharma.

Bioprojet Pharma reserves the right, at any time, to discontinue enrolment of additional patients into the study, at any site; or to discontinue the study, for medical or administrative reasons and will inform all study stakeholders.

9.2. Setting

9.2.1. Physician Selection and Initiation

9.2.1.1. *Type of Physician*

Physician selection will aim to recruit physicians specialized in sleep medicine who receive, in medical consultation, OSA patients with diagnosis of EDS and who are likely to treat them with OZAWADE (sleep specialists, pulmonologists, cardiologists, otorhinolaryngologists and neurologists).

9.2.1.2. *Sampling*

A feasibility study is on-going to identify physicians that could be interested in participating in the study, to evaluate the patient potential and the clinical routine care of OSA patients in the four countries where the study will take place. For the purpose of this feasibility study, the Sponsor established a pre-identified list of about 15 centers experienced in sleep disorders and distributed throughout each country. The study will then be proposed to all physicians that declared to have an interest in participating in the study.

A recruitment mail containing the study summary, the site qualification questionnaire and a reply coupon will be sent to all identified physicians.

9.2.1.3. *Site Initiation*

Participating physicians will receive a study kit once all the necessary administrative procedures have been completed (confidentiality agreement, financial agreement, CV, etc., where applicable).

The study kit includes at least the following:

- The study protocol;
- The physician identification form;
- The patient information note and non-opposition note or the patient information note and Informed Consent Form where applicable;
- The medical records release forms;
- Blood pressure monitors;
- Patient diaries;
- The patient Contact Order Form;
- The sample baseline and follow-up Case Report Forms (CRFs) and questionnaires; The eCRF manual user;

- The patient log;
- Pre-paid envelopes.

Upon receipt of the study kit, an initiation telephone call will be organized by the CRO in charge of the project to explain the protocol, data collection, and the practical aspects of the study.

9.2.2. Patient Selection, Enrolment and Follow-up

9.2.2.1. *Selection Criteria*

Inclusion Criteria

A patient must meet all of the following criteria to be eligible for participation in the study:

1. Patients with OSA, treated or not by primary therapy (e.g., CPAP, MAD).
2. Patients eligible for treatment by OZAWADE® as per SmPC (being prescribed or not with OZAWADE®).
3. Patients naive of treatment with any wake-promoting agent or patients previously treated with wake-promoting agent for less than six months and having discontinued the treatment for at least three months.
4. Patient informed about the study and who either did not oppose to their data collection or who signed the Informed Consent Form when applicable.

Reminder: OZAWADE® shall be prescribed according to the SmPC and treatment guidelines to patients diagnosed with OSA. The decision to prescribe OZAWADE® will necessarily precede and will be independent of the decision to enrol the patient into the study.

Exclusion Criteria

A patient who meets the following criterion is not eligible for participation in the study:

1. Patient participating in a clinical trial.
2. Patient under curatorship or deprived of liberty.

Reminder: contraindications to OZAWADE® as identified in the SmPC are:

- Hypersensitivity to the active substance or to any of the excipients of OZAWADE®;
- Severe hepatic impairment (Child-Pugh C);
- Breastfeeding.

9.2.2.2. *Patient Enrolment*

During the enrolment period, participating physicians will be asked to report in a patient log all eligible patients presenting for consultation. This log will therefore list all eligible patients whether they accept to participate in the study or not. The overall representativeness of the patients enrolled in the study population will be assessed from the data collected in this patient log.

During the 2-year enrolment phase, 502 patients are planned to be recruited in four to five countries where OZAWADE® is available on the market *(i.e.,* France, Germany, Italy and possibly Netherlands, Belgium or Spain), in approximately 8 to 15 centers per country. In each center, participating physicians will enrol all eligible patients consecutively according to a systematic sampling technique (*i.e.,* in chronological order of their arrival at the consultation) irrespective of the treatment decision (i.e. patients prescribed and not prescribed OZAWADE®) until the recruitment target is reached globally in both groups or until the end of the enrolment period.

During the recruitment phase, and for each patient, participating physicians will:

- Explain the study to the patient, in particular, the objective of the study and its observational nature. Indications will be given on the aim and timelines for visits, as per routine clinical practice.
- Give the patient, either the "patient information and non-opposition note" or the "patient information note and Informed Consent Form", where locally applicable, and ask the patient to read it. After sufficient time to consider his/her decision, the patient will confirm (or not) his/her oral agreement (for non-opposition) to participate (which will be also recorded in the patient medical records) or sign (or not) the Informed Consent Form (when locally applicable).
- For patients who agree to participate in the study: give the baseline patient reported outcome (PRO) questionnaires and ask the patient to complete the questionnaires.

9.2.2.3. *Planned follow-up*

The data will be collected during the normal course of patient care at approximately 6, 12, 24, 36, 48 and 60 months. During the follow-up visits, participating physicians will complete the eCRF with the data required to properly answer to the study objectives.

9.3. Variables

The data collected will be those data that the investigating centers are used to assess during routine visits, exception made of some Clinician- or Patient- Reported Outcomes (ClinROs, PROs) questionnaires (see below) planned to properly answer to the study objectives. The following assessments have no obligation to be performed and only the available measures and assessments will be collected in the CRF.

9.3.1. Site Selection Questionnaire

To assess potential selection bias of the participating physicians, the following data will be collected from all physicians contacted during the selection process.

- Country;
- Specialty;
- Age;
- Department;
- Institution type/patient flow.

9.3.2. Demographic and Baseline Characteristics

The following patient's demographic and baseline characteristics will be collected:

- Only at study inclusion:
  - Age (MONYYYY);
  - Gender (Male/Female);
  - Height;
  - Socio-professional status;
  - Date of OSA diagnosis (MONYYY);
  - Relevant medical history including (but not limited to) the following past cardiovascular risk factors:
    - Arterial hypertension, defined according to international guidelines, or the current use of antihypertensive drugs (international non-proprietary name);
    - Atrial fibrillation;
    - Diabetes mellitus (Type 1 or Type 2);
    - Hypercholesterolemia (HDL and LL cholesterol) (6.42 mmol/l in peripheral blood or current use of treatment);
    - Stroke, or transient ischemic attack;

- Ischemic heart disease with or without myocardial infarction;
- Carotid stenosis (more than 50% Doppler).

- At study inclusion and at each follow-up visits:
  - Weight;
  - Waist circumference;
  - Smoking status:
    - Never smoker;
    - Former smoker. If yes, number of pack-year and the year when they stopped smoking;
    - Current smoker. If yes, number of pack-year.
  - Current daily alcohol consumption (in glass: 1 glass = 10 g alcohol);
  - Physical activity (sport duration per week [hours]);
  - Duration of sleep (hours) as reported by the patients;
  - Perceived sleepiness at driving (assessment of 4 questions) (will not be done at the 6-month follow-up visit).

