NCT number: **NCT02611687**

Protocol ID: **P11-06/BF2.649**

Title: **Double blind, multicentre, randomized, placebo-controlled trial to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy, followed by a prolonged open-label period.**

Document: **Protocol, Version 3.0_30 September 2020**

PROTOCOL P11-06 / BF 2.649

DOUBLE BLIND, MULTICENTRE, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE SAFETY AND EFFICACY OF PITOLISANT IN CHILDREN FROM 6 TO LESS THAN 18 YEARS WITH NARCOLEPSY WITH/WITHOUT CATAPLEXY, FOLLOWED BY A PROLONGED OPEN-LABEL PERIOD

Sponsor:
BIOPROJET
9 Rue Rameau
75002 PARIS, FRANCE
Tel.: [redacted] - Fax: [redacted]

Medical Project Director:
[redacted]
BIOPROJET
Tel: [redacted]
email: [redacted]

Pharmacovigilance:
[redacted]
BIOPROJET
Tel: [redacted]
Mobile: [redacted]
Fax: [redacted]
email: [redacted]

Coordinator- Investigator: **Giuseppe Plazzi, MD, Ph D**
[redacted]

Signature Page

PROTOCOL P11-06 / BF 2.649

DOUBLE BLIND, MULTICENTRE, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE SAFETY AND EFFICACY OF PITOLISANT IN CHILDREN FROM 6 TO LESS THAN 18 YEARS WITH NARCOLEPSY WITH/WITHOUT CATAPLEXY, FOLLOWED BY A PROLONGED OPEN-LABEL PERIOD

The study will be conducted in compliance with the following protocol and will be carried in accordance with Good Clinical Practice (GCP) as required by the ICH GCP E6 and local applicable regulatory requirements in the participating countries.

I give my complete agreement on this protocol which gives all necessary information to conduct this study. I hereby accept to coordinate this study:

The Coordinator - Investigator
Giuseppe Plazzi, MD, PhD, Università di Bologna, Italy

Signature [redacted] Date: 30 SEP 2020

The Sponsor [redacted]

Signature: [redacted] Date: October 2nd, 2020

The Medical Project Director [redacted]

Signature: _____ Date: 01 OCT 2020

Signature Page

PROTOCOL P11-06 / BF 2.649

DOUBLE BLIND, MULTICENTRE, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE SAFETY AND EFFICACY OF PITOLISANT IN CHILDREN FROM 6 TO LESS THAN 18 YEARS WITH NARCOLEPSY WITH/WITHOUT CATAPLEXY, FOLLOWED BY A PROLONGED OPEN-LABEL PERIOD

The signature below constitutes the approval of this protocol P11-06/BF2.649 and the attachments, and provides the necessary assurances that this trial will be conducted in accordance with all stipulations of the protocol, including all statements regarding confidentiality, and in accordance with local legal and GCP regulatory requirements and ICH guidelines.

The site Investigator:

Name: ……

Hospital: ……

Address: ……

……..

Date:_____ Signature:_____

TABLE OF CONTENTS

SYNOPSIS - PROTOCOL P11-06 / BF2.649

Title	Double blind, multicentre, randomized, placebo-controlled trial to evaluate safety and efficacy of pitolisant in children from 6 to less than 18 years with narcolepsy with/without cataplexy, followed by a prolonged open-label period.
Study Phase	Phase III
Rationale	Pitolisant (BF2.649) is an orally active histamine H3 receptor antagonist / inverse agonist. [redacted]
Main Objectives	• To evaluate the efficacy of pitolisant in reducing residual Excessive Daytime Sleepiness (EDS) and the number of cataplectic episodes (for patients with cataplexy) • To determine safety in children and adolescents • To assess the long-term safety of BF2.649 in the treatment of EDS in narcoleptic patients with or without cataplexy • To assess the drug-drug interactions with possible concomitant therapies • To assess the efficacy of long-term therapy with BF2.649 on EDS after a prolonged treatment period
Study population	Male and female children from 6 to less than 18 years of age suffering from narcolepsy with/without cataplexy – meeting the International Classification of Sleep Disorders (ICSD-3) criteria (Narcolepsy type 1 and 2). More or less (at least 40%) equally balance between age groups (6 to 11 included and 12 to 17 included). Each age groups should be also more or less equally balance between genders (at least 40%).
Sample Size	Initially, at least 60 evaluable patients for the primary endpoint (40 patients being administered pitolisant, and 20 patients receiving placebo). Besides, the analysis of sample size justified in the context of an adaptive sample size was performed on 29 enrolled patients including 27 randomized patients and among them 25 patients provided endpoint values at V6 and V7. The statistical outcomes highlighted the need for increase

	of the sample size. At least 96 patients (64 patients being administrated pitolisant, and 32 patients receiving placebo) should be needed for a power of at least 0.75, given the observed values of SD and baseline correlation. A new sample size was calculated further the change of the main endpoint and adjustment of the corresponding variability (SD and baseline correlation): A difference of at least UNS=3 between the studied treatment and placebo with the observed values of SD and baseline correlation will be detected as significant with a power of 85%, once the sample size is at least 36+72 patients for control and tested drug groups, respectively, thus a total of 108 patients.
Study duration for participants	Inclusion period 4 weeks (including 2-week baseline period). Followed by, Double-blind period, treated by pitolisant or placebo for 8 weeks, Followed by, Single blind wash-out period, treated by placebo for 1 week and then Followed by a prolonged open-label period depending on patient wish.
Main inclusion criteria	1) Male and female children from 6 to less than 18 years of age (until V8) suffering from narcolepsy with or without cataplexy - meeting the International Classification of Sleep Disorders (ICSD-3) criteria (narcolepsy type 1 and 2). Diagnosis confirmed with polysomnography and Multiple Sleep Latency Test for patients without cataplexy (if these examinations were not performed within the last 12 months) 2) PDSS score ≥ 15 during baseline period (V1+V2) / 2. 3) Patients should be free of non-authorized medication, in particular psychostimulant treatments as from the screening visit (V0) onwards. 4) Parents – and patients old enough to understand who have expressed a willingness to participate in the study, who have signed and dated the informed consent form prior to beginning protocol required procedures. 5) In the opinion of the investigator, the patient must have adequate support to comply with the entire study requirements as described in the protocol (e.g., transportation to and from trial site, self rating scales and diaries completion, drug compliance, scheduled visits, tests). 6) Female pubescent patients shall use a birth control method, judged efficient by the investigator, throughout the study and during the month following treatment discontinuation. 7) Patients should benefit from appropriate healthy insurance system (only applicable where mandatory e.g. in France).
Main non-inclusion criteria	1) Any other conditions that can be considered the primary causes of EDS: such as sleep related breathing disorders as defined by a sleep Apnea Index ≥ 5 per hour or/and an Apnea/Hypopnea Index ≥ 10 per hour, chronic sleep deprivation, circadian sleep wake rhythm disorder or any other medical or neurological causes that could account for narcolepsy symptoms associated with EDS.

	2) Cataplectic patients treated by anticataplectics (SNRI, SSRI, sodium oxybate) which are not under a stable treatment since at least 4 weeks at the time of inclusion (V2). 3) Patients treated for cataplexy or any other pathology, by tricyclic antidepressants (clomipramine, imipramine, mirtazapine, desmethylimipramine and protriptyline) are not authorized because they display histamine H1 receptor antagonist activity. 4) The use of pitolisant within a 30-day period prior to initial screening visit (V0) for this trial. 5) Current or recent (within one year) history of a substance abuse or dependence disorder including alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 6) Any significant abnormality of the electrocardiogram and particularly Fridericia's QTc interval ($QTcF = QT/\sqrt[3]{60/HR}$) higher than 450ms. 7) Patients with severe depression (CDI $\geq$ 16) 8) Patient with suicidal risk (C-SSRS) 9) Positive urinary drug testing (test applicable to patients from 12 years) 10) Pregnancy (defined as positive β-HCG blood test), breast-feeding, or patients and unable to use an efficient method of birth control shall not be included in the study (for pubescent female only). 11) Patients with severe hepatic Impairment (Child Pugh C) or with any other significant abnormality in the physical examination or clinical laboratory results. 12) Psychiatric and neurological disorders, such as moderate or severe psychosis or dementia, depression, history of seizure disorder or other problem that, in the investigator's opinion, would preclude the patient's participation and completion of this trial or comprise reliable representation of subjective symptoms. 13) Active clinically significant illness, including unstable cardiovascular, endocrine, neoplastic, gastrointestinal, haematological, hepatic, immunologic, metabolic, neurological (other than narcolepsy/cataplexy), pulmonary, and/or renal disease which could interfere with the study conduct or counter-indicate the study treatments or place the patient at risk during the trial or compromise the study objectives. 14) Prior severe adverse reactions to CNS stimulants. 15) Known hypersensitivity to the tested treatment including active substance and excipients. 16) The inability to continue daily activities safely, without the use of treatment against EDS. 17) Any patient presenting congenital galactosemia, glucose-galactose malabsorption or lactase deficiency due to the presence of lactose in investigational treatments. 18) Patients participating in another study or being in a follow–up period for another study. 19) Cannot be contacted in case of emergency.
Dosage, treatment regimen, route of	Starting dose of 5 mg, increasing to a maximum oral dose of 20 or 40 mg once daily, according to efficacy, tolerability and patient weight. Patients with a weight less than 40kg will be treated with a maximum daily

administration	dose of to 20mg. Treatment taken the morning before breakfast.
Control(s)	Placebo
Primary efficacy endpoint	Change in the intensity and frequency of symptoms of narcolepsy (EDS and cataplexy) as measured by the Ullanlinna Narcolepsy Scale (UNS) between baseline: [V1 score (D-14) + V2 score (D0)]/2 and the end of treatment: [V6 score (D49) + V7 score (D56)]/2. We will compare the results between pitolisant and placebo groups.
Main secondary endpoint(s) with time(s) of assessment	- Changes in EDS as measured by the maintenance of wakefulness test (MWT) between baseline and V7, in pitolisant and placebo groups. - Change in EDS measured by the Paediatric Daytime Sleepiness Scale (PDSS) between baseline: [V1 score (D-14) + V2 score (D0)]/2 and the end of treatment: [V6 score (D49) + V7 score (D56)]/2. We will compare the results between pitolisant and placebo groups. - Changes in EDS as measured by the Child and Adolescent Sleepiness Scale (CASS) between baseline and the end of treatment, in pitolisant and placebo groups. - Changes in the average number of cataplexy episodes per weeks (recorded in sleep diary by patient and/or parent/teacher) between the 2 weeks of baseline and the 2 weeks of end study treatment period (V6, V7), in pitolisant and placebo groups. - Differences in weekly frequency of cataplexy episodes (recorded in sleep diary by patient and/or parent/teacher) between baseline and the 4 weeks of stable treatment period (V4 to V7), in pitolisant and placebo groups. - Severity of EDS measured by the Clinical Global Impression of severity and change. Changes between baseline and V6, V7, in pitolisant and placebo groups. - Severity of cataplexy measured by the Clinical Global Impression of severity and change. Changes between baseline and V6, V7, in pitolisant and placebo groups. - Changes between baseline and V6 will be compared for the TEA-Ch test, in pitolisant and placebo groups. - Comparison between placebo and pitolisant groups on: - Withdrawal symptoms questionnaire (DSM IV) - Patients' Global Opinion on treatment effect at the end of treatment if able to express himself. If not will be reported either by parents or teachers. - Changes between baseline and at each visit of the open-label period in EDS. - Safety assessment will be done on monitoring of adverse events, physical examination, vital signs, ECG and Blood Laboratory tests modifications and the mood appraisal throughout the study.
Authorized treatments	Double-blind period: ▪ If Patients are treated with sodium oxybate, a stable dosage is required for a minimum period of 4 weeks prior to inclusion (V2), and this dosage should be maintained stable throughout the study.

	▪ Other purported anticataplectic treatments e.g. SSRI (fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine) or norepinephrine/serotoninergic uptake inhibitor (venlafaxine), norepinephrine uptake inhibitors (viloxazine, duloxetine, reboxetine, atomoxetine) are authorized only if they are maintained at stable dose for a minimum period of 4 weeks prior to inclusion (V2), and their dose should not be changed throughout the trial. ▪ Antihistamic H1 which do not cross blood brain barrier (BBB) (2nd and 3rd generation) ▪ Any change in the dosage of the other authorized concomitant treatments should be recorded in the CRF. Open label period: Concomitant treatments against EDS and cataplexy such as modafinil, sodium oxybate, methylphenidate or antidepressants (except tricyclics) are authorized. The investigator will be free to adapt posology.
Non-authorized treatments	Double blind period: At V0, all ongoing prohibited treatments are discontinued. At V1, first visit with baseline assessment, all prohibited treatments should have been stopped for at least 2 weeks. ▪ From screening visit (V0) throughout V8, subjects should be free of all other drugs or substances, namely; - with a psychotropic effect, including psychostimulants for the treatment of EDS (amphetamine and amphetamine-like CNS stimulants, methylphenidate or others, such as modafinil); - medication with sedating properties (e.g. benzodiazepines, non-benzodiazepine anxiolytics, hypnotics sedatives, neuroleptics, opioids, antihistaminic products (1st generation), and anticonvulsants). ▪ Tricyclic antidepressants such as clomipramine, imipramine, Mirtazapine, desmethylimipramine and protriptyline are not authorized because they display histamine H1 receptor antagonist activity and possibly interfere with the effect of pitolisant by abrogating the effect of endogenous histamine released in brain by pitolisant. Open label period: Medication with sedating properties (e.g. benzodiazepines, non-benzodiazepine anxiolytics, hypnotics sedatives, neuroleptics, opioids, antihistaminic products (1st generation), and anticonvulsants) are prohibited. Tricyclic antidepressants such as clomipramine, imipramine, mirtazapine, desmethylimipramine and protriptyline are not authorized because they display histamine H1 receptor antagonist activity and possibly interfere with the effect of pitolisant by abrogating the effect of endogenous histamine released in brain by pitolisant.
Statistical Analysis	The primary selection will be the Full Analysis Set (FAS), defined as all the randomized patients irrespective of their outcome, this analysis with the best conformity with Intent To Treat principle.