9.3.3. Electrocardiogram (ECG)

Patients with cardiac disease, hypertension, at risk of major adverse cardiovascular events (MACE), co-medicated with other QT-prolonging medicinal products or known to increase the risk of repolarization disorders, or co-medicated with medicinal products that significantly increase pitolisant Cmax and AUC ratio or patients with severe renal or moderate hepatic impairment should be carefully monitored.

ECG data are required to analyse the QT interval (Fridericia's QTc interval) when available. ECG data will be centrally read and interpreted in order to detect prolonged QT interval. ECG data will be collected both at study inclusion and at each follow-up visit.

9.3.4. Blood pressure and heart rate

Blood pressure and heart rate will be collected both at study inclusion and at each follow-up visit, and it will be measured as follows:

- One assessment during each follow-up site visit;
- Self-assessment during the month following each visit: patients will use blood pressure monitors and will report the data in a patient diary.

9.3.5. Beck Depression Inventory (BDI)

The BDI is a validated self-administrated questionnaire to measure the severity of depression. It is composed of 13 multiple-choice questions (with four possible answer choices, ranging in intensity) about how the patient has been feeling in the last week. Each question is rated on a 4-point scale (0-3). The total BDI score is obtained by summing the score of the 13 items (0-39). The total score is compared to a key to determine the depression's severity (0-3: No depression; 4-7: mild depression; 8-15: moderate depression; 16-39: severe depression). BDI data will be collected both at study inclusion and at each follow-up visit (except for the 6-month follow-up visit).

9.3.6. Disease activity

OSA and EDS will be evaluated according to routine clinical practice by the tool and ClinROs/PROs questionnaires described below:

- Apnoea-hypopneoa index (AHI)

The AHI is a diagnostic tool for determining the presence and severity of OSA. AHI is measured with CPAP device or by polysomnography. It is calculated by dividing the total number of apnoeic and hypoapnoeic events by the total number of hours of sleep by night. The data can be systematically collected from CPAP software in those under CPAP during each follow-up visits. AHI data will be collected both at study inclusion and at each follow-up visit.

- Epworth Sleepiness Scale (ESS)

The ESS is a short validated self-administered questionnaire (PRO) to measure a subject's usual level of daytime sleepiness or average sleep propensity [14, 34]. It is composed of 8 questions, each describing a different daily life situation. Each question is rated on a 4-point scale (0-3) and total ESS score is obtained by summing the scores of the eight items (0-24). The higher the ESS score, the higher that person's average sleep propensity in daily life or their daytime sleepiness. ESS data will be collected both at study inclusion and at each follow-up visit.

- Maintenance of wakefulness test (MWT) or Multiple Sleep Latency Test (MSLT)

The MWT is a validated polysomnographic test for the evaluation of daytime sleepiness/wakefulness [35]. It evaluates a subject's ability to remain awake while resisting the pressure to fall asleep during soporific circumstances.

MSLT evaluates the tendency to fall asleep under controlled conditions [36]. The test consists of four to five naps given two hours apart during the day, following a standardized procedure. Both tests allow the measure of the mean sleep latency as the measure of sleepiness.

MWT and MSLT data will be collected both at study inclusion and at each follow-up visit (except for the 6-month follow-up visit).

- Fatigue Severity scale (FSS)

The FSS is a validated self-report scale of nine items which measures the severity of fatigue and its effect on a patient's activities and lifestyle. Answers are scored on a seven point scale (1-7). The total FSS score is obtained by summing the score of the nine items (9-63). The higher the score, the more severe the fatigue and the more it affects the person's activities. FSS data will be collected both at study inclusion and at each follow-up visit (except for the 6-month follow-up visit).

9.3.7. Exposure and adherence to OZAWADE®

9.3.7.1. *Treatment exposure*

Exposure to OZAWADE® will be collected at inclusion and at follow-up visits (if not started at inclusion), with the date of prescription and the prescribed dose.

At each follow-up visit, dose modifications, treatment interruptions and permanent discontinuation will be collected. Reasons of changes will also be collected.

9.3.7.2. *Adherence*

Adherence to OZAWADE® will be assessed at each follow-up visit using the Morisky Medication Adherence Scale 8-item (MMAS-8) questionnaire. A paper questionnaire will be provided by the participating physician during the follow-up visits and will be self-administered by the patient in the waiting room.

The MMAS-8 questionnaire is a validated 8-item self-report measure of medication-taking behaviour [37]. Each of the eight items measures a specific medication-taking behaviour and not a determinant of adherence behaviour. Response categories are yes/no for each item with a dichotomous response and a 5-point Likert response for the last item. Total MMAS-8 scores can range from 0 to 8 and have been categorized into three

levels of adherence: high adherence (score = 8), medium adherence (score of 6 to < 8), and low adherence (score < 6). MMAS-8 data will be collected only at each follow-up visit.

9.3.8. Prior and concomitant medications or therapies

- OSA primary therapy

The use of CPAP of alternative therapy (e.g., MAD) will be collected both at study inclusion and at each follow-up visits. The following data will be collected:

  - Start date (MONYYYY);
  - Mean number of hours of use per night during the last three months;
  - Discontinuation (Yes/No). If yes: date and primary reason of discontinuation.

- Prior and concomitant medications

Prior (last three months before inclusion) and concomitant medications will be recorded as text fields. The data on prior medication will be collected only at study inclusion. The data on concomitant medications will be collected both at study inclusion and at each follow-up visits. For concomitant medications, the dosage regimen, the route of administration, and the dates of use will also be collected.

9.3.9. Laboratory assessments

Biological assessments of less than 12 months (cholesterol, glycemia and triglyceridemia) will be collected at study inclusion and at each follow-up visit (except for the 6-month follow-up visit).

9.3.10. Adverse events and special situations (cardiovascular events)

All AEs, Serious Adverse Events (SAE), Adverse Events of Special Interest (AESI) i.e. cardiovascular events and Special Situations (SS) occurring from each patient's enrolment to the end of the study will be collected in accordance with the process described in **Section 11**. All AEs will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

The participating physicians and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, AESI or SS and remain responsible for following up events.

The following data will be collected:

- Non-serious AEs and Serious AEs.
- AESIs defined as cardiovascular events based on the following list:

  Major Adverse Cardiovascular Event (MACE) [38]

  - Acute myocardial infarction;
  - Acute coronary syndrome / ischemic heart disease;
  - Stroke (ischemic, haemorrhagic);
  - Heart failure;
  - Cardiovascular death.

  Non-Major Adverse Cardiovascular Events (non-MACE)

  - New onset of angina;
  - Unstable angina;
  - Transient ischemic attack;
  - New onset atrial fibrillation;
  - Unscheduled interventional cardiology procedure (stenting, CABG);
  - New onset hypertension > 140/90 mm Hg (with new hypertension treatment or a posology adjustment of hypertension treatment);
  - New onset or worsening of peripheral vascular disease or unscheduled intervention;

- Stent thrombosis;
- QT prolongation (calculated with the electrocardiogram Fridericia's corrected QT interval strictly higher than 450 ms (QTcF interval: QTc=QT/$\sqrt[3]{}$ [RR]).

The list may not be exhaustive, it could be enlarged during the course of the study and the review of the adverse events. The adverse events will be reviewed by an Independent Committee as specified in **Section 9.4**.

- Special Situations (SS) (as listed in **Section 11.1.3**), including pregnancies:
  - Female patients and male patients with a female partner are requested to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy and neonatal condition.
    - Pregnancy history (date confirmed);
    - Pregnancy outcome (full-term, pre-term, foetal loss/stillbirth, miscarriage, induced abortion).
    - Neonatal characteristics:
      - Respiratory distress or other complication;
      - Admission to Neonatal Intensive Care Unit and length of stay;
      - Congenital abnormalities.

9.3.11. Patient non-inclusion log

Data collected from eligible patients not enrolled in the study will be collected in such log in order to assess potential selection bias. The following data will be collected for all eligible not-enrolled patients who came to a consultation.

- Demographic data: age, gender; year of OSA diagnosis;
- Reason(s) why the patient is not participating in the study.

9.4. Data sources

This is a prospective, observational study, and patient data collected from the participating physicians will be abstracted from medical records and from administration of baseline and follow-up assessments and questionnaires (PROs and ClinROs).

The patient data will be collected from the patient medical file (original files, hospital reports, laboratory tests reports, various correspondence, etc.). Data will be entered into the electronic case report form (eCRF) using electronic data capture (EDC) via an internet browser interface.

Patients participating in the study will be identified by a unique number (pseudonymized).

Sites will be trained to the use of the eCRF. Data will be recorded by participating physicians or qualified designee.

All original source documents from which the information reported in the eCRF will be obtained must be kept up-to-date and readily available. By signing the eCRF, the participating physician will confirm the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.

Paper PRO and ClinROs questionnaires will be used and answers will be recorded directly into the eCRF by the sites.

A yearly blinded review of the adverse events and adjudication of the events (major adverse cardiovascular events [MACE] and non-major adverse cardiovascular events [non-MACE]) will be centrally performed by an Independent Committee.

9.5. Sample size

[redacted]

9.6. Data management

At the study initiation, the data manager will transpose all data management steps into a Data Management Plan (DMP) to be carried out and the applicable procedures. The data management system, stakeholders, applicable procedures, data flow, organisation of data collection and coding methods will be detailed.

An electronic database specific to the study will be developed. Its characteristics will be described by an annotated CRF and a dictionary of variables and they will be validated prior to the development of the data entry tool.

The input masks will be developed and validated before they are put into production.

Procedures for checking the reliability and validity of the data entered will be defined (training, creation of input guide, double entry, reconciliation, quality control).

Data review meetings will be held around tables, listings and graphs representing the contents of the database. The strategy of taking into account the missing, outliers, etc. will be decided in agreement with Bioprojet Pharma. The set of deviations from the protocol will also be described, in particular the list of patients wrongly included. If it becomes necessary to define different patient populations for analysis, these populations will be described. All the decisions taken during this data review, prior to the analysis, will be recorded in a specific report kept in the study file.

Once this report is approved, the patient database will be locked and sent to the statistician for analysis.

9.7. Data analysis

This part summarizes the primary principles of the statistical analysis, further detailed in a SAP expected to be finalized before the first interim database lock.

9.7.1. Patient non-inclusion log

The number and percentage of eligible patients enrolled in the study will be presented as well as the reason why patients not enrolled are not participating in the study.
Moreover, age and gender will be described and compared between patients enrolled and patients not enrolled in the study, using standard statistical tests (chi-square or exact Fisher test for gender and Student t-test or Mann-Whitney Wilcoxon test for age).

9.7.2. Study populations

In this observational study, all included patients are eligible to the analysis.

9.7.3. Statistical Methodology

9.7.3.1. *Missing data handling*

The strategy for missing data handling may be discussed depending on the nature of missing data and the endpoint they are related to. To be in conformity with the ICHE9-R1 guidelines, these strategies for analysis may be described in a specific section of the SAP in which the concept of estimands and intercurrent events will be defined.

9.7.4. Disposition, Demographic, and Baseline Characteristics Analyses

Disposition of patients, demographics, and all baseline characteristics (as described **in Section 9.3.2**) will be summarized overall on the study population and by treatment group (OZAWADE® vs non-OZAWADE®).

9.7.5. Primary Analyses

The main objective of the study is to demonstrate that OZAWADE® supplementation does not increase CV events compared with control (non-inferiority). The following analysis will be conducted:

The annual CV morbidity incidence will be estimated by the occurrence of CVE per patient per year equivalent to the proportion of patients with at least one CVE.

The CV risk is known to be higher for OSA patient with existing CV history, using or not CPAP, and well-known risk factors: diabetes, cholesterol, weight, hypertension, demographics (age, gender), lifestyle (fitness, alcohol use, smoking habits).

A generalized linear mixed model featuring Poisson regression will be based on a post stratification model based on the following fixed covariates or random effects:

- $nCVE_b$, prior CV history measured by the number of CV events experienced before baseline, expected as the essential predicting covariates;

- Risk factors (RF): diabetes, cholesterol, weight, hypertension, alcohol use, and smoking habits reported at baseline;

- Demographics: gender, age, country, study center

- Matched classes propensity clusters: the treatment will be non-randomized but determined by the investigator, involving an expected imbalance between groups on baseline conditions. The decision of prescribing a given medicine will be assumed on a set of baseline covariates defined in the statistical plan. As too many covariates are expected, finding sufficient exact matches is unfeasible, and the goal of subclassification is to form matched subclasses (clusters), such that in each the distribution of covariates for the treated and control groups are as similar as possible. The propensity score will be used as the scalar distance with a two-stage algorithm starting with the nearest neighbour matching and optimized by a full matching procedure [39, 40, 41].

The final model is:

$CVE \sim nCVE_b + \Sigma_i RF_i$ + gender + age + trt + {country} + Offset (log-exp) + {center|country} + {cluster}

The notation $\Sigma_i RF_i$ covers the above mentioned considered risk factors. The obvious effect of the exposure duration is measured by the offset of its logarithm. The last fixed factor is the treatment (trt) binary effect (0=control, 1=pitolisant). Country, site effect nested within country, and cluster (matched group) effects will be used as random factors (between {}).

Sensitivity Analysis

For patients with prior CV history, the $nCVE_b$ covariate summarizes the CV history of the patient and was considered into the main model. For sensitivity purposes (a) the time passed between the first occurrence of

a CV event and the start of pitolisant treatment expected to estimate the CV event duration will be used as an added covariate in the model.