	The main endpoint is the UNS measuring the quantity and intensity of symptoms of narcolepsy in particular of EDS and cataplexies. Metric properties of this scale are summarized as follows: Total scores range from 0 to 44 with higher scores denoting greater narcoleptic tendencies. The significance of the active tested drug compared with placebo on the change of UNS will be assessed by Analysis of Covariance on Final UNS estimate (the summary mean of the two Final UNS measures V6 and V7) adjusted for baseline (summary mean of the two pre-treatment UNS values V1 and V2). ANCOVA will be conducted with a Mixed Linear Model taking into account centre heterogeneity. A standardized mean difference of at least 0.5 on the UNS (considered as the minimum clinically significant difference) will be detected at a two-sided 0.05 confidence level with a type 2 risk of 0.15 (power $\geq$ 0.85), assuming a baseline-final correlation R=0.4, and a sample size ratio 1:2 when the sample size/group is at least 36+72 patients for control and tested drug groups, respectively, thus a total of 108 patients. For patients terminating the trial before completion, the final value will be calculated as the mean of the two last known values (baseline if needed). The independent Data Safety Monitoring Board (DSMB) will regularly follow the progress of the clinical trial, monitor safety data and critical efficacy variables and be consulted concerning the opportunity of modifying the sample size (see next point), or terminate a trial for futility (see next point). - A one–stage Futility stopping will be based on Conditional Power (CP), (probability to detect a significant result at the end of the study), given the results observed at an intermediate time. CP will be estimated through B-values and (Lan & Wittes, 1988, Lan & Zucker, 93). This analysis was planned when at least 20 patients are available, and futility threshold will be CPmin=.10 involving a slight increase of type 2 error (β=0.1/.9=.111-.10$\cong$.01) (Proschan, 1999). This intermediate futility analysis does not require any type-I adjustment, this trial does not plan g rejection of the null hypothesis before its end. This analysis was delayed sine die due to necessity of reconsideration of the sample size and a proposal of change of the main endpoint. This analysis will be conducted as soon as the sample size is definitely fixed and the main endpoint endorsed by the European regulatory authority.
Safety	Adverse events and drug safety: • Monitoring of adverse events at each visit: investigators will assess, among other things, the severity and the relationship of each adverse event to study medication. *N.B.: hallucinations, sleep paralysis, dyssomnia and automatic behaviour, which are part of the usual associated symptoms of narcolepsy will only be considered as adverse events if the number of occurrences, or severity, is increased during the study treatment period.* • Cardiovascular safety: 1. Vital sign checking at each visit including blood pressure, heart rate and body weight. 2. ECG at each visit and calculation of Fridericia's corrected QTc interval

	(QTcF = QT/$^{3}\sqrt{}$ (60/HR)). If the QTcF is ≥ 500 ms or if the difference between the QTcF on treatment and the QTcF at baseline is ≥ 60 ms, (observed on two consecutive occasions, i.e. after performing a recheck a few hours later) the treatment shall be discontinued and the corresponding ECG forwarded to Bioprojet. • Mood appraisal adapted to children (CDI<16) at visits: V1, V4, V6, and V8 • Columbia-Suicide Severity Rating Scale (C-SSRS) from V1 to V8. • Blood laboratory tests (haematology, blood chemistry), at the initial screening visit (V1), at the final treatment phase evaluation visit (V7), and for any subject who withdraws prior to treatment phase completion, within five days after the last treatment intake. • Withdrawal symptom questionnaire (DSM-IV) at T1 (D59 ± 1) and at V8. The independent Data Safety Monitoring Board (DSMB) will regularly follow the progress of the clinical trial, monitor safety data and critical efficacy variables and be consulted concerning the opportunity of modifying the sample size, or terminate a trial for futility.
Study design and conduct	**<u>V0 – Screening visit and start of wash out period (Day-28 = only for patients under prohibited medications and cataplectic patients under anti-cataplectic treatment)</u>** The investigator will provide the patient and parents with the necessary information regarding the study objectives, the investigational product (pitolisant), the expected benefit, the potential risks and the study procedures. The informed consent will be signed by patient and parents prior to the study entry for each patient. Prohibited treatments will be discontinued at V0. A complete medical examination, detailed questionnaires on his/her medical history and narcolepsy history will be recorded. A complete physical examination including, weight, height and BMI. Vital signs (blood pressure, heart rate) Questioning on previous and concomitant medication used and possible occurrence of adverse events. Delivery of two sleep diaries (one per week) which has to be completed by the patient (if old enough to understand) and/or parents every evening. (Hour of bedtime in the evening, wake-up time in the morning, and number of sleepiness periods during the day, number of (total or partial) cataplexy attacks, number of hallucinations and sleep paralysis). **<u>V1 – Screening visit and Baseline period (Day -14)</u>** *<u>If no V0 visit is required, the investigator will provide the patient and parents with the necessary information regarding the study objectives, the investigational product (pitolisant), the expected benefit, the potential risks and the study procedures.</u>* *<u>The informed consents will be signed by patient and parents prior to the study entry for each patient.</u>* Patients who fulfil all inclusion and exclusion criteria and after providing informed consent, could be enrolled in the study and complete the procedures: Complete physical examination (including height and weight), Detailed questioning on medical history and narcolepsy history,

Questioning on previous and concomitant medication used and possible occurrence of adverse events,
Vital signs (blood pressure, heart rate),
12-lead ECG (QTcF control),
A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),
A urine drug testing (for patients from 12 years),
The following questionnaires should be performed:

- Pediatric Daytime Sleepiness Scale (PDSS),
- Child and Adolescent Sleepiness Scale (CASS)
- Ullanlinna Narcolepsy Scale (UNS),
- Test of Everyday Attention for Children (TEA-Ch),
- Clinical Global Impression of Severity (CGI-S) on EDS and on cataplexy,
- Childhood Depression Inventory (CDI),
- Columbia-Suicide Severity Rating Scale (C-SSRS),
- Retrieval of the 2 first sleep diaries (when applicable) and check by the investigator. Delivery of two sleep diaries (one per week) which has to be daily completed by the patient (if old enough to understand) and/or parents every evening. (Hour of bedtime in the evening, wake-up time in the morning, and number of sleepiness periods during the day, number of (total or partial) cataplexy attacks, number of hallucinations and sleep paralysis).

<u>V2 – Randomization and start of escalating period (Day 0)</u>

- A physical examination including vital signs shall be carried out.
- Adverse events and concomitant medication recording
- 12-lead ECG (QTcF value),
- Maintenance of Wakefulness Test (MWT) (four sessions of 30-minute tests),
- Polysomnography with Multiple Sleep Latency Test will be performed the day preceding V2, unless performed during the previous year,
- The following questionnaires should be performed:
  - PDSS,
  - CASS,
  - UNS,
  - CGI-S on EDS and on cataplexy,
  - C-SSRS,
  - Retrieval of the 2 first sleep diaries and delivery of two other sleep diaries which have to be completed every day throughout the baseline period,
- Treatment dispensation for the next two weeks
  - First week with 5mg of pitolisant (or placebo) per day in the morning, before breakfast,
  - Second week with a 10mg of pitolisant (or placebo) per day in the morning before breakfast.

<u>V3 - Dose adjustment visit (D 14 ± 2 days)</u>

- A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,

- 12-lead ECG (QTcF value),
- The following questionnaires should be performed:
  - PDSS,
  - CASS,
  - C-SSRS,
  - Retrieval of sleep diary of the previous visit and delivery of one other sleep diary which have to be completed every evening until the next visit,
- Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the assessment of investigators on the basis of efficacy and tolerance,

Patients taking pitolisant 10 mg/d (or placebo) continue the same dose or could reduce to pitolisant 5 mg/d (or placebo) or increase to 20 mg (or placebo).

V4 - Dose adjustment visit (D21 ± 2 days)

- A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,
- 12-lead ECG (QTcF value),
- The following questionnaires should be performed:
  - PDSS,
  - CASS,
  - CDI,
  - C-SSRS,
  - Retrieval of sleep diary of the previous visit and delivery of one other sleep diary which have to be completed every evening until the next visit,
- Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the assessment of investigators on the basis of efficacy, tolerance and weight,

Patients taking pitolisant 5 mg/d (or placebo) continue the same dose or could increase to 10 mg (or placebo),
Patients taking pitolisant 10 mg/d (or placebo) continue the same dose or could reduce to pitolisant 5 mg/d (or placebo) or increase to 20 mg (or placebo),
Patients taking pitolisant 20 mg/d (or placebo) continue the same dose or could reduce to pitolisant 10 mg/d (or placebo) or increase to 40 mg (or placebo). Patients with a weight less than 40kg could be treated with a maximum daily dose of 20 mg.

V5 – Dose adjustment visit (D28 ± 2 days)

- A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,
- 12-lead ECG (QTcF value),
- The following questionnaires should be performed:
  - PDSS,
  - CASS,
  - C-SSRS,

- Retrieval of sleep diary of the previous visit and delivery of one other sleep diary which have to be completed every evening until the next visit,

- Investigational treatment allocation: No increase of pitolisant dosage will be authorized, the dose of pitolisant will be individually adjusted according to the assessment of investigators on the basis of efficacy, tolerance and weight,

Patients taking pitolisant 5 mg/d (or placebo) continue the same dose,
Patients taking pitolisant 10 mg/d (or placebo) continue the same dose or could reduce to pitolisant 5 mg/d (or placebo),
Patients taking pitolisant 20 mg/d (or placebo) continue the same dose or could reduce to pitolisant 10 mg/d (or placebo),
Patients taking pitolisant 40 mg/d (or placebo) continue the same dose or could reduce to pitolisant 20 mg/d (or placebo),
From this date onwards, no dosage change will be allowed. Beginning of the 4-week stable dose period.

<u>V6 – Control treatment visit (D49 ± 2 days)</u>

- A complete interrogation including control of the treatment compliance, count of remaining tablet and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,
- 12-lead ECG (QTcF value),
- The following questionnaires should be performed:
  - PDSS,
  - CASS,
  - CDI,
  - C-SSRS,
  - UNS,
  - TEA-Ch,
  - Clinical Global Impression of Change (CGI-C) on EDS and on cataplexy,
  - Retrieval of sleep diary of the previous visit and delivery of one other sleep diary which have to be completed every evening until the next visit.
- No dispensation performed at V6.

<u>V7 – End of Double Blind Period (D56 ± 2 days)</u>

- A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,
- 12-lead ECG (QTcF value),
- A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),

A urine drug testing (for patients from 12 years),

- Maintenance of Wakefulness Test (MWT) (four sessions of 30-minute tests),
- The following questionnaires should be performed:
  - PDSS,
  - CASS,

	- C-SSRS, - UNS, - CGI-C on EDS and on cataplexy, - Retrieval of sleep diary of the previous visit and delivery of one other sleep diary which have to be completed every evening until the next visit, - Global opinion on the effect of investigational treatment will be reported by patient if able to express himself. If not will be reported either by parents or teachers. - Investigational treatment allocation: start 1-week wash-out period. **<u>T1 - Telephone contact at D59 (± 1 day)</u>** During this telephone contact, the investigator should: - Ascertain that the treatment discontinuation is well tolerated - Record all adverse events that have occurred - Withdrawal symptoms questionnaire **<u>V8 - End of study visit after 1 week of placebo wash out or (D63 ± 2 days) / Start of Open label or Premature withdrawal visit (within 5 days after last treatment intake)</u>** The premature withdrawal patients should be followed by a visit performed within a maximum of 5 days after the last dose of study drug. - A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake, - Adverse events and concomitant medication recording, - A physical examination including vital signs shall be carried out, - 12-lead ECG (QTcF value), - A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick). (only for premature withdrawal patients), - The following questionnaires should be performed: - PDSS, - CASS, - UNS (only for premature withdrawal patients), - CGI-C on EDS and on cataplexy, - CDI, - C-SSRS, -Global opinion on the effect of investigational treatment will be reported by patient if able to express himself. If not will be reported either by parents or teachers. (only for premature withdrawal patients), - Retrieval of sleep diary. -Withdrawal symptoms questionnaires. Patients willing to continue the study in the prolonged open label period will receive a new pack of investigational treatment and will start an escalating dose treatment. Those patients will receive one sleep diary which have to be filled out daily during the 7 days prior to the next visit. Patients not willing to continue in the study will be followed under usual practice.

Patients completing V8 will have the possibility to continue the treatment with pitolisant in open conditions until BF2.649 (pitolisant) is available on the market for children/adolescent from 6 to 17 years included or as soon as the patient becomes older than 18 years. Then he will have access to the treatment already on the market for adults.