9.7.6. Secondary Analyses

The following secondary analyses will be conducted:

- The cumulative incidence, CI(t), of events at time t will be estimated using the incidence density at that time, ID(t), in the equation $CI(t)=1-\exp^{-ID(t)*t}$. Each point of the graph provides the cumulative incidence after t years of follow-up in the study, expressed as a percentage.
- A Cox proportional model will be adapted to multiple unordered events: the Time-varying covariates will be used, this technique is acceptable for unordered events (events can occur in any order). The cluster term will be used to compute a robust variance for the model. The term cluster(id) where each value of id is unique produces an approximate jackknife estimate of the variance. If the id variable is not unique, but identifies clusters of correlated observations, then the variance estimate is based on a grouped jackknife. The model will be used according to the following notes:
  1- Time-varying covariates will need to replace one record by n records, such as each new record describes a time-slice where covariates are fixed (inter-visit periods). Each such record remains independent while the endpoint occurrence only happens once (single event). If multiple events occur during the follow up, the time-slices are not independent for the same patient, thus the covariance between each row must be accounted by using sandwich robust variance cluster option. This technique is acceptable for unordered events (events can occur in any order). The cluster term is used to compute a robust variance for the model (approximate jack knife estimate).
  2- Time-varying effect means that PH is not constant in time. The major assumption of CPH is the lack of interaction of the covariates with time. This will be tested in the Schoenfeld test, on each covariate. If one or more covariate provides evidence of interaction with time, strata(variable) where variable is categorical, allows to model baseline F(t) calculated separately for each category of the variable.
  3- The model will be built both in stratifying with and without regrouped center and country.

9.7.6.1. *Effectiveness analysis*

All effectiveness parameters (ESS, MWT/MSLT and Fatigue Severity Scale) will be described at inclusion, six months after inclusion (only ESS scale) and every year until the end of the study, on the study population overall and by treatment group (OZAWADE® vs. non-OZAWADE®). Changes from inclusion may be calculated if relevant.

9.7.6.2. *Adherence*

The adherence to OZAWADE® assessed by the MMAS-8 questionnaire will be described at six months and then every year until end of the study. The adherence will be presented in terms of:

- Total score (0 – 8)
- Level of adherence (Low: < 6 / Medium: [6 ; 8[/ High: 8)

Adherence to continuous positive airway pressure (CPAP) will also be collected and described.

9.7.7. Other Safety Analyses

Adverse Events (AEs) will be coded with the Medical Dictionary for Regulatory Activities (MedDRA), version 25.1 or higher.

Firstly, incidences of all AEs, SAEs, AESIs (defined as cardiovascular events), and AEs related to study treatment will be described by treatment group (OZAWADE® vs. non-OZAWADE®) and overall by System Organ Class (SOC) and Preferred Term (PT).

To compute incidences, if a patient reported several AEs of a same PT in the period, only one AE will be counted. Denominator will then be the total number of patients and numerator will be the number of patients who reported at least one AE of the PT. Frequencies and percentages will be provided in the table.

More details on the types of events that will be described by SOC and PT and on listings that will be presented will be provided in the SAP.

Moreover, ECG results, blood pressure and heart rate will be described at each collection time by treatment group (OZAWADE® vs. non-OZAWADE®) and overall on the study population. The depression scale total score will also be described at each collection time except at the 6-month follow-up visit. Changes from inclusion may be calculated if relevant.

9.7.8. Other assessments

Abdominal perimeter, weight and biological assessments will be described at each collection time (except at the 6-month follow-up visit for the biological assessments) by treatment group (OZAWADE® vs. non-OZAWADE®) and overall. Changes from inclusion may be calculated if relevant.

Car/traffic occurrence will also be assessed by a dedicated questionnaire and described.

9.7.9. Sub-Group Analyses

In order to study the impact of primary therapy use, analyses may also be presented by primary therapy condition (primary therapy use vs. no use of primary therapy) within each treatment group (OZAWADE® vs. non-OZAWADE®). Details on analyses performed according to primary therapy condition will be provided in the SAP.

9.8. Quality control

9.8.1. Monitoring procedures and data quality

Study initiation will be performed prior to the start of recruitment at the site.

A risk-based monitoring strategy will allow to monitor key variables throughout the study, during on-site or remote visits. A clinical research assistant (CRA) will ensure an ongoing quality control (adherence to the protocol, completeness, consistency, and accuracy of the data being entered on the eCRF forms).

Physicians agree to cooperate to ensure that any problems detected in the course of these quality control activities are resolved.

The electronic data entry system will contain automatic checks for data completeness as well as to identify inconsistent data. Respective queries will be generated when necessary.

The participating physician must maintain source documents for each patient in the study and all information recorded on eCRFs must be traceable to source documents in the patient's file.

Any correction or modification will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures. Records and documents pertaining to the conduct of this study including eCRFs, Informed Consent Forms (where applicable), must be retained by participating physicians for at least 15 years after completion or discontinuation of the study. After that period of time, the documents may be destroyed.

At the end of the study/trial, the participating physician will maintain adequate study/trial records, including eCRFs, medical records, laboratory reports, Informed Consent/assent documents, drug disposition records, safety reports, information regarding participants who discontinued, and other relevant data.

All records are to be retained by the participating physician /institution following the end of the study/trial according to the local regulatory requirement(s). The participating physician will contact the Sponsor for authorisation prior to the destruction of any study/trial records or in the event of accidental loss or destruction of any study/trial records. The participating physician will also notify the Sponsor should he/she

relocate or move the study/trial related files to a location other than that specified to the Sponsor. The Sponsor should inform the participating physician(s)/institution(s) in writing of the need for record retention and should notify the participating physician(s)/institution(s) in writing when the trial related records are no longer needed.

The Sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) region and until there are no pending or contemplated marketing applications in an ICH region. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

Pharmacovigilance data and documents will be kept for at least 10 years after the marketing authorisation for the medicinal product has been withdrawn.

9.8.2. Confidentiality of patients data

The participating physician should ensure that personal data of patients, including their identity and medical information are kept confidential at any time.

The participating physician agrees, in accordance with local regulations and ethical considerations, that a representative of the Sponsor or the Competent Authority consults directly and/or copies any study document enabling him/her to check the eCRF, ensuring that the patient identity remains confidential.

Patients' names will not be transmitted. Only the site number and the patient number will appear on eCRFs. Patients' and participating physician's data will be collected in accordance with European Regulation 2016-679 of 27 April 2016 (General Data Protection Regulation - GDPR) and for France, Law 78-17 of 6 January 1978 on information technology, files and liberties amended.

No information enabling the identification of persons will be given to third parties other than those authorised by regulations to hold this information (and who are subject to professional secrecy). The study Sponsor does not have access to personal patient identification.

All personal data of patients collected and treated in the study, will be collected by the participating physician with the appropriate precautions to ensure the confidentiality of such data.

Patients participating to the study will be identified by a numerical code made of 5 digits, consisting of the site number made of 3 digits and an incremental number by sites made of 2 digits *(example: the third patient included in site No. 2 will have the patient code: 002-03).*

Only the participating physician will retain the file with the link between the patient identity and the patient number in the study file.

In all the presentations of the study results at meetings or in publications, the patient identity will remain confidential, and all data will be pseudonymized.

As part of the data confidentiality, the computerised file used for data entry and data treatment will be compliant with local requirements.

9.9. Limitations of the research methods

The design of this study was carried out in order to limit the major usual biases for this type of study. However, as any observational research this study is subject to risks of bias.

Patient selection bias: selection bias should be taken into account when interpreting the results of the study, especially the limitation on generalizability of study data. It is planned to have a sample of 195 patients exposed to OZAWADE® and 195 not exposed. These results will thus provide a good insight on OZAWADE® data outside the context of an interventional study by providing descriptive data in a real-life context. The

description and follow-up of this subset of patients followed in four countries will be of scientific value. However, to limit selection bias, any physician specialized in sleep medicine who receive, in medical consultation, OSA patients with diagnosis of excessive daytime sleepiness and who are likely to treat them with OZAWADE (sleep specialists, pulmonologists, cardiologists, otorhinolaryngologists and neurologists) will be selected.

Information bias / measurement bias: each subject included in the study has his/her own physician, and therefore, it is expected that information issued from source dossier (i.e. medical file) will be different from a subject to another and may possibly lead to an information and measurement biases. Response and safety assessments may not be uniform. This bias is inherent to the usual physician practice and such study design, and cannot be avoided. To minimize this bias, a training session during on-site study initiation meetings will be provided to all physicians involved in the study, in which clear definitions of the variables measured will be explained.

Site selection bias: Site involvement is voluntary and the final sample of participating sites may not be representative. This potential bias is inevitable in this type of study and its impact is difficult to evaluate. However, this bias will be minimized by the selection of a balanced number of centers in each participating country and by the fact that a feasibility study is on-going to identify physicians that could be interested in participating in the study. For this reason, refusal of few centers is not expected to have a significant impact on sites representativeness. The number of physicians solicited, having answered, having refused, having accepted, the number of sites initiated as well as the number of active sites will be presented. The reasons for refusal will be described.

Sampling bias: due to the exhaustive nature of the collection of subject data, the number of subjects may not be homogeneous between the sites and sites with a higher potential for recruitment may include more patients than others. However, to limit this bias a feasibility study is on-going to identify physicians that will be able to recruit a certain amount of patients. In addition, only physicians specialized in sleep medicine who receive, in medical consultation, OSA patients with diagnosis of excessive daytime sleepiness and who are likely to treat them with OZAWADE (sleep specialists, pulmonologists, cardiologists, otorhinolaryngologists and neurologists) will be selected.

Attrition bias: Patients lost to follow-up are the main source of attrition bias. Attrition can threaten sample representativeness if the patients lost to follow-up differ from the other patients in their baseline characteristics or in their outcomes. To decrease this bias, the centers will contact patients who did not attend their follow-up visits.

10. Protection of human subjects

10.1. Study conduct

This study will be conducted in adherence with the ethical principles stated in the Declaration of Helsinki amended version, Fortaleza, Brazil, October 2013 and according to the ethics recommendations and Good Epidemiologic Practices French version 2007 Good Pharmacovigilance Practices and local applicable regulations. Each personal member involved in the study will have the necessary qualifications (education, training and experience) to perform the task(s) entrusted to him/her.

Before any inclusion in the study, the subject (and/or his/her legal representative) will be informed by the participating physician about the nature and the study objectives and not oppose to them. He/she will also be informed about his/her right to refuse, to grant or to correct any access to his/her medical data.

All patients data collected during the study will be identified by a unique number (pseudonymization).

10.2. Subject information and non-opposition note or Informed Consent

An information note will be given to each subject (and/or to their legal representative) by the study physician in order to inform them of the purpose of the processing, the collected data, the nature of data transmitted, the recipients of data and of their right of access, rectification, limitation, restriction of processing or to object to processing as well as their right to refuse the transmission of their data.

The information and non-opposition note or the information note and written consent form (where applicable) must be submitted by the participating physician to the patient with an oral explanation. Non-opposition to data collection will be orally collected before any study-related procedure starts and patient's decision will be reported in his/her medical files. Where Informed Consent is applicable, the consent must be agreed and signed by the patient before any study-related procedure starts. The consent form is signed in duplicate: the original copy is kept by the Participating physician and one copy is given to the patient.

10.3. Personal data protection

This study will be conducted in accordance with the European General Data Protection Regulation 2016/679 of 27 April 2016 and for France, the French Law n°78-17 of 6 January 1978 on Technology, Data Files and Civil Liberties amended.

Bioprojet Pharma is the data controller responsible for processing data collected in the course of the study and will process the data in a lawful, fair and transparent manner.

Bioproject Pharma will perform all the regulatory proceedings required by the regulations related to the data processing of personal data in the field of health.

Indirect nominative data of subjects will be collected, therefore the subject's name will never be conveyed to Bioprojet Pharma. Only subject/patient number will appear on CRF. If the name of the subject is included on another document, it will be masked before this document is supplied to Bioprojet Pharma.

10.4. Ethics Committee

This study is non-interventional. It will not modify the usual care of the subjects, and will not involve any risk or constraint, all acts will be practiced and all products will be used in the usual way. Where applicable, the OZAWADE study will be submitted to the opinion of an Ethics Committee (EC) prior to its implementation. Upon receipt, the EC opinion and the study summary will be sent to the Competent Authority for information.

10.5. Protocol amendments or premature study discontinuation

No protocol amendment and/or no change to the subject information note should be done without prior authorisation of Bioprojet Pharma.

If applicable, the approval of the participating physicians will be required before the implementation of these changes.

Bioprojet Pharma retains the right to terminate the study at any time and will inform the participating physicians.

The participating physicians may interrupt his/her participation to the study at any time and will immediately inform Bioprojet Pharma.

10.6. Audit and inspection

The study may be subjected to audits at the request of the Sponsor. It can be an audit of the Company in charge of the study conducted by another independent relevant company in the epidemiological domain.

The study may be subjected to inspections at the request of the Health Authorities. In case of inspection, the participating physician will inform the Sponsor that could participate to the inspection.

The participating physician should be available to answer any questions of the auditors/inspectors and will make every effort to facilitate the proper conduct of the audit/inspection.

The participating physician must accept that the study source documents should be made available to the auditors/inspectors after appropriate notification.

11. Management and reporting of adverse events/adverse reactions

11.1. Definitions

11.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal product, whether or not the event is considered causally related to the use of the medicinal product.

Such an event can result from use of the drug as stipulated in the labelling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE.

11.1.2. Serious Adverse Event

If an AE meets any of the following criteria, it is considered a Serious Adverse Event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the participating physician, would have resulted in immediate fatality if medical intervention had not been taken. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Hospitalisation:	An event that results in an admission to the hospital for any length of time. **This does not include hospitalisation planned before entry into the study, hospitalisation for elective treatment of a pre-existing condition, an emergency room visit or admission to an outpatient facility which do not result in overnight hospitalisation**.
Prolongation of Hospitalisation:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly/Birth defect:	An anomaly detected at or after birth, or any anomaly that results in foetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (*e.g.*, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalisation, but based on medical judgment may jeopardise the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalisation, prolongation of hospitalisation, congenital anomaly, or persistent

	or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.
Suspected transmission of any infectious agent via a medicinal product	Any suspected transmission via a medicinal product of an infectious agent is also considered as serious adverse reaction.