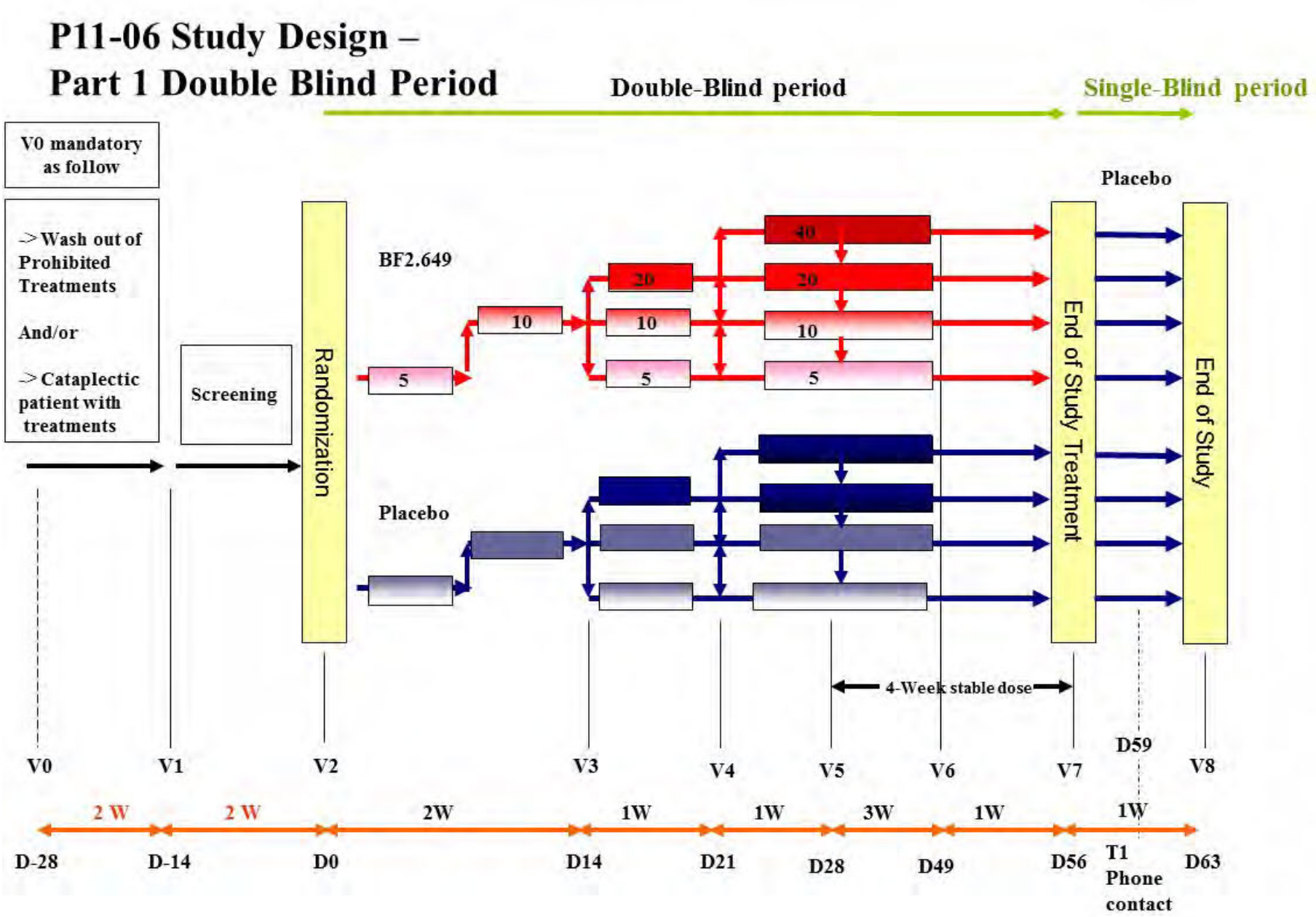
V9 - Dose adjustment visit (D77 ± 2 days)

- A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,
- 12-lead ECG (QTcF value),
- The following questionnaires should be performed:
  - PDSS,
  - CGI-C on EDS and on cataplexy,
  - CDI,
  - C-SSRS,
  - Global opinion on the effect of investigational treatment will be reported by patient if able to express himself. If not will be reported either by parents or teachers,
- Retrieval of sleep diary. (Sleep diary will be filled out daily during the 7 days prior to the next visit) and delivery of one other.
- Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the assessment of investigators on the basis of efficacy and tolerance,

V10 - Dose adjustment visit (D84 ± 2 days)

- A complete interrogation including control of the treatment compliance, count of remaining tablets and verification of the forgotten treatment intake,
- Adverse events and concomitant medication recording,
- A physical examination including vital signs shall be carried out,
- 12-lead ECG (QTcF value),
- A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),
- The following questionnaires should be performed:
  - PDSS,
  - CGI-C on EDS and on cataplexy,
  - CDI,
  - C-SSRS,
  - Global opinion on the effect of investigational treatment will be reported by patient if able to express himself. If not will be reported either by parents or teachers,
  - Retrieval of sleep diary. (Sleep diary will be filled out daily during the 7 days prior to the next visit) and delivery of one other.
- Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the assessment of investigators on the basis of efficacy, tolerance and weight.

	6 treatment daily dose regimens are available: 5mg, 10mg, 15mg, 20mg, 30mg and 40mg/d from the visit 10 until the end of study. **T2 - Telephone contact at D91 (± 1 day)** During this telephone contact: - The investigator should assess the efficacy and tolerance. In opinion of investigator, if patient needs a dose adjustment, the dose could be re-adjusted according the effectiveness/tolerability of treatment to patient. In case of need, it is possible to plan a visit on site within the week following phone contact for obtaining new bottles of treatment with the corresponding dose. - Record all adverse events that have occurred. **V11 - Dose adjustment visit (D112 ± 7 days)** Idem to the visit V9 **V12 - Dose adjustment visit (D196 ± 7 days)** Idem to the visit V11 **V13 - Dose adjustment visit (D364 ± 7 days)** Idem to the visit V12 + a blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick). **All subsequent visits are performed each 6 months.** Idem to the visit V13 **Phone visits during the COVID-19 pandemic** In order to limit the risk for the patient to spread/acquire the infection, special measures are put in place to maintain the participants in the study. The investigator should assess during these calls the efficacy and tolerance and the dose of treatment should be adjusted accordingly, when applicable. Direct shipment of study treatment from the site, or hospital pharmacy, to the patient's home is allowed via a courier with the full documentation of shipment and receipt by the patient/parents. Patients will return all medication at his/her subsequent site visit. Diaries to be documented daily are sent to the patient with the study treatment.
Study Duration and planned dates	The actual overall study duration or patients recruitment period may vary according to the number of screened patients presenting the main inclusion and exclusion criteria. Study duration for each patient: 13 weeks (2 week of wash-out + 2 weeks for baseline + 8 weeks under double blind study treatment + 1 week for study treatment wash-out). Followed by a prolonged open-label period. Planned dates for the Clinical Study: Start Q1 2016


P11-06 Study Design –
Part 1 Double Blind Period
Double-Blind period
Single-Blind period
V0 mandatory as follow
-> Wash out of Prohibited Treatments
And/or
-> Cataplectic patient with treatments
Screening
Randomization
BF2.649
Placebo
5
10
20
40
End of Study Treatment
End of Study
4-Week stable dose
V0
V1
V2
V3
V4
V5
V6
V7
D59
V8
2 W
2 W
2W
1W
1W
3W
1W
1W
D-28
D-14
D0
D14
D21
D28
D49
D56
T1 Phone contact
D63

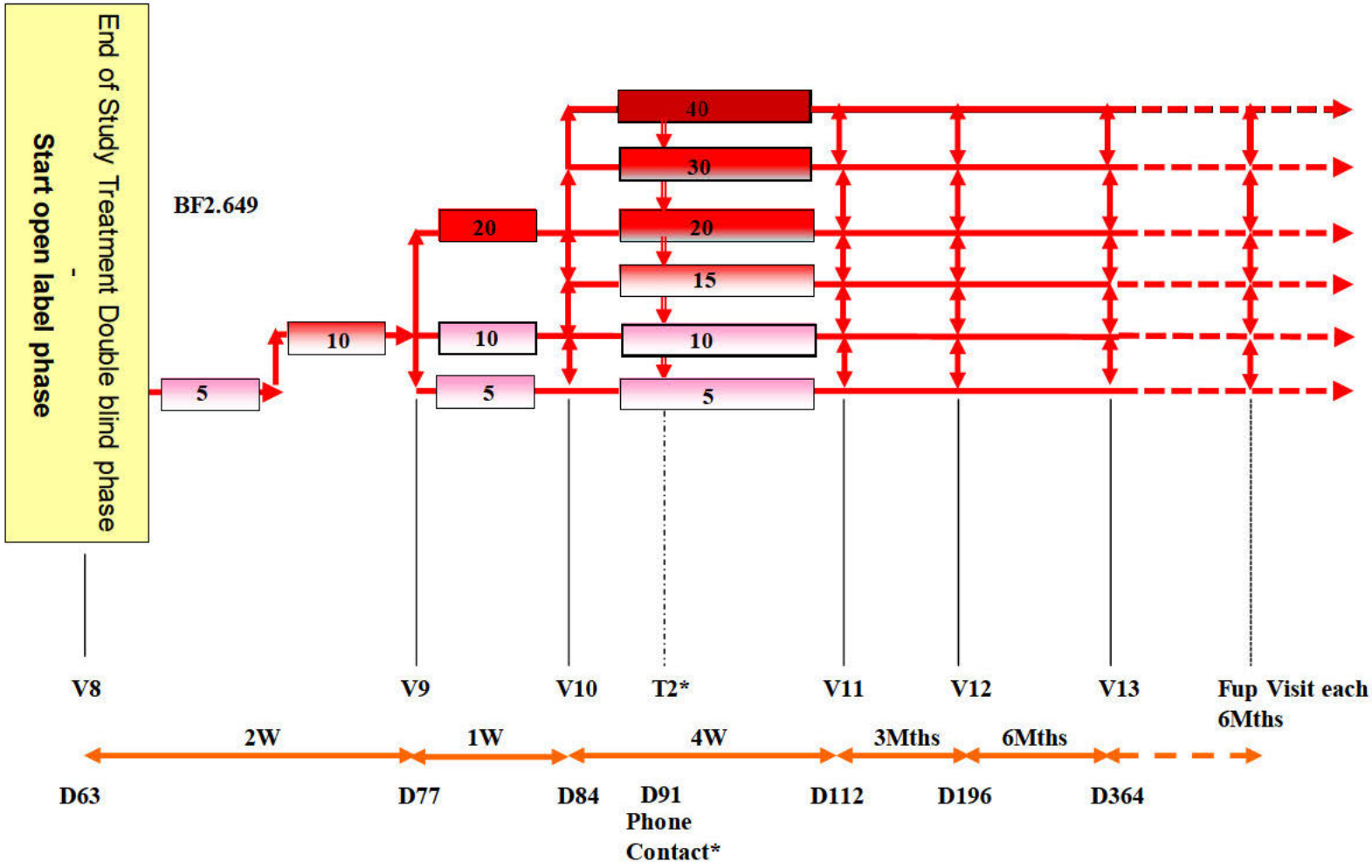
Part 1 Double Blind Period - Overall time and events schedule:

Visits / Procedures	Screening V0[8]	V1	Inclusion V2	V3	V4	V5	V6	Endpoint V7	T1- Phone Contact	V8	Premature withdrawal [3]
Study day	**D-28**	**D-14**	**D0 ±2**	**D14 ±2**	**D21 ±2**	**D28 ±2**	**D49 ±2**	**D56 ±2**	**D59 ±1**	**D63 ±2**	**+ 5**
Informed consent	X	X*									
Narcolepsy history, Medical history and prior medications	X	X									
Physical examination, vital signs	X	X	X	X	X	X	X	X		X	X
ECG [6]		X	X	X	X	X	X	X		X	X
Lab tests [2]		X						X			X
Selection criteria	X	X	X								
Polysomnography - MSLT			X[7]								
MWT			X					X			
PDSS		X	X	X	X	X	X	X		X	X
CASS		X	X	X	X	X	X	X		X	X
Ullanlinna narcolepsy scale		X	X				X	X			X
TEA-Ch		X					X				
CGI EDS + CGI Cataplexy		X	X				X	X		X	X
Childhood Depression Inventory (CDI)		X			X		X			X	X
C-SSRS		X	X	X	X	X	X	X		X	X
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Dispensation of study drugs[1]			X	X	X	X		X			
Drug accountability				X	X	X	X	X		X	X
Withdrawal symptoms questionnaire (DSM IV)									X	X	X
Patients' global opinion[5]								X			X
Sleep diary delivery	X	X	X	X	X	X	X	X			
Sleep diary retrieval[4]		X	X	X	X	X	X	X		X	X

1 The 4-week escalating dosage phase is followed by a 4-week stable-dose period during which the dose will be 5-, 10-, 20, or 40 mg/d of pitolisant or placebo
2 Complete biological examination including: Red Blood Cells, White Blood Cells (differential count, absolute value), Hemoglobin, haematocrit, Mean corpuscular volume (MCV), platelet count, quick time, sodium, potassium, chloride, creatinine, alkaline phosphatases, urea, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma glutamyl transpeptidase (GGT), total bilirubin, glucose, triglycerides, total cholesterol, βHCG (only for pubescent female). Dipstick urinalysis. A urinary drug testing (test applicable to patients from 12 years).
3 The premature withdrawal from the study should be followed by a visit performed within a maximum of 5 days after the last dose of study drug.
4 The sleep diary has to be completed every evening from V0 to V8.
5 The global opinion will be reported by patient if able to express himself. If not will be reported either by parents or teachers.
6 ECG: calculation of the QTcF value and delta of QTcF values between baseline ECG and ECGs performed at each subsequent visits.
7 Polysomnography-MSLT will be performed the day preceding V2, unless performed during the previous year.
8 V0 is required to ensure proper selection of patients under prohibited medications. For patients not using any prohibited medication study or patients cataplectic not using anti-cataplectic treatments may start at V1.

* Inform consent will be signed once either at V0 or V1 when applicable.

P11-06 Study Design - Part 2 Open Label Period



* An unscheduled visit should be planned within the week following the phone contact in order to decrease the dose, if needed.