11.1.3. Special Situations

Special situation (SS) is any incidence of drug exposure during pregnancy (whether the foetus is exposed via the mother taking the product or transmission via semen following paternal exposure) or breastfeeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse, lack of therapeutic effectiveness, suspected transmission of infectious agents via a medicinal product whilst using the medicinal product. Any SS should be collected by the participating physician and reported to Bioprojet Pharma whether or not these SSs are associated with an AE.

11.1.3.1. *Pregnancy or Breastfeeding*

Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the medicinal product has interfered with a contraceptive method. If pregnancy occurs whilst using the medicinal product, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered to be related to interference by the medicinal product with a contraceptive method.

The participating physician must instruct all female participants to inform them immediately should they become pregnant whilst using the study medication. Details of all pregnancies in female participants will be collected from the non-opposition/Informed Consent of participants (as per local requirements) and until the end of the study. The participating physicians have to report to Bioprojet Pharma if they become aware of a pregnancy occurring in the partner of a participant participating in the study. If the female partner gives her consent, the pregnancy outcome should be followed-up and reported.

Breastfeeding

Any use of the medicinal product during lactation/breastfeeding must be collected.

11.1.3.2. *Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error*

Overdose

Any dose higher than the maximum recommended dose in local label/SmPC, or in the protocol. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labelling text will be assessed as ‘overdose’.

Off-label Use

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Abuse

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Occupational exposure

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Medication error

Medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the participant.

11.1.4. Adverse Events of Special Interest

The Adverse Events of Special Interest (AESI) for this study are those defined in **Section 9.3.10**.Patients should be advised to contact the participating physician immediately if they develop any of these or any other unusual symptoms.

11.2. Intensity, causality, expectedness and outcome assessment

11.2.1. Intensity Assessment

The participating physicians will use the adjectives mild, moderate, or severe to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- **Mild:** Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living;
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient;
- **Severe:** The event interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic interventions.

Note the distinction between the intensity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the seriousness criteria, listed above.

11.2.2. Causality Assessment

The participating physician is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions will be used to assess the relationship of the above mentioned AE to the use of OZAWADE®:

- **Related**: an AE where there is evidence to suggest a causal relationship between the product and the AE;

- **Not related:** an AE where there is no evidence to suggest a causal relationship between the product and the AE.

In case of suspected causal relationship to OZAWADE®, follow-up by the participating physician is required until the event or its sequelae resolve or stabilise at a level acceptable to the participating physician.

If the participating physician's final determination of causality is unknown and the participating physician does not know whether or not OZAWADE® may have contributed to the event, then the event will be handled as "related to OZAWADE®" for reporting purposes.

11.2.3. Outcome Assessment

All Adverse Event outcomes should be documented according to the following criteria: ongoing, recovered, recovered with sequelae, recovering, not recovered, death. If an adverse event is ongoing at the last patient visit, the patient must be followed-up until the event or its after-effects are resolved or stabilized at level acceptable to the prescribing physician and the Sponsor.

11.3. Expectedness of events

The expectedness of an AE shall be determined by the Sponsor according to the SmPC or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the marketing authorisation.

NOTE: Unlisted character of an event is only relevant for the Sponsor's reporting obligations but is not determining reporting requirements of the participating physician to the Sponsor or Marketing Authorization Holder.

11.4. Collection and reporting of AEs, SAEs and SSs

11.4.1. Collection of the AEs, SAEs, SSs in the eCRF

The collection and reporting of AEs will follow the guidelines on Good Pharmacovigilance Practices (GVP) module VI, Revision 2.

All AEs, whether they are serious/non-serious, related/unrelated should be collected during the course of the study in the dedicated AE eCRF form. AEs will be assessed according to intensity, causality, outcome, action taken and seriousness.

SSs should be collected as AEs in the AE eCRF form whether or not they were associated with a clinical event.

AESIs should be collected as AEs in the AE eCRF form and collected as SAEs if they meet the seriousness criteria. Full details of these events must be collected in the eCRF.

For each patient, the collection period for AEs starts from the time that the patient provides consent to participate in the study/non-opposition for data collection (as foreseen by local regulation) and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of OZAWADE®.

11.4.2. Reporting of events to Sponsor Pharmacovigilance

11.4.2.1. *Initial reporting*

Participating physicians must report to Bioprojet Pharma pharmacovigilance all the following events using the dedicated reporting form:

- All SAEs – related and non-related to OZAWADE®;
- All related non-serious AEs (Adverse Drug Reactions);
- All AESIs (as defined in **Section 11.1.4**) – related or not, serious or not;
- All SSs including pregnancy cases (as defined in **Section 11.1.3**).

Safety Event	Collected on the eCRF	Reported on the dedicated Form to Bioprojet Pharma Pharmacovigilance
Non-Serious AEs	All AEs related or not	Only the related AEs - within 7 calendar days of awareness
SAEs	All SAEs related or not	All - within 24 hours of awareness
AESIs	All AESIs related or not, serious or not	All - within 24 hours of awareness
SSs (including pregnancy cases)	All SSs related or not (regardless of whether associated with an AE)	All - within 24 hours of awareness

All SAEs, AESIs, and SSs (including pregnancy cases) will be recorded and reported to Bioprojet Pharma or Designee immediately and under no circumstance no later than 24 hours of awareness.

The primary mechanism for reporting SAEs, AESIs, and SSs (including pregnancy cases) to Bioprojet Pharma pharmacovigilance will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper AE or the paper SAE (according to the event reported) data collection tool in order to report the event within 24 hours and will send it to pharmacovigilance@bioprojet.com.

All non-serious related AEs will be recorded and reported to Bioprojet Pharma or Designee immediately and under no circumstance no later than 7 calendar days of awareness.

All AEs will be processed by Bioprojet Pharma according to their relevant Standard Operating Procedures. This includes the follow up of AE reports with the participating physicians, as required.

If an AE occurs with a “non Bioprojet Pharma product”, the participating physician should consider informing the competent authority in the Member State where the event occurred or the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

11.4.2.2. *Follow-up*

After the initial report, the participating physician is required to proactively follow each patient at subsequent visits. All related AEs, SAEs, AESIs, SSs (including pregnancy cases) (as defined in **Section 11.1.3**), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

The participating physician will submit any updated related AEs/SAEs/AESIs/SSs (including pregnancy cases) data to Bioprojet Pharma within 24 hours of it being available. New or updated information will be recorded in the originally completed eCRF.