Part 2 Open Label Period - Overall time and events schedule:

Procedures \ Visits	V8	V9	V10	T2- Phone Contact[7]	V11	V12	V13	Fup Visit / Premature withdrawal[3]
Study day	**D63 ±2**	**D77 ±1**	**D84 ±2**	**D91 ±1**	**D112±7**	**D196 ±7**	**D364 ±7**	**Every 6 months**
Physical examination, vital signs	X	X	X		X	X	X	X
ECG [6]	X	X	X		X	X	X	X
Lab tests [2]			X				X	X
PDSS	X	X	X		X	X	X	X
CASS	X							
CGI EDS + CGI Cataplexy	X	X	X		X	X	X	X
Childhood Depression Inventory (CDI)	X	X	X		X	X	X	X
C-SSRS	X	X	X		X	X	X	X
Adverse events and concomitant medications	X	X	X	X	X	X	X	X
Dispensation of study drugs[1]	X	X	X	X	X	X	X	X
Drug accountability	X	X	X	X	X	X	X	X
Patients' global opinion[5]		X	X		X	X	X	X
Sleep diary delivery	X	X	X		X	X	X	X
Sleep diary retrieval[4]	X	X	X		X	X	X	X

1 Treatment administration of open label period will start by an escalating dose phase for all patients.
2 Complete biological examination including: Red Blood Cells, White Blood Cells (differential count, absolute value), Hemoglobin, haematocrit, Mean corpuscular volume (MCV), platelet count, quick time, sodium, potassium, chloride, creatinine, alkaline phosphatases, urea, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma glutamyl transpeptidase (GGT), total bilirubin, glucose, triglycerides, total cholesterol, βHCG (only for pubescent female). Dipstick urinalysis. A urinary drug testing (test applicable to patients from 12 years).
3 The premature withdrawal from the study should be followed by a visit performed within a maximum of 5 days after the last dose of study drug.
4 The sleep diary has to be completed daily the 7 days prior to the next visit.
5 The global opinion will be reported by patient if able to express himself. If not will be reported either by parents or teachers.
6 ECG: calculation of the QTcF value and delta of QTcF values between baseline ECG and ECGs performed at each subsequent visits.
7 In case of dose decrease, an unscheduled visit should be planned within the week following the phone contact in order to decrease the dose from 20 to 10 mg. The other doses decrease, from 40 to 20 and 10 to 5 mg, don't require a visit.

ABBREVATIONS USED IN THE PROTOCOL

AEs	Adverse events
ALAT	Alanine aminotransferase
ANCOVA	Analysis of Covariance test
ASAT	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
CASS	Child and Adolescent Sleepiness Scale
CDI	Childhood Depression Inventory
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
Cmax	Maximum observed concentration
CNIL	Commission Nationale de l'Informatique et des Libertés
CNS	Central nervous system
CRF	Case report form
CRO	Contract Research Organization
CSF	Cerebral Spinal Fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DMB	Data Management Book
DSM-IV	Diagnostic System Medical, fourth version
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDS	Excessive Daytime Sleepiness
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GMP	Good Manufacturing Practice
H3R	Histamine H3 receptor
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
ICSD	International Classification of Sleep Disorders
IEC	Independent Ethics Committee
IRB	Institutional Review Board

KO	Knock-out
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NOAEL	No observable adverse effect levels
OSA	Obstructive Sleep Apnoea syndrome
PDSS	Pediatric Daytime Sleepiness Scale
PS	Paradoxical sleep
PSG	Polysomnography
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SD	Standard Deviation
TEA-Ch	Test of Everyday Attention for Children
ß-hCG	Human chorionic gonadotropin
SWS	Slow Wave Sleep
Tmax	Time to Cmax

1. INTRODUCTION

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness (EDS). The age-at-onset may be childhood, and even more disabling symptoms such as cataplexy attacks can very often occur (80 % of cases approximately, according to renowned European neurologists). Cataplexy attacks facilitate the Δg since, in young children, sleepiness may take on the form of an increased rather than a decreased activity, including irritability, aggressiveness, and inattentiveness (resembling the attention-deficit/hyperactivity disorder).

Pharmacological treatments consist of psychostimulants (modafinil, methylphenidate), whereas sodium oxybate is used to reduce the frequency and intensity of cataplexy attacks.

However, a great number of adverse events (more particularly, confusion, dizziness, suicidal ideation, high blood pressure…) together with its administration rhythm requiring a nocturnal intake (not easily followed by patients) restrict its use.

Pitolisant, an inverse agonist of H3 receptor, has been developed in adult, narcoleptic patients with or without cataplexy, during several phase II (P04-03, P05-03, P06-06) and phase III (P07-03, P07-07, P09-15) clinical studies, with a good tolerance followed by favorable efficacy results, since it significantly reduced the diurnal sleepiness, as well as the number of cataplexy attacks.

1.1. SUMMARY OF RELEVANT NONCLINICAL STUDIES

1.1.1. Pharmacological Profile

[redacted]

[redacted]

[redacted]

1.2. SUMMARY OF RELEVANT CLINICAL STUDIES

1.2.1. Phase I studies

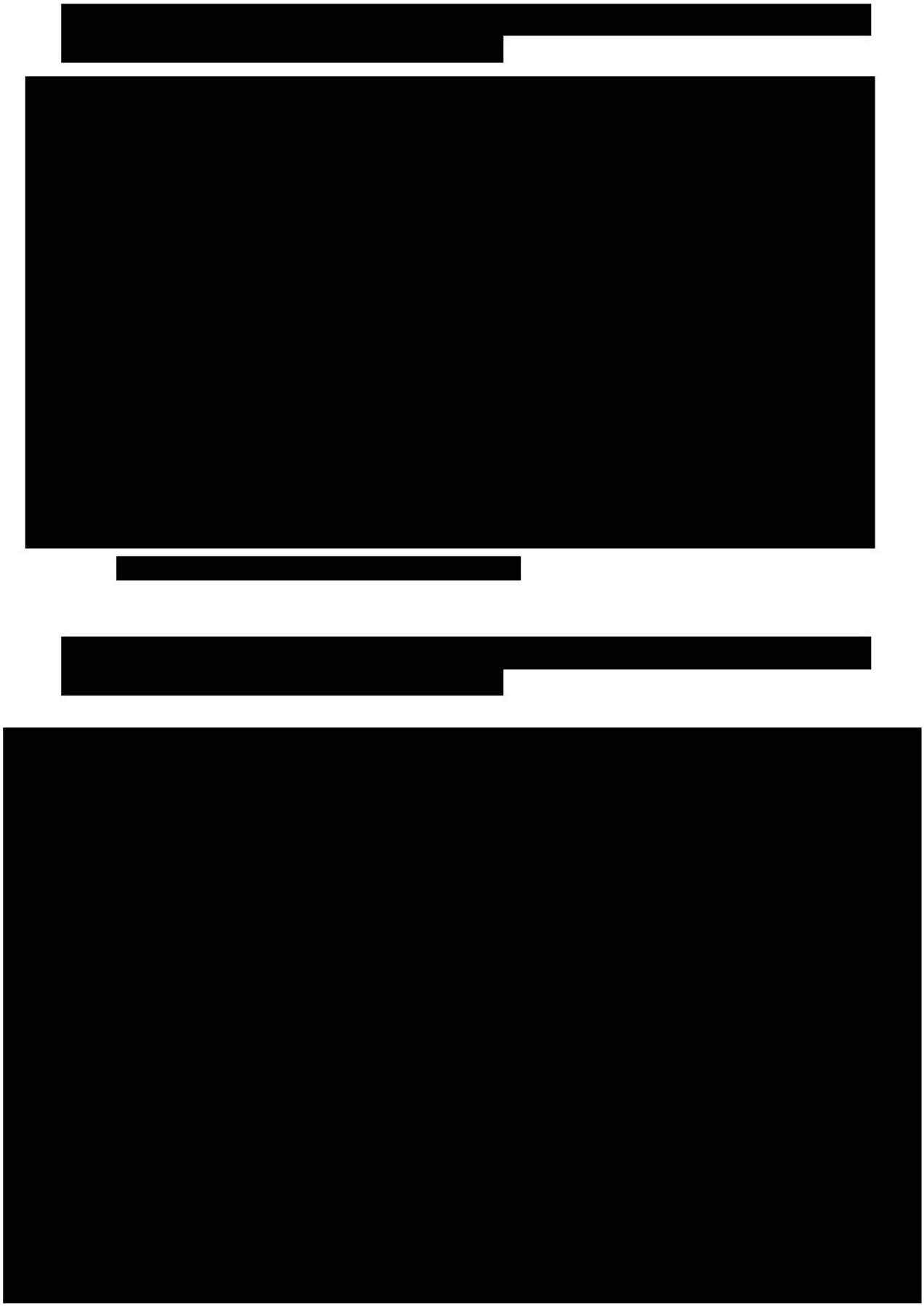
1.2.1.1. Phase I studies in adults

[redacted]

[redacted]

[redacted]

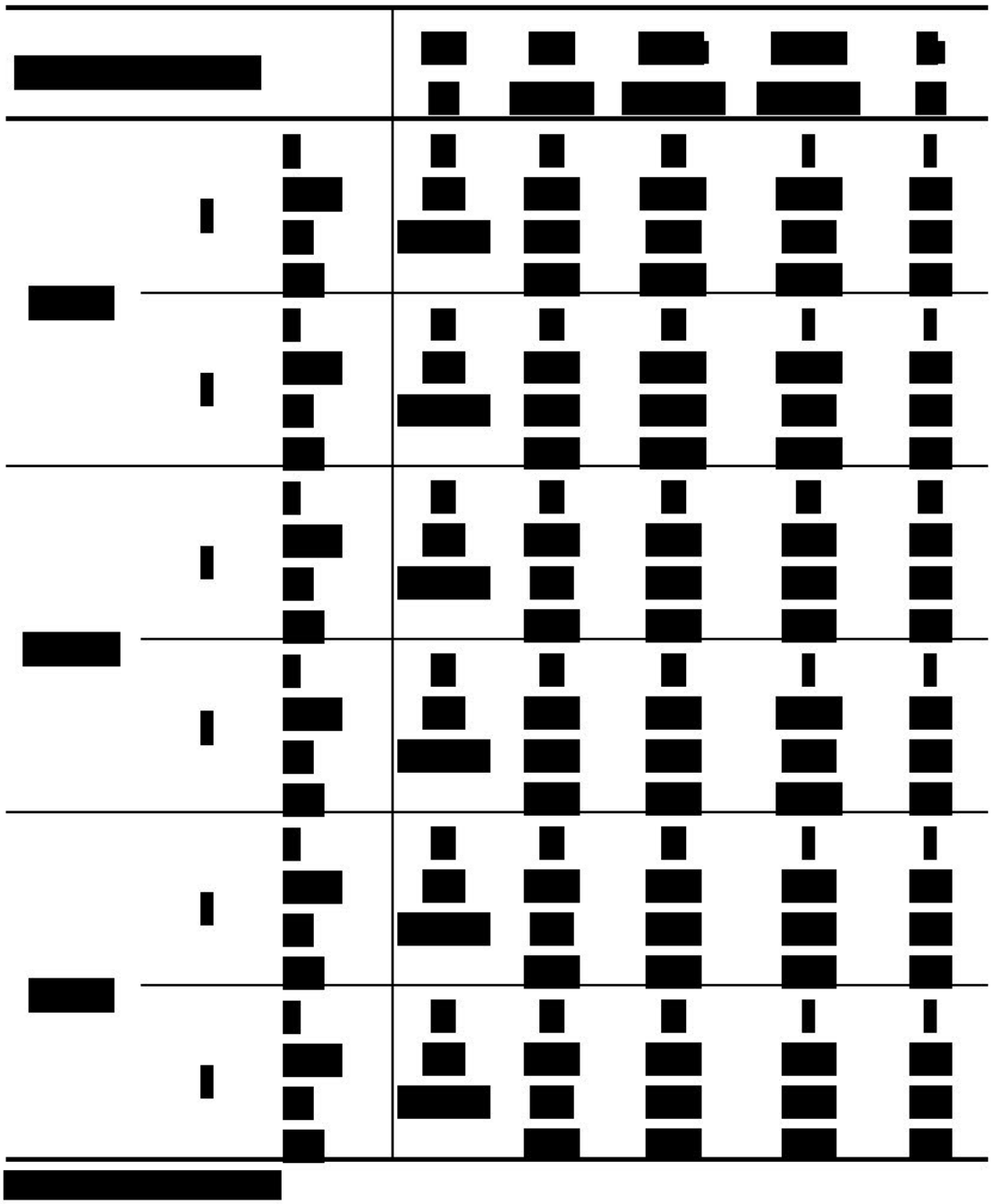
[redacted]



[redacted]

[redacted]

[redacted]

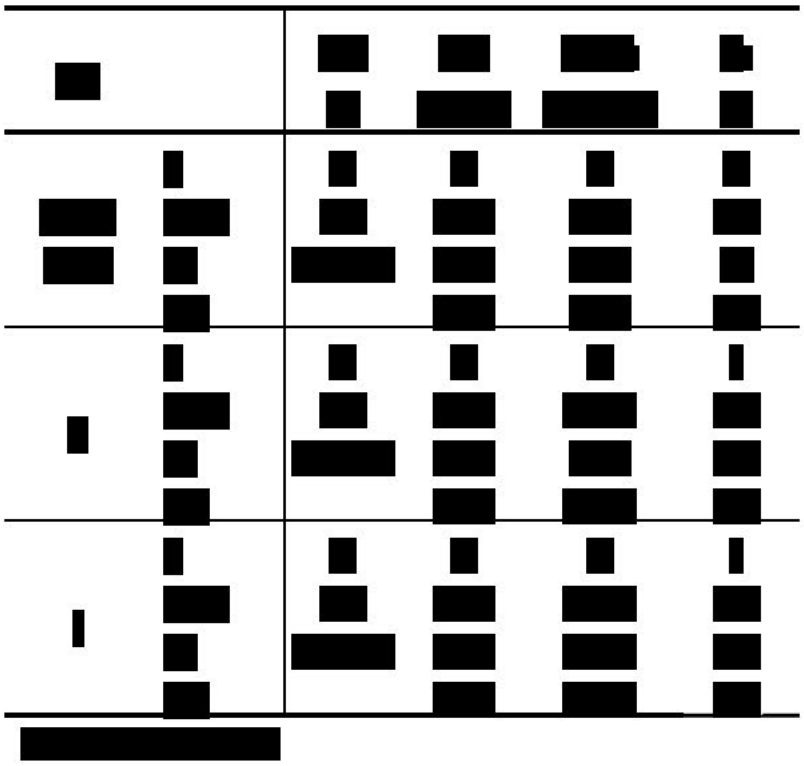


[redacted]

[redacted]

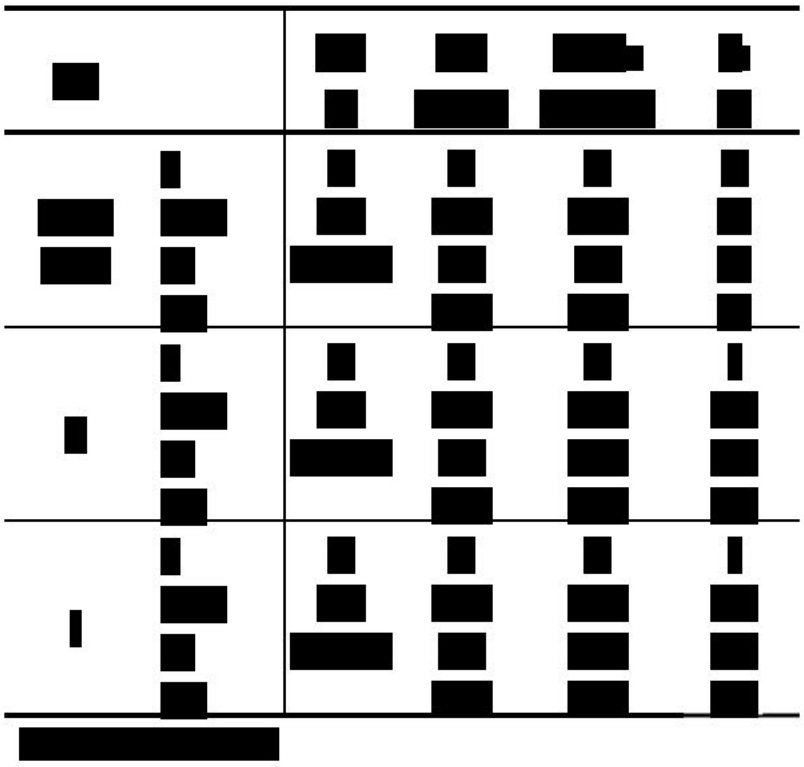
[redacted]

[redacted]



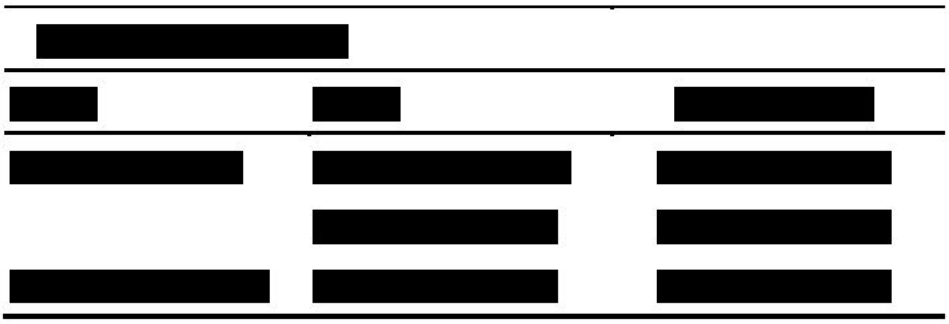
[redacted]

[redacted]



[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3. SUMMARY OF THE KNOWN AND POTENTIAL RISKS AND BENEFITS TO HUMAN SUBJECTS

The exposure to pitolisant in healthy volunteers was assessed in six pharmacokinetic studies in 66 subjects that received doses of pitolisant in single administration up to 120 mg and during 28 days with 50 mg once daily. The compound was well tolerated up to 90 mg by single dose; however the single dose at 120 mg led to irritability. The repeated administration (28 days up to 50 mg/day) was well tolerated.

[redacted]

Phase II studies demonstrated the positive effect of pitolisant in Excessive Daytime Sleepiness reduction in the indications intended for clinical trials.
The tolerance was good and the most common adverse events with pitolisant were headache (9.5%), insomnia (9.3%) and middle insomnia (0.9%), nausea (4.3%) and irritability (3.2%). These adverse events were most of the time of mild to moderate intensity.

Both phase III pivotal studies performed in 94 and 165 narcoleptic patients with or without cataplexy, respectively, all of them being treated by pitolisant, modafinil, or placebo during 8 weeks and analyzed, confirmed the efficacy of pitolisant on excessive daytime sleepiness with effects statistically superior to those of the placebo at the level of the main efficacy endpoint (ESS score), but also at the level of secondary criteria such as MWT, SART, CGI (on EDS), and above all the "ESS responder" criterion (ESS ≤ 10, or ESS Final – ESS Baseline ≥ 3).
The analysis of sleep diaries completed by the patients during 7 days prior to each visit showed a possible reduction of the risks of cataplexy, which remains to be confirmed by a new clinical study in this indication.
Tolerance was checked in more than 50 patients treated during 12 months by pitolisant only, or in association with other products (P09-10). It was found to be excellent in both groups.

2. RATIONALE FOR THE STUDY

[redacted]

[redacted]

3. TRIAL DESCRIPTION

3.1. TRIAL OBJECTIVES

During this trial, pitolisant will be compared to placebo, with regard to EDS on the one hand, and to the number of cataplexy episodes, if any, on the other hand.
The clinical and biological tolerance of pitolisant will also be checked.

This trial will characterize the efficacy of pitolisant (5-, 10-, 20-, 40 mg/d in Double Blind Period and 5-, 10-, 15-, 20-, 30-, 40 mg/d in Open Label Period) compared to placebo in showing an incremental improvement to the situation particularly in terms of a reduction of EDS as measured by the UNS, and also on the number of cataplexy episodes, if any.

3.2. TRIAL DESIGN

Randomized, double blind, placebo-controlled, parallel group, multicentre trial comparing the effects of pitolisant or placebo for the treatment during 8 weeks (double-blind period) of narcoleptic patients with or without cataplexy. After 4-week of individual up-titration scheme from 5 to a maximum of 40 mg/d pitolisant or placebo, the treatment will be administered at a stable dose during 4 weeks, followed by 1 week placebo period.
Then, patients willing to continue will receive the study treatment during a prolonged open-label period.

3.3. STUDY ENDPOINTS

3.3.1. Primary Endpoint

The primary endpoint of efficacy will be the **changes in UNS (Ullanlinna Narcolepsy Scale) measuring the intensity and frequency of symptoms of narcolepsy (Excessive Daytime Sleepiness (EDS) and cataplexies),** based on the change from baseline (mean of two pre-treatment measures at [(V1 + V2)/2]) of the UNS score and at the end of double-blind phase (mean of the last two measures [(V6 + V7)/2]).

[redacted].

3.3.2. Secondary endpoints

As secondary endpoints the study will assess efficacy and safety endpoints in pitolisant and placebo groups:

- Changes in EDS as measured by the maintenance of wakefulness test (MWT) between baseline and V7,
- Changes in EDS measured by the Paediatric Daytime Sleepiness Scale (PDSS) between baseline: [V1 score (D-14) + V2 score (D0)]/2 and the end of treatment: [V6 score (D49) + V7 score (D56)]/2,
- Changes in EDS as measured by the Child and Adolescent Sleepiness Scale (CASS) between baseline and the end of treatment,
- Changes in the average number of cataplexy episodes per weeks: (recorded in sleep diary by patient and/or parent/teacher) between the 2 weeks of baseline and the 2 weeks of end study treatment period (V6, V7),
- Differences in weekly frequency of cataplexy episodes (recorded in sleep diary by patient and/or parent/teacher) between baseline and the 4 weeks of stable treatment period (V4 to V7),
- Severity of EDS measured by the clinical Global Impression of severity and change. Changes between baseline and V6, V7,
- Severity of cataplexy measured by the clinical Global Impression of severity and change. Changes between baseline and V6, V7,
- Changes between baseline and V6 will be compared for the TEA-Ch test,
- Comparison between placebo and pitolisant groups on:
    - Withdrawal symptoms questionnaire (DSM IV) on D59 during a phone call (T1) and at the end-of-study visit on D63 (V8) after a one-week period on placebo,
    - Patients' Global Opinion on treatment effect at the end of treatment if able to express

himself. If not will be reported either by parents or teachers.

- ,Tolerability as measured by Treatment Emergent Adverse Events (TEAE),
- Changes in Physical examination and Vital signs,
- ECG and calculation of Fridericia's corrected QTc interval (QTcF = QT/$^3\sqrt{}$ 60/HR),
- Blood laboratory tests (haematology, blood chemistry),
- Mood appraisal adapted to children (CDI and C-SSRS).

- Changes between baseline and at each visit of the open-label period in EDS,
- Safety assessment will be done on monitoring of adverse events, physical examination, vital signs, ECG and Blood Laboratory tests modifications and the mood appraisal throughout the study.

3.4. STUDY POPULATION

The study will be performed on 108 narcoleptic children to assess the effects of pitolisant compared with placebo in the relief of Excessive Daytime Sleepiness (EDS): children from 6 to less than 12 years of age and adolescents from 12 to less than 18 years of age more or less equally balance between age groups (at least 40%). Each age groups should be also more or less equally balance between genders (at least 40%), all of them suffering from narcolepsy with or without cataplexy.

Patients are allowed to continue their anticataplectic drugs, if they are at stable dosage for at least 4 weeks before the inclusion (V2), and this dosage should be maintained stable throughout the study (from V2 to V8).
The previous use of drug with a psychotropic effect, including psychostimulants for the treatment of EDS should be discontinued at V0 (D-28).
At V1 (D-14), all prohibited treatments should be stopped for at least 14 days.

3.4.1. Inclusion criteria

1) Male and female children from 6 to less than 18 years of age (at V8) suffering from narcolepsy with or without cataplexy - meeting the International Classification of Sleep Disorders (ICSD-3) criteria (Narcolepsy type 1 and 2). Diagnosis confirmed with polysomnography and Multiple Sleep Latency Test for patients without cataplexy (if these examinations were not performed within the last 12 months)
2) PDSS score ≥ 15 during baseline period (V1+V2) / 2.

3) Patients should be free of non-authorized medication, in particular psychostimulant treatments as from the screening visit (V0) onwards.
4) Parents – and patients old enough to understand who have expressed a willingness to participate in the study, who have signed and dated the informed consent form prior to beginning protocol required procedures.
5) In the opinion of the investigator, the patient must have adequate support to comply with the entire study requirements as described in the protocol (e.g., transportation to and from trial site, self rating scales and diaries completion, drug compliance, scheduled visits, tests).
6) Female pubescent patients shall use a birth control method, judged efficient by the investigator, throughout the study and during the month following treatment discontinuation.
7) Patients should benefit from appropriate healthy insurance system (only applicable where mandatory e.g. in France).

3.4.2. Non inclusion criteria

1) Any other conditions that can be considered the primary causes of EDS: such as sleep related breathing disorders as defined by a sleep Apnea Index ≥ 5 per hour or/and an Apnea/Hypopnea Index ≥ 10 per hour, chronic sleep deprivation, circadian sleep wake rhythm disorder or any other medical or neurological causes that could account for narcolepsy symptoms associated with EDS.
2) Cataplectic patients treated by anticataplectics (SNRI, SSRI, sodium oxybate) which are not under a stable treatment since at least 4 weeks at the time of inclusion (V2).
3) Patients treated for cataplexy or any other pathology, by tricyclic antidepressants (clomipramine, imipramine, mirtazapine, desmethylimipramine and protriptyline) are not authorized because they display histamine H1 receptor antagonist activity.
4) The use of pitolisant within a 30-day period prior to initial screening visit (V0) for this trial.
5) Current or recent (within one year) history of a substance abuse or dependence disorder including alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).
6) Any significant abnormality of the electrocardiogram and particularly Fridericia's QTc interval ($QTcF = QT/\sqrt[3]{60/HR}$) higher than 450 ms.
7) Patients with severe depression (CDI ≥ 16).
8) Patient with suicidal risk (C-SSRS).
9) Positive urinary drug testing (test applicable to patients from 12 years)

10) Pregnancy (defined as positive β-HCG blood test), breast-feeding, or patients and unable to use an efficient method of birth control shall not be included in the study (for pubescent female only).
11) Patients with severe hepatic Impairment (Child Pugh C) or with any other significant abnormality in the physical examination or clinical laboratory results.
12) Psychiatric and neurological disorders, such as moderate or severe psychosis or dementia, depression, history of seizure disorder or other problem that, in the investigator's opinion, would preclude the patient's participation and completion of this trial or comprise reliable representation of subjective symptoms.
13) Active clinically significant illness, including unstable cardiovascular, endocrine, neoplastic, gastrointestinal, haematological, hepatic, immunologic, metabolic, neurological (other than narcolepsy/cataplexy), pulmonary, and/or renal disease which could interfere with the study conduct or counter-indicate the study treatments or place the patient at risk during the trial or compromise the study objectives.
14) Prior severe adverse reactions to CNS stimulants.
15) Known hypersensitivity to the tested treatment including active substance and excipients.
16) The inability to continue daily activities safely, without the use of treatment against EDS.
17) Any patient presenting congenital galactosemia, glucose-galactose malabsorption or lactase deficiency due to the presence of lactose in investigational treatments.
18) Patients participating in another study or being in a follow–up period for another study.
19) Cannot be contacted in case of emergency.