11.4.3. Regulatory reporting requirements

All ADRs (serious and non-serious) will be recorded in the Sponsor Pharmacovigilance database according to the EU-GVP Module VI. ADRs (serious and non-serious) will be reported to Competent Authorities in accordance with provisions of the EU-GVP Module VI. The reports should be classified as solicited reports.

Bioprojet Pharma has a legal responsibility to notify the regulatory agencies about the safety of OZAWADE® by submitting to EudraVigilance database:

- Related SAEs within 15 days of awareness by the Sponsor;
- Related non-serious AEs within 90 days of awareness by the Sponsor.

Pharmacovigilance department should ensure that all reports of serious adverse events and suspected adverse reactions (serious and non-serious) have been received from the prescribing physician. In compliance with the Good Pharmacovigilance practices (Modules VI and VIII), all valid reports of adverse reactions

suspected to be related to OZAWADE® have to be reported by the pharmacovigilance department to the regulatory authorities.

Other adverse events will be summarized in the Periodic Safety Updated Reports and Study Report. The national legislation will be followed for the reporting of cases of serious and non-serious adverse reactions to the local Ethics Committees and Investigators.

If the Sponsor is aware of an AE in a patient participating in this non-interventional study through another way that the reporting described above, the report will be considered as spontaneous. Where available, reports of spontaneous ADRs will be summarised in the Study Report.

Bioprojet Pharma will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), when applicable.

12. Plans for disseminating and communicating study results

The data and research results are the exclusive property of the Sponsor. No information or publication may be made without prior authorization of the Sponsor.

The completed study will be summarised in a final report that will accurately and fully present the study objectives, the methods used, the results, the study limits, and the interpretation of results.

The participating physician should inform the Sponsor of any publication or presentation of the study data and obtain written agreement. Any publication or presentation of results (abstracts in newspaper or scientific journal, oral presentations, etc.), wholly or partially, by the participating physicians or their representatives should be reviewed by Bioprojet Pharma 30 days prior to submission.

13. References

1. Benjafield, A.V., et al., *Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis.* Lancet Respir Med, 2019. **7**(8): p. 687-698.
2. Levy, P., et al., *Obstructive sleep apnoea syndrome.* Nat Rev Dis Primers, 2015. **1**: p. 15015.
3. Kapur, V.K., et al., *Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline.* J Clin Sleep Med, 2017. **13**(3): p. 479-504.
4. Societe de Pneumologie de Langue, F., et al., *[Recommendations for clinical practice. Obstructive sleep apnea hypopnea syndrome in adults].* Rev Mal Respir, 2010. **27**(7): p. 806-33.
5. Pepin, J.L., et al., *Hypertension and sleep: overview of a tight relationship.* Sleep Med Rev, 2014. **18**(6): p. 509-19.
6. Parati, G., et al., *Recommendations for the management of patients with obstructive sleep apnoea and hypertension.* Eur Respir J, 2013. **41**(3): p. 523-38.
7. Bucks, R.S., et al., *Reviewing the relationship between OSA and cognition: Where do we go from here?* Respirology, 2017. **22**(7): p. 1253-1261.
8. Leng, Y., et al., *Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment: A Systematic Review and Meta-analysis.* JAMA Neurol, 2017. **74**(10): p. 1237-1245.
9. Lal, C., et al., *Excessive Daytime Sleepiness in Obstructive Sleep Apnea. Mechanisms and Clinical Management.* Ann Am Thorac Soc, 2021. **18**(5): p. 757-768.
10. Stepnowsky, C., et al., *Comorbidities, Health-Related Quality of Life, and Work Productivity Among People With Obstructive Sleep Apnea With Excessive Sleepiness: Findings From the 2016 US National Health and Wellness Survey.* J Clin Sleep Med, 2019. **15**(2): p. 235-243.
11. Garbarino, S., et al., *Obstructive Sleep Apnea With or Without Excessive Daytime Sleepiness: Clinical and Experimental Data-Driven Phenotyping.* Front Neurol, 2018. **9**: p. 505.
12. Kim, H. and T. Young, *Subjective daytime sleepiness: dimensions and correlates in the general population.* Sleep, 2005. **28**(5): p. 625-34.
13. Bjorvatn, B., et al., *Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea.* Sleep Breath, 2015. **19**(4): p. 1387-93.
14. Johns, M.W., *A new method for measuring daytime sleepiness: the Epworth sleepiness scale.* Sleep, 1991. **14**(6): p. 540-5.
15. Johns, M. and B. Hocking, *Daytime sleepiness and sleep habits of Australian workers.* Sleep, 1997. **20**(10): p. 844-9.
16. Rosenberg, R., et al., *Residual excessive daytime sleepiness in patients treated for obstructive sleep apnea: guidance for assessment, diagnosis, and management.* Postgrad Med, 2021. **133**(7): p. 772-783.
17. Craig S., et al., *Investigation and management of residual sleepiness in CPAP-treated patients with obstructive sleep apnoea: the European view*. Eur Respir Rev, 2022. **31**(164):210230.
18. Bratton, D.J., et al., *Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis.* Lancet Respir Med, 2015. **3**(11): p. 869-78.
19. Schwartz, M., et al., *Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis.* Sleep Breath, 2018. **22**(3): p. 555-568.
20. Pepin, J.L., et al., *CPAP Therapy Termination Rates by OSA Phenotype: A French Nationwide Database Analysis.* J Clin Med, 2021. **10**(5).
21. Gasa, M., et al., *Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure.* J Sleep Res, 2013. **22**(4): p. 389-97.

22. Pepin, J.L., et al., *Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study.* Eur Respir J, 2009. **33**(5): p. 1062-7.

23. Black, J.E. and M. Hirshkowitz, *Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome.* Sleep, 2005. **28**(4): p. 464-71.

24. Chapman, J.L., et al., *Modafinil improves daytime sleepiness in patients with mild to moderate obstructive sleep apnoea not using standard treatments: a randomised placebo-controlled crossover trial.* Thorax, 2014. **69**(3): p. 274-9.

25. Schweitzer, P.K., et al., *Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial.* Am J Respir Crit Care Med, 2019. **199**(11): p. 1421-1431.

26. Strollo, P.J., Jr., et al., *Solriamfetol for the Treatment of Excessive Sleepiness in OSA: A Placebo-Controlled Randomized Withdrawal Study.* Chest, 2019. **155**(2): p. 364-374.

27. *European Medicines Agency recommends restricting the use of modafinil; https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-restricting-use-modafinil.* 2010.

28. Dauvilliers, Y., et al., *Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study.* Sleep, 2019. **42**(11).

29. Dauvilliers, Y., et al., *Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial.* Lancet Neurol, 2013. **12**(11): p. 1068-75.

30. Szakacs, Z., et al., *Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial.* Lancet Neurol, 2017. **16**(3): p. 200-207.

31. Dauvilliers, Y., et al., *Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment. A Randomized Trial.* Am J Respir Crit Care Med, 2020. **201**(9): p. 1135-1145.

32. Pepin, J.L., et al., *Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial.* Chest, 2021. **159**(4): p. 1598-1609.