3.5. STUDY TREATMENT

Patients will be outpatients followed in ambulatory way during the whole study period and they will all receive the investigational study treatment pitolisant or placebo as described § 4.2.
Patients will be asked to take the study drug every day before breakfast, according to the investigator's prescription regarding the dose regimen of patients, based on the product efficacy and tolerance.

The total treatment duration of this double blind study is 8 weeks. Patients will start pitolisant treatment with escalating doses scheme on the first 4 weeks, as follows:

- V2 - 5 mg of BF2.649 or placebo / day during the first week,
  - 10 mg of BF2.649 or placebo /day during the second week,
- V3 - Increase to 20 mg/d or maintain at 10 mg/d or reduce to 5 mg/d of BF2.649 (or placebo) per day for 7 days depending on efficacy and tolerability.

- V4 – It will also be possible to reduce the dose administered to the patients, or to increase it without exceeding 40 mg/d. Patients with a weight less than 40kg could be treated with a maximum daily dose of 20mg.
- V5 – It will be possible to reduce the dose administered to the patients, but not to increase it.

  As from V5 onwards, no dosage change of the study treatment will be authorized.
- At the end of the double blind treatment (V7), the investigator will provide placebo to all patients for the one-week wash out period.

In open-label period patients will start pitolisant treatment with escalating doses scheme, as follows:

- V8 - 5 mg of BF2.649 or placebo / day during the first week.
  - 10 mg of BF2.649 or placebo /day during the second week.
- V9 – The third week according to investigator prescription and evaluation on efficacy and tolerance, the dose will be maintained or increased at 20 mg/d or reduced at 5 mg/d.
- V10 – According to investigator prescription and evaluation on efficacy, tolerance and weight, the dose will be maintained, reduced or increased at 5, 10, 15, 20, 30 or 40 mg/d (only if patient weight is above 40kg) for the next 4-week

  During the phone contact (T2), in opinion of investigator, the dose could be re-adjusted according the effectiveness/tolerability of treatment to patient.

  In case of need, it is possible to plan a visit on site within the week following phone contact for obtaining new bottles of treatment with the corresponding dose.
- V11 – According to investigator prescription and evaluation on efficacy, tolerance and weight, the dose will be maintained, reduced or increased at 5, 10, 15, 20, 30 or 40 mg/d (only if patient weight is above 40kg) for the next 3-month.
- V12 – According to investigator prescription and evaluation on efficacy, tolerance and weight, the dose will be maintained, reduced or increased at 5, 10, 15, 20, 30 or 40 mg/d (only if patient weight is above 40kg) for the next 6-month.
- All subsequent visits, the treatment dispensation will be done like V12.

3.6. CONCOMITANT TREATMENTS

The investigator must report all concomitant medications in the CRF and record all changes in the dosages during the study.

3.6.1. Authorized concomitant treatments

Double-blind period:

- If Patients are treated with sodium oxybate, a stable dosage is required for a minimum period of 4 weeks prior to inclusion (V2), and this dosage should be maintained stable throughout the study.
- Other purported anticataplectic treatments e.g. SSRI (fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine) or norepinephrine/serotoninergic uptake inhibitor (venlafaxine), norepinephrine uptake inhibitors (viloxazine, duloxetine, reboxetine, atomoxetine) are authorized only if they are maintained at stable dose for a minimum period of 4 weeks prior to inclusion (V2), and their dose should not be changed throughout the trial.
- Antihistamic H1 which do not cross blood brain barrier (BBB) (2nd and 3rd generation).
- Any change in the dosage of the other authorized concomitant treatments should be recorded in the CRF.

Open label period:

Concomitant treatments against EDS and cataplexy such as modafinil, sodium oxybate, methylphenidate or antidepressants (except tricyclics) are authorized. The investigator will be free to adapt posology.

3.6.2. Prohibited concomitant treatments

Double-blind period:

At V0, all ongoing prohibited treatments are discontinued. At V1, first visit with baseline assessment, all prohibited treatments should have been stopped for at least 2 weeks.

- From screening visit (V0) throughout V8, patients should be free of all other drugs or substances, namely:

  - with a psychotropic effect, including psychostimulants for the treatment of EDS (amphetamine and amphetamine-like CNS stimulants, methylphenidate or others, such as modafinil);

  - medication with sedating properties (e.g. benzodiazepines, non-benzodiazepine anxiolytics, hypnotics sedatives, neuroleptics, opioids, antihistaminic products (1st generation), and anticonvulsants).
- Tricyclic antidepressants such as clomipramine, imipramine, Mirtazapine, desmethylimipramine and protriptyline are not authorized because they display histamine

H1 receptor antagonist activity and possibly interfere with the effect of pitolisant by abrogating the effect of endogenous histamine released in brain by pitolisant.

Open label period:

Medication with sedating properties (e.g. benzodiazepines, non-benzodiazepine anxiolytics, hypnotics sedatives, neuroleptics, opioids, antihistaminic products (1st generation), and anticonvulsants) are prohibited.

Tricyclic antidepressants such as clomipramine, imipramine, mirtazapine, desmethylimipramine and protriptyline are not authorized because they display histamine H1 receptor antagonist activity and possibly interfere with the effect of pitolisant by abrogating the effect of endogenous histamine released in brain by pitolisant.

3.7. EVALUATION CRITERIA

Medical history and demographic data including age, height, weight, gender will be obtained for each patient screened for entry into the study.

The following measures will be used to assess the safety and efficacy of pitolisant:

3.7.1. Efficacy criteria

3.7.1.1. Primary endpoint: Ullanlinna Narcolepsy Scale score (UNS)

The Ullanlinna Narcolepsy Scale (Appendix 1) is an 11-item scale used to measure the intensity and frequency of symptoms of narcolepsy (EDS and cataplexy). The first four items address typical manifestations of cataplexy occurring in situation as laughing, feeling glad or angry or any exciting situation. The 7 other items measure the sleep latency and the propensity to fall asleep in various situations. The total score varies from 0 to 44.

The UNS will be evaluated at Visits V1 and V2 (i.e., prior to randomization) as baseline evaluation and at Visits V6 and V7 (i.e., end of the double-blind treatment period) and reviewed by the investigator.

The difference of baseline UNS and during the treatment are computed (V1-V2 and V6-V7).

The primary measure of efficacy is based on the change from baseline of the score of the UNS by comparing the mean of UNS performed at [(V6 + V7)/2] (end of double-blind period) to the mean of UNS performed at [(V1 + V2)/2] (baseline period). A comparison between pitolisant and placebo will be made on the score difference between baseline and the end of the treatment period.

[redacted]

3.7.1.2. Secondary endpoints

3.7.1.2.1. Child and Adolescent Sleepiness Scale (CASS)

In the ESS version adapted for children (6 and over) and adolescents (CASS), this is a simple instrument constituted by 10 items (Sitting and reading, Watching TV, Playing a video or computer game, Playing outside with friends, Travelling in a car or train for longer than one hour, In class during the morning, In class just after lunch, During break time (recess) at school, On Sundays if you lie down for a rest, In the morning when you wake up) each of them scored in 4 categories (Appendix 2). Each of the ten questions is rated from 0 = *never*, 1 = *sometimes,* 2 = *often* to 3 = *always* (want to sleep). The scores are summarized to yield a score between 0 and 30 with higher scores representing greater sleepiness.
A score greater than 14 is considered as abnormal sleepiness.

CASS will be evaluated at each study visit of double-blind phase and reviewed by the investigator. CASS should be handed out to the patient at approximately the same time of the visit day and with same delay after the investigational treatment intake in order to standardize the possible impact of the treatment on the evaluation.
The patient should be helped in the comprehension of the questionnaire until he/she fully understands the ten questions of the score. It will be reminded to patients, parents, and/or teachers that the CASS measures the subjective sleepiness with regard to the immediate past week.
It occurs frequently that some questions on specific situations are not encountered by the patient in his/her daily life. It is advised to give the patient equivalence to a similar situation in order to have a complete questionnaire filled.
The sum of the rated questions will be made by the investigator and reported in the CRF.
As supportive measure the calculation of responders' rate defined as a reduction of 3 points of the CASS score from baseline or the normalization of the CASS score at 10 or below.

3.7.1.2.2. Pediatric Daytime Sleepiness Scale scores (PDSS)

This is a simple instrument constituted by 8 items ("How often do you fall asleep or get drowsy during class periods", "How often do you get sleepy or drowsy while doing your homework", "Are you usually alert most of the day", "How often are you ever tired and grumpy during the day", "How often do you have trouble getting out of bed in the morning", "How often do you fall back to sleep after being awakened in the morning", "How often do you need someone to

awaken you in the morning", "How often do you think that you need more sleep") each of them scored in 5 categories (Appendix 3).

Each of the eight questions is rated from 0 = never, 1 = seldom, 2 = sometimes, 3 = often, frequently to 4 = very often, always. The total score ranges between 0 and 32 with higher scores representing greater sleepiness. A score greater than 13 is considered as abnormal sleepiness.

PDSS will be evaluated at each study visit and reviewed by the investigator. PDSS should be administrated to the patient at approximately the same time of the visit day and with same delay after the investigational treatment intake in order to standardize the possible impact of the treatment on the evaluation.

The patient should be helped in the comprehension of the questionnaire until he fully understands the eight questions of the score. It will be reminded to the patient that the PDSS measures the subjective sleepiness with regard to the immediate past week.

It occurs frequently that some questions on specific situations are not encountered by the patient in his/her daily life. It is advised to give the patient equivalence to a similar situation in order to have a complete questionnaire filled. The sum of the rated questions will be made by the investigator and reported in the CRF.

3.7.1.2.3. Clinical Global Impressions of Change

The severities of EDS and of cataplexy will be measured at baseline period V1 and V2 by the Clinical Global Impression of Severity (CGI-S) in order to describe the population : a 6-grade scale ranging from "no sign of illness", "borderline ill", "slightly ill", "moderately ill", "markedly ill", "among the most extremely ill patients" (Appendix 5). This corresponds to the first version of the test. When the patient is on treatment, the test enables to assess the improvement.

At visits V6 and V7 (during double-blind phase) and all visits of open-label period, the patients' change in EDS and in cataplexy (for narcoleptic patients also experiencing cataplexy) compared to baseline will be rated by the same investigator using Clinical Global Impression of Change (CGI-C) to document the perceived change in patients' illness: a 7-grade scale ranging from "very much improved", "much improved", "minimally improved", "no change", "minimally worse," "much worse", "very much worse".

3.7.1.2.4. Test of Everyday Attention for Children (TEA-Ch)

The Test of Everyday Attention for Children (TEA-Ch) assesses the cognitive functions with a version intended for children and another one for adolescents. This cognitive test shall be performed at V1 and at V6 visits.

3.7.1.2.5. Maintenance of Wakefulness Test 30-minute version

The Maintenance of Wakefulness Test (MWT) is used in this study to assess an individual's ability to maintain awake while resisting the pressure to fall asleep.

Patients will be administrated four 30-minute MWT sessions at 2-hour intervals at inclusion visit (V2) and at endpoint visit (V7 or the last on-study visit), according to validated standard *[Doghramji K et al, Electroencephalogr Clin Neurophysiol. 1997; 103:554-62]*[8].

Patients will be required to have sufficient nocturnal sleep (minimum 6 hours) and not drink alcohol during the night prior to this visit. The patient will be required to take their morning treatment and a light breakfast before 8.00 a.m. and arrive in the trial center around 9.00 a.m.; lunch immediately after the termination of the second session. They should refrain from drinking any stimulatory beverage such as coffee, tea or Coca-Cola this morning until the end of this visit.

The first session begins at 10.00 a.m. Patients are required to recline comfortably in a quiet, dimly lit bedroom at ambient temperature (as close to 22°C as possible). Patients are instructed to remain awake for as long as possible. Sleep onset is defined by either 3 consecutive 30-s epochs of stage 1 sleep or any single 30-s epoch of stage 2, 3, 4 or REM sleep.

Each session is terminated either at the first unequivocal onset of sleep defined as above or, if sleep onset is not achieved, after maximum in-bed duration of 30 minutes. Polysomnographic recordings are made to determine sleep onset, and mean sleep latency is calculated (maximum score 30 minutes).

3.7.1.2.6. Patient sleep diary

Patient sleep diary (Appendix 6) information from V1 (or from V0 when applicable) to V8 will be analyzed.

Patients (or assisted by their parents or legal representative or teacher) shall fill in the document on a daily basis throughout the double blind phase (13 weeks) and the 7-day prior to the next visit during the open-label period. During the first screening visit (V1 or from V0 when applicable), patients will be instructed on the daily use of diary by study investigators.

At each visit the patient should bring back his/her diary to the site for review by the investigator. The investigator should review these records with the patient.

In the active treatment group and in the placebo group, the score difference between the average number of cataplexy episodes (partial and total) per weeks between the 2 weeks of baseline and the 2 weeks of end study treatment period (V6, V7) and the differences in weekly frequency of cataplexy episodes between baseline and the 4 weeks of stable treatment period (V4 to V7).

In the open-label period, the difference between, the average number of cataplexy episodes

(partial and total) per weeks, the differences in weekly frequency of cataplexy episodes, between baseline and the 7-day prior all visits of the open-label period will be compared.

From the sleep diary, it will also be possible to check: Investigator should review the patients' and parents' estimate with them

- Hour of bedtime in the evening, wake-time in the morning.
- Number of diurnal involuntary sleep attacks and episodes of severe daytime sleepiness.
- Occurrence and number of cataplexy attacks (total or partial).
- Number of hallucinations and sleep paralysis.

3.7.1.2.7. Patient's Global Opinion on the effect of treatment

At V7 and all visits of open-label period, patients' global opinion will be reported by patient if able to express himself. If not, either their parents or their main teachers should evaluate the Global effect of the treatment by comparing the period prior to that visit with the patient's pre-study condition.

The following six-level scale will be used:

- Marked effect (complete or nearly complete remission of EDS)
- Moderate effect (partial remission of EDS)
- Minimal effect (slight decrease in EDS that does not substantially alter the status of the patient)
- No change
- Minimally worse (slight increase in EDS)
- Much worse (substantial increase in EDS)

3.7.1.3. Compliance

The compliance with study medication will be assessed by comparing the amount of medication remaining at each visit with the amount predicted to remain if the patient is compliant with the prescription.

3.7.2. Safety criteria

The safety criteria will include:

- Adverse and unexpected events, emergent or not, reported during the study course (frequency, severity, relationship to study drug, incidence and occurrence)
- Change of vital signs parameters (heart rate, blood pressure, body weight) from baseline values

- Physical examination: abnormalities in each system class and change from baseline
- ECG parameters: in particular, calculation of the QTcF value and comparison with the QTcF value of the ECG performed at baseline. If the QTcF is ≥ 500 ms or Δ between the QTcF on treatment and the QTcF at baseline is ≥ 60 ms, the treatment shall be discontinued and the corresponding ECG forwarded to Bioprojet.
- Laboratory abnormalities (e.g. AEs will be defined as laboratory test results that are outside the reference range as defined by the normal range for laboratory test and clinically signification).
- Occurrence of withdrawal symptoms (to be checked during the phone call at D59 ± 1 and at V8 end-of-study visit (D63).

3.7.2.1. Cardiovascular safety: vital signs and ECG

Vital signs including blood pressure, heart rate and body weight will be checked at the each visit.

ECG will be performed at each visit from the screening visit (V1) to the end of the double blind-phase (V8) or at early withdrawal visit and all visits of the open-label period. The main ECG parameters including calculation of Fridericia's corrected QTc interval ($QTcF = QT/\sqrt[3]{(60/HR)}$) and intra individual changes in these parameters will be reported and analyzed locally. If the QTcF value is ≥ 500 ms, or if the change from baseline is ≥ 60 ms, (observed on two consecutive occasions, i.e. after performing a recheck a few hours later) the treatment shall be discontinued and ECGs (baseline and abnormal ECG) shall be dispatched to Bioprojet.

All ECGs will be reviewed a posteriori by a central reviewer.

3.7.2.2. Physical examination

A full physical examination will be performed at screening period (V0 (when applicable) and V1) and at each visit from V2 to V8 (or at early withdrawal visit) and all visits of the open-label period. Any significant abnormality and change from baseline will be recorded in the CRF and in the source document and will be analyzed as safety parameters. Any significant changes will be reported in the AE pages of the CRF.

3.7.2.3. Adverse events and Treatment Emergent Adverse Events

The safety will be assessed by the occurrence of adverse events, spontaneously reported by the patient or discovered during investigator's interview at each visit.

All of them must be reported by the investigator in the special form placed at the end of the CRF, whatever the nature, the intensity, the severity and the supposed causality from the study

compound.

For each adverse event, the investigator shall report the nature, the anteriority (emergent or not), the date of apparition, the intensity, the severity and the action taken in regard to the study treatment, and the concomitant therapies.
When the event ends or at the end of the study, the investigator must report the evolution from the event and evaluate the relationship to the study compound.
The events will be categorized by System Organ Class and Preferred Terms (MedDRA) and type, severity and relationship to the treatment.
All Adverse Events and unexpected events, emergent or not, reported during the study course (frequency, severity, relationship to study drug, incidence and occurrence) will be analyzed.
Treatment Emergent Adverse Events (TEAE) defined as any event not present prior the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment, will be analyzed as **the main safety parameters**.

3.7.2.4. Blood Laboratory tests, urinalysis, urinary drug testing

A full laboratory test should be performed at screening (V1), at the final double-blind treatment phase evaluation visit (V7) and at early withdrawal visit and during the open-label period at V10, V13 and all subsequent visits. Blood samples will be collected and all laboratory tests will be performed according to the Good Laboratory Practice (OECD GLP Principles) by site-dependent Laboratory. The results of laboratory tests will be interpreted by the investigator. Laboratory abnormalities will be defined as laboratory test results that are outside the reference range as defined by the normal range from the testing laboratory. Clinically significant abnormal value at V1 will be determined by the investigator and will exclude patients from study participation. The results of abnormal values of laboratory tests will be reported in the CRF beside the normal range value given by the testing laboratory, the original document containing all the tested values will be kept in the patient study file.

Blood laboratory test parameters and intra individual changes in these parameters will be reported and analyzed in all patients.
- Hematology: Red Blood Cells, White Blood Cells (differential count, absolute value), hemoglobin, haematocrit, Mean corpuscular volume (MCV), platelet count.
- Biochemistry: sodium, potassium, chloride, creatinine, alkaline phosphatases, urea, alanineaminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma glutamyl

transpeptidase (GGT), total bilirubin, glucose, triglycerides, total cholesterol, quick time.

- Hormonology: βHCG (only for pubescent female).

- Urinalysis: semi-quantitative ("dipstick") analysis for pH, ketone bodies, proteins, glucose, blood. If any of these parameters gives a positive result, a quantitative analysis will be performed to characterize or count: crystals, casts, epithelial cells, white blood cells, red blood cells and bacteria if required by the investigator.

- Urine drug testing: test of abuse of drugs will be performed on urine samples from 12 years. Screened drugs are amphetamines, barbiturates, benzodiazepines, cannabinoids (THC) and Opioids.

3.7.2.5. Childhood Depression Inventory

The Childhood Depression Inventory scale is a self-administrated 27-item questionnaire commonly used in research to assess depression. The short version 2 of 12 items is used in the study (Appendix 4). The patient is asked to pick out the statement in each of the 12 items which best describes the way he feels right now at the moment of the assessment.

The range of scores for the scale are 0-4 = none or minimal; 4-7 = mild; 8-15 = moderate; ≥ 16 = severe depression.

The CDI questionnaire will be evaluated during double blind period at visits V1, V4, V6 and V8 and all subsequent visits for the open-label period**.** Patients presenting severe depression (CDI ≥ 16) should be immediately withdrawn from the study for security.

3.7.2.6. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be evaluated at all visits of the study.

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

The interview is semi-structured with a flexible format. Questions are provided as helpful tools – it is not required to ask any or all questions – just enough to get the appropriate answer.

Most important: gather enough clinical information to determine whether patient is suicidal or not. If it is established that a patient has not engaged in any suicidal behavior and/or ideation, then no further questions are required.

3.7.2.7. Withdrawal symptoms

A specific questionnaire provided 1 week after discontinuation of the study drug will investigate

the possible occurrence and pattern of amphetamine like withdrawal symptoms (DSM-IV) which are defined as dysphoria and two or more of the following symptoms: fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite and psychomotor retardation or agitation.

4. INVESTIGATIONAL TREATMENT

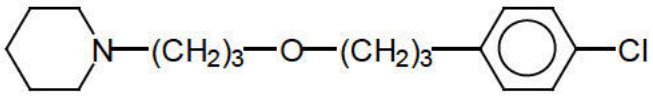
4.1. DESCRIPTION OF STUDY TREATMENT: BF 2.649

4.1.1. Chemical structure

BF2.649 (pitolisant) is 1-{3-[3-(4-chloro-phenyl)-propoxy]-propyl}-piperidinium, hydrochloride.

STRUCTURAL FORMULA

BF2.649



, HCl

MOLECULAR FORMULA

[redacted]

RELATIVE MOLECULAR MASS

[redacted]

4.1.2. Composition and form of investigational treatments

The investigational treatments (BF2.649 5 mg and placebo) are provided in film-coated tablets, white, round, of 3.7 mm diameter engraved "5" on one side. BF2.649 5 mg and placebo tablets **are identical in appearance** (form, dimension and color) to maintain the blind.

The investigational treatment (BF2.649 20 mg and placebo) are provided in film-coated tablets, white, round, of approximately 7,5 mm in diameter, engraved "20" on side. BF2.649 20 mg and placebo tablets **are identical in appearance** (form, dimension and color) to maintain the blind.

The ingredients of unitary BF2.649 tablets are described in the table below:

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Placebo tablets will contain only lactose to ensure that neither the patient nor the investigator nor members of the clinical staff know the identity of the study medication.

4.2. DOSAGE REGIMEN

Following the completion of inclusion procedures, patients will start **pitolisant (BF2.649) treatment with escalating doses scheme** as follows:

– V2 (D0):

- Week 1: BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg or placebo in the morning during 7 days.
- Week 2: BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg or placebo in the morning during 7 days.

– V3 (D14± 2):

- Week 3: according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg or placebo in the morning during 7 days, or
BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg or placebo in the morning during 7 days, or
BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg or placebo in the morning during 7 days.

- V4 (D21± 2):

- Week 4: according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg or placebo in the morning during 7 days, or
BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg or placebo in the morning during 7 days, or
BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg or placebo in the morning during 7 days, or
BF2.649 at 40 mg/day: 2 tablets of BF2.649 20 mg or placebo in the morning during 7 days.
Treatment dosage at 40mg/day not allowed for patient with a weight less than 40 kg.

- V5 (D28± 2): No increase of BF2.649 dosage will be authorized, but it will be possible to decrease the dose, if the tolerance requires it. From this visit onwards, no dose change will be allowed.

- Week 5 to week 8: according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg or placebo in the morning during 28 days, or
BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg or placebo in the morning during 28 days, or
BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg or placebo in the morning during 28 days, or
BF2.649 at 40 mg/day: 2 tablets of BF2.649 20 mg or placebo in the morning during 28 days.
Treatment dosage at 40mg/day not allowed for patient with a weight less than 40kg.

- V7 (D56± 2): Prescription of 1-week of placebo for all patients.

In open-label period patients will start pitolisant treatment with escalating doses scheme, as follows:

- V8 (D63 ± 2)

- Week 10: BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg in the morning during 7 days.
- Week 11: BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg in the morning during 7 days.

- V9 (D77± 2):

- Week 12: according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg in the morning during 7 days, or

BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg in the morning during 7 days, or
BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg in the morning during 7 days, or

– V10 (D84± 2):

- From Week 13: according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg in the morning during 28 days, or
BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg in the morning during 28 days, or
BF2.649 at 15 mg/day: 3 tablets of BF2.649 5 mg in the morning during 28 days, or
BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg in the morning during 28 days, or
BF2.649 at 30 mg/day: 2 tablets of BF2.649 5 mg and 1 tablet of BF2.649 20 mg in the morning during 28 days, or
BF2.649 at 40 mg/day: 2 tablets of BF2.649 20 mg or placebo in the morning during 28 days.
Treatment dosage at 40mg/day not allowed for patient with a weight less than 40 kg.

At D91 during the phone contact the dose will be reduce in case of poor tolerance, when applicable.

– V11 (D112± 2):

According to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg in the morning during 3-month, or
BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg in the morning during 3-month, or
BF2.649 at 15 mg/day: 3 tablets of BF2.649 5 mg in the morning during 3-month, or
BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg in the morning during 3-month, or
BF2.649 at 30 mg/day: 2 tablets of BF2.649 5 mg and 1 tablet of BF2.649 20 mg in the morning during 3-month, or
BF2.649 at 40 mg/day: 2 tablets of BF2.649 20 mg or placebo in the morning during 3-month.
Treatment dosage at 40mg/day not allowed for patient with a weight less than 40 kg.

– V12 (D196± 2):

According to the investigator's prescription patients for whom the optimal dose level is

estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product.

BF2.649 at 5 mg/day: 1 tablet of BF2.649 5 mg in the morning during 6-month, or

BF2.649 at 10 mg/day: 2 tablets of BF2.649 5 mg in the morning during 6-month, or

BF2.649 at 15 mg/day: 3 tablets of BF2.649 5 mg in the morning during 6-month, or

BF2.649 at 20 mg/day: 1 tablet of BF2.649 20 mg in the morning during 6-month, or

BF2.649 at 30 mg/day: 2 tablets of BF2.649 5 mg and 1 tablet of BF2.649 20 mg in the morning during 6-month, or

BF2.649 at 40 mg/day: 2 tablets of BF2.649 20 mg or placebo in the morning during 6-month.

Treatment dosage at 40mg/day not allowed for patient with a weight less than 40 kg.

- All subsequent visits, the treatment dispensation will be done as V12.

4.3. PACKAGING AND LABELLING OF TREATMENT

The medications will be supplied, packaged and labelled in compliance with the Good Manufacturing Practices (GMP) appendix 13 of drugs and ICH of used in clinical trial.

Each label will be labelled in the local language of the investigational centre.

Each treatment unit will contain the study medication for all the duration of the study, i.e. 9 weeks.

4.4. MANAGEMENT AND STORAGE OF THERAPEUTIC UNITS

Storage conditions:

The investigational treatments do not require any special storage conditions.

Management of therapeutic units:

The therapeutic units will be provided to each investigational site. Bioprojet will provide the pharmacist or investigator with all necessary documents on BF2.649 information, in accordance with the Good Clinic Practice (GCP) (ICH topic E6 and local regulations). The hospital pharmacist (or investigator) will be responsible for the correct storage and handling of the study products (reception, storage, dispensation log, update of the delivery list, return of empty packaging and unused units and return of therapeutic units to the sponsor).

As soon as treatment units are received on site, the pharmacist or investigator will return the

enclosed acknowledgement of receipt sheet to Bioprojet representative, filled and signed.

Treatments under the Pharmacist's or investigator's responsibility have to be stored in a secure limited access area in accordance with required storage conditions, and disclosed only to authorized persons having access to this storage room.

In accordance with GCP regulations (ICH topic E6 and local regulations) all study materials (unused treatment units, packaging as well as individual code envelopes) have to be returned by the pharmacy to Bioprojet supplier at the end of the study, the attestation of return will indicate for each patient:

- Date of treatment reception and quantity,
- Number of administered and unused therapeutic units,
- Number of undelivered units,
- Number of therapeutic units finally returned and dispatch date.