33. https://www.ema.europa.eu/en/documents/product-information/ozawade-epar-product-information_en.pdf

34. Johns, M.W., *Sleepiness in different situations measured by the Epworth Sleepiness Scale.* Sleep, 1994. **17**(8): p. 703-10.

35. Mitler, M.M., K.S. Gujavarty, and C.P. Browman, *Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence.* Electroencephalogr Clin Neurophysiol, 1982. **53**(6): p. 658-61.

36. Arand, D.L. and M.H. Bonnet, *The multiple sleep latency test.* Handb Clin Neurol, 2019. **160**: p. 393-403.

37. Morisky, D.E., et al., *Predictive validity of a medication adherence measure in an outpatient setting.* J Clin Hypertens (Greenwich), 2008. **10**(5): p. 348-54.

38. Bosco, E., et al., *Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review*. BMC Med Res Methodol (2021) 21:241

39. Hansen, B.B., *Full matching in an observational study of coaching for the SAT*. J Am Stat Assoc, 2004. **99**(467): p.609-18.

40. Rosenbaum, P.R. (2002). *Observational Studies*. 2nd edition. Springer-Verlag, New York.

41. Ho, D.E., Imai, K., King, G., Stuart, E.A. (2007). *Matching as Nonparametric Preprocessing for Reducing Model Dependence in Parametric Causal Inference*. Political Analysis, 15(3), 199–236, URL http: //www.R-project.org/.

42. Barbé et al., *Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea*; JAMA, 2012. 307(20): p2161-68

43. Lehert P. *Efficacy of Pitolisant 20 mg in Reducing Excessive Daytime Sleepiness and Fatigue in Patients with Obstructive Sleep Apnoea Syndrome: An Individual Patient Data Meta-analysis*. Clin Drug Investig. 2022 Jan;42(1):65-74. doi: 10.1007/s40261-021-01104-8. Epub 2021 Dec 2. PMID: 34859394; PMCID: PMC8755655.

44. Ahmad M, Makati D, Akbar S. *Review of and Updates on Hypertension in Obstructive Sleep Apnea*. Int J Hypertens. 2017;2017:1848375.

45. Sahni AS, Carlucci M, Malik M, Prasad B. *Management Of Excessive Sleepiness In Patients With Narcolepsy And OSA: Current Challenges And Future Prospects*. Nat Sci Sleep. 2019;11:241-252

46. Peker Y, Carlson J, Hedner J. *Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up*. Eur Respir J. 2006 Sep;28(3):596-602. doi: 10.1183/09031936.06.00107805. Epub 2006 Apr 26. PMID: 16641120.

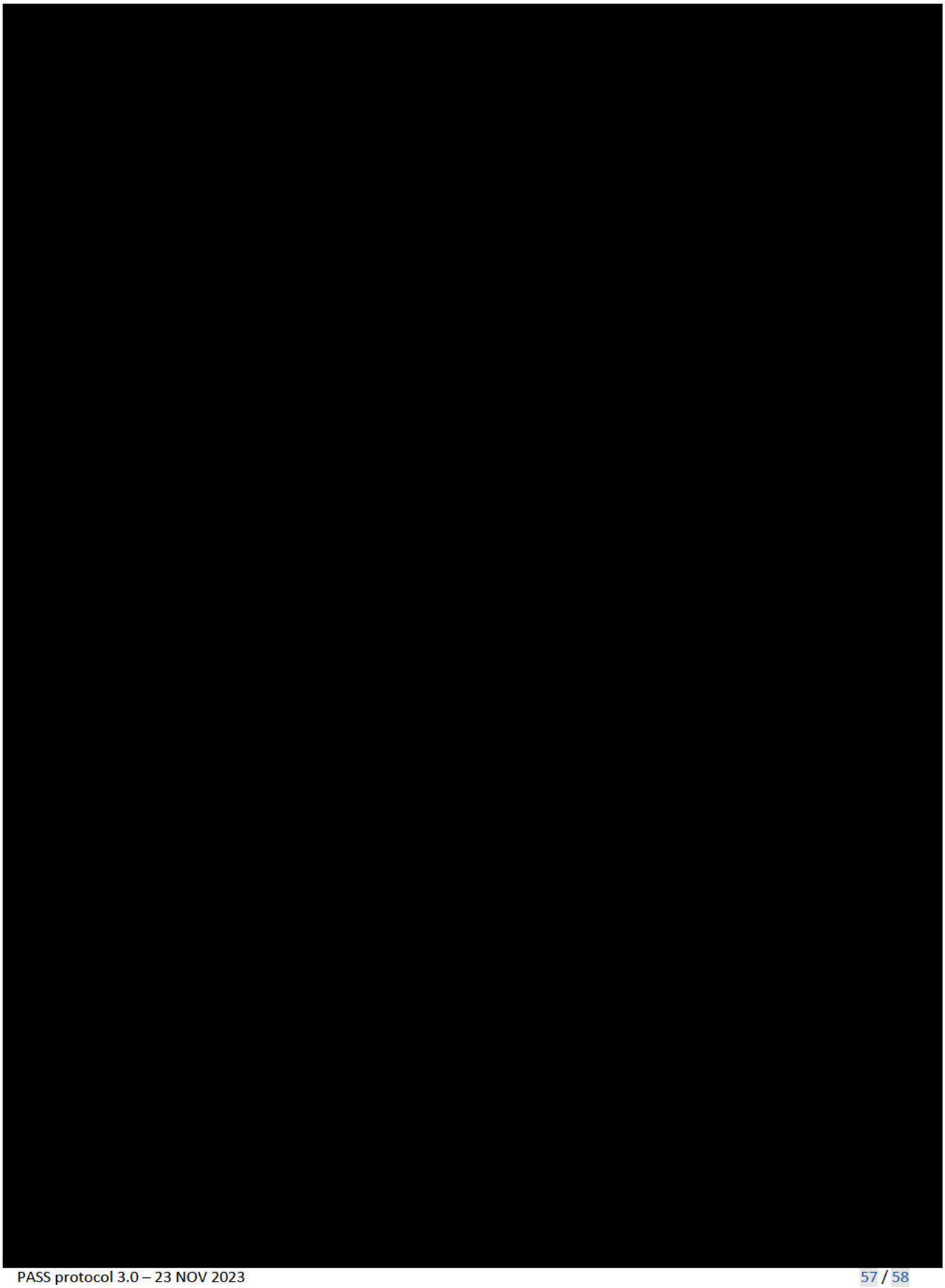
47. Choi C.C., *Sample size in clinical trials with dichotomous endpoints, use of covariables*, Journ of Biopharmaceut Statistics, 8 (3), 367-375 (1998)

48. Gu K., et al. *Testing the Ratio of Two Poisson Rates*. Biometrical Journal: Journal of Mathematical Methods in Biosciences. 50 (2008) 2:283-298.

APPENDIX 1

Sample size calculation

1-Hypotheses



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