In case of a therapeutic unit loss, the investigator or the hospital's Pharmacist in charge of the treatment management will have to justify this loss in a written statement, signed and dated, enclosed with the attestation of return.
The unused therapeutic units will be retrieved by the supplier at the end of the study (i.e. after final study report signature) and after reconciliation of dispensation log of therapeutic units.

4.5. TREATMENT DISPENSATION

4.5.1. Patient Study Number

The investigational treatment will be assigned to each patient after the completion of the inclusion visit (V2) and verification of all inclusion and exclusion criteria. A study number will be assigned to the patient by following the sequential number of the study site. The number is composed by the site number on 2 digits, followed by a sequential number on 2 digits starting by 01, e.g. first patient included by site number 01 will be 0101, and the second patient will be 0102. The study number will be assigned chronologically and in the sequential order without skipping any number.

A tracking list of the number allocated with the identification of patients i.e. the first letter of first name and of family name of patients will be filled by the investigator and kept in his study records.

4.5.2. Investigational treatment allocation

When the patient receives his/her study number, the corresponding investigational treatment identified by the treatment number will be allocated to the patient according to the randomization list established by an independent company and managed by Interactive Web Response Services (**IWRS**) according to randomization.

4.5.3. Procedure to open the individual randomization code in emergency

The double blind design of the study will result in the ignorance of the assigned treatment to the patients. In the situation where the knowledge of the treatment appears imperative and urgent, a procedure to open the code for the individual patient exists. A set of sealed envelopes, identified by the study number, will contain the type of treatment assigned to the corresponding patient. These envelopes must be only opened in cases where there is an imperative need to know the assign treatment to protect the patient health and well-being such as voluntary or not overdosing. The code break will be documented on the envelope and in the patient's CRF, with date and time and reasons of disclosure and signed by investigator. All envelopes will be tracked by the sponsor at the completion of the study.

4.6. TREATMENT COMPLIANCE AND ACCOUNTABILITY PROCEDURES

The study treatment will be dispensed only under the restricted condition defined in the present protocol. The treatment will be dispensed only by the investigator under his direct supervision or the pharmacist. Time of dispensation and initials of the person dispensing the drug will be recorded in the CRF. The tear-off label of each pack will be stuck on the prescription form.
At each visit the compliance to the treatment will be investigated. Details of the quantities of each medication dispensed will be entered into the accountability form. The patients will be asked whether the investigational treatment is taken as prescribed. If not, any change in the treatment and the number of forgotten tablets will be recorded in the case report form (CRF). In addition, the number of remaining tablets in the pill-box will be counted and compared to the theoretical number. Any mismatch will be investigated with the patient.

5. CONDUCT OF THE STUDY

5.1. EXPECTED DURATION OF SUBJECT PARTICIPATION

The expected duration of patient participation from the screening visit (V0) until the final visit

(V8) will be 13 weeks:

Baseline period without investigational treatments (from V0 to V2): 4 weeks.

- Low and medium dose titration phase (from V2 to V3): 2 weeks
- Individual dose adjustments (from V3 to V5): 2 weeks
- Stable dose phase (from V5 to V7): 4 weeks
- 1-week study drug wash out (placebo) after study drug discontinuation

During the double blind phase, the patient will be followed in an ambulatory way by 9 visits on the site.

The double blind phase will be followed by a prolonged open-label period if patient wishes, until BF2.649 (pitolisant) is available on the marketfor children/adolescent from 6 to 17 years included or as soon as the patient becomes older than 18 years. Then, he will have access to the treatment already on the market for adults.

The first inclusion of this study is scheduled in Q1 2016. The end of the double-blind phase is expected by Q1 2022.

5.2. STUDY PROCEDURES AT EACH VISIT

All visits should be done in the morning at the same time to ensure identical evaluation conditions along the study, if possible.

5.2.1. V0-screening visit and start of wash-out period: at D-28

Visit V0 is applying only for patients under prohibited medications and for cataplectic patients under anti-cataplectic treatment.

The investigator will provide the patient with the necessary information regarding the study objectives, the investigational product pitolisant (BF2.649), the expected benefit, the potential risks and the study procedures.

Then, the signed informed consent will be obtained prior to the study entry and before any study procedure for patient willing to participate.

Both parents and the patient, if old enough to understand, will sign the inform consent form after carefully read and signed the patient information sheet about the investigational medical product and the study requirements.

Prohibited treatments will be discontinued at V0 and duration of authorized treatments will be checked.

Patients with cataplexy treated by sodium oxybate shall continue this treatment at stable dose during four (4) weeks prior to inclusion and throughout the study. The same applies to all other purported anticataplectic treatments, if any.

The patient will undergo the following tests and procedures:

-A complete medical examination (including age, gender), detailed questionnaires on his/her medical history and narcolepsy history will be recorded.

- A complete physical examination including height (cm), weight (kg) and BMI kg/m².

-Vital signs including: blood pressure (SBP and DBP) and heart rate.

-Questioning on previous and concomitant medication used and possible occurrence of adverse events.

-Delivery of two sleep diaries (one per week) which has to be daily completed by the patient (if old enough to understand) and/or parents every evening. (Hour of bedtime in the evening, wake-time in the morning. Number of diurnal involuntary sleep attacks and episodes of severe daytime sleepiness. Occurrence and number of cataplexy attacks (total or partial). Number of hallucinations and sleep paralysis).

5.2.2. V1-screening visit and Baseline period: at D-14

If no V0 visit is required, the investigator will provide the patient with the necessary information regarding the study objectives, the investigational product pitolisant (BF2.649), the expected benefit, the potential risks and the study procedures.

Then, the signed informed consent will be obtained prior to the study entry and before any study procedure for patient willing to participate.

Both parents and the patient, if old enough to understand, will sign the inform consent form after carefully read and signed the patient information sheet about the investigational medical product and the study requirements.

The patient will undergo the following tests and procedures: *All tests performed at V0 will be not repeated at V1.*

A complete medical examination (including age, gender), detailed questionnaires on his/her medical history and narcolepsy history will be recorded.

The history of a substance abuse including alcohol dependence and other psychiatric/neurological disorders should be ruled out.

Narcolepsy diagnosis history including the patient actual symptoms of narcolepsy (nature, severity, and duration), and documentation of the previously performed examinations about illness such as: polysomnography, MSLT (to be performed if not available during the year prior to inclusion),

Complete physical examination (including height and body weight),
Questioning on previous and concomitant medication used (including any current and previous treatments of EDS and cataplexy and any other types of treatment), and possible occurrence of adverse events,

The patient will undergo the following tests and procedures:
Vital signs (blood pressure, heart rate),
A complete physical examination including height (cm), weight (kg) and BMI kg/m².
12-lead ECG recording with calculation and control of QTcF,
A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),
A urine drug testing (for patients from 12 years),

The following questionnaires should be performed:
- Pediatric Daytime Sleepiness Scale (PDSS),
- Child and Adolescent Sleepiness Scale (CASS)
- Ullanlinna narcolepsy scale (UNS),
- Test of Everyday Attention for Children (TEA-Ch),
- Clinical Global Impression of Severity (CGI-S) on EDS and on cataplexy,
- Childhood Depression Inventory (CDI),
- Columbia-Suicide Severity Rating Scale (C-SSRS),
- Retrieval of the first sleep diary (when applicable) and check by the investigator. Delivery of a new sleep diary which has to be daily completed by the patient (if old enough to understand) and/or parents every evening. (Hour of bedtime in the evening, wake-time in the morning. Number of diurnal involuntary sleep attacks and episodes of severe daytime sleepiness. Occurrence and number of cataplexy attacks (total or partial). Number of hallucinations and sleep paralysis).

Patients who meet all inclusion criteria and none of the non-inclusion criteria will be allowed to participate in the study.

- The HLA typing for DQB1*06:02 will be asked if not known in advance and recorded if available.
- The value of the CSF hypocretin-1 (measured with standardized RIA) will be stored in the CRF if it is known. (This helps to analyze the results separately for type 1 and type 2 narcolepsy according to the new ICSD-3 classification).

5.2.3. V2- Randomization and start of escalating period: at D0

This visit should be **imperatively** done in the morning (around **9.30 a.m.**) and all further visits should be done at the same time of day, if possible, to ensure identical evaluation conditions along the study.

Patients will be required to have sufficient nocturnal sleep (minimum 6 hours) and not drink alcohol during the night prior to this visit. The patient will be required to take a light breakfast before 8.00 a.m. and arrive at the trial center around 9.00 a.m. They should refrain from drinking any stimulatory beverage such as coffee, tea or Coca-Cola this morning until the end of this visit.

The first session of MWT will approximately start at 10.00 a.m.

A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,

A physical examination including vital signs shall be carried out.

12-lead ECG recording with calculation and control of QTcF,

Polysomnography with Multiple Sleep Latency Test will be performed the day preceding V2, if this exam was not performed during the previous year,

The following questionnaires should be performed:

- PDSS,
- CASS,
- UNS,
- CGI-S on EDS and on cataplexy,
- C-SSRS,
- Retrieval of the 2 first sleep diaries (when applicable) and check by the investigator. Delivery of two other sleep diaries which have to be completed every day throughout the baseline period,

Patients who meet all inclusion criteria and none of the non-inclusion criteria will be allowed to participate in the study.

Treatment dispensation for the next two weeks:

- First week with 5mg/day of pitolisant or placebo in the morning, before breakfast,
- Second week with a 10mg/day of pitolisant or placebo in the morning before breakfast.

Investigator will remind patient to bring back the investigational treatment packs at the next visit.

5.2.4. V3 – Dose adjustment visit (Day 14 ± 2 days)

A complete interrogation including occurred of possible adverse events and concomitant

medication used will be done and recorded,

A physical examination including vital signs shall be carried out,

12-lead ECG recording with calculation and control of QTcF,

The following questionnaires should be performed:

- PDSS,
- CASS,
- C-SSRS,
- Retrieval of sleep diary of the previous visit and check by the investigator. Delivery of one other sleep diary which have to be completed every evening until the next visit,

Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product. Dose allocation: either 5, 10 or 20 mg/day or placebo in the morning during 7 days.

The treatment pack bring back from previous visit by patient is checked by investigator for the compliance. Investigator will remind patient to bring back the investigational treatment packs at the next visit.

5.2.5. V4 – Dose adjustment visit (Day 21 ± 2 days)

A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,

A physical examination including vital signs shall be carried out,

12-lead ECG recording with calculation and control of QTcF,

The following questionnaires should be performed:

- PDSS,
- CASS,
- CDI,
- C-SSRS,
- Retrieval of sleep diary of the previous visit and check by the investigator. Delivery of one other sleep diary which have to be completed every evening until the next visit.

Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and

with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product. Dose allocation: either 5, 10, 20 or 40 mg/day or placebo in the morning during 7 days. Patients with a weight less than 40kg could be treated with a maximum daily dose up to 20 mg.

The treatment pack bring back from previous visit by patient is checked by investigator for the compliance. Investigator will remind patient to bring back the investigational treatment packs at the next visit.

5.2.6. V5 – Dose adjustment visit (Day 28 ± 2 days)

A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,

A physical examination including vital signs shall be carried out,

12-lead ECG recording with calculation and control of QTcF,

- The following questionnaires should be performed:
- PDSS,
- CASS,
- C-SSRS,
- Retrieval of sleep diary of the previous visit and check by the investigator. Delivery of one other sleep diary which have to be completed every evening until the next visit,

Investigational treatment allocation: No increase of pitolisant dosage will be authorized, the dose of pitolisant will be individually adjusted according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or the level dose will be reduced based on the tolerance to the product. Dose allocation: either 5, 10, 20 or 40 mg/day or placebo in the morning during 28 days.

The treatment pack bring back from previous visit by patient is checked by investigator for the compliance. Investigator will remind patient to bring back the investigational treatment packs at the next visit.

5.2.7. V6 – Control treatment visit (Day 49 ± 2 days)

A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,

A physical examination including vital signs shall be carried out,

12-lead ECG recording with calculation and control of QTcF,

The following questionnaires should be performed:

- PDSS,

- CASS,
- CDI,
- C-SSRS,
- UNS,
- TEA-Ch,
- Clinical Global Impression of Change (CGI-C) on EDS and on cataplexy,
- Retrieval of sleep diary of the previous visit and check by the investigator. Delivery of one other sleep diary which have to be completed every evening until the next visit.

No dispensation performed at V6.

5.2.8. V7 – End of Double Blind period (Day 56 ± 2 days)

This visit should be **imperatively** done in the morning (around **9.30 a.m.**) and all further visits should be done at the same time of day, if possible, to ensure identical evaluation conditions along the study.

Patients will be required to have sufficient nocturnal sleep (minimum 6 hours) and not drink alcohol during the night prior to this visit. An optional polysomnography can be done in accordance with the processes of sites, the evening preceding the MWT test to confirm a sufficient nocturnal sleep. The patient will be required to take a light breakfast before 8.00 a.m. and arrive at the trial center around 9.00 a.m. They should refrain from drinking any stimulatory beverage such as coffee, tea or Coca-Cola this morning until the end of this visit.
The first session of MWT will approximately start at 10.00 a.m.

A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,
A physical examination including vital signs shall be carried out,
12-lead ECG recording with calculation and control of QTcF,
A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),
A urine drug testing (for patients from 12 years),
The following questionnaires should be performed:

- PDSS,
- CASS,
- C-SSRS,
- UNS,
- CGI-C on EDS and on cataplexy,

- Retrieval of sleep diary of the previous visit and check by the investigator. Delivery of one other sleep diary which have to be completed every evening until the next visit,
-Patient's Global Opinion on the effect of investigational treatment if able to express himself. If not will be reported either by parents or teachers.

Investigational treatment allocation: start 1-week wash-out period.
The treatment pack bring back from previous visit by patient is checked by investigator for the compliance.

5.2.9. T1 – Telephone contact (Day 59± 1 day)

This phone call between patients (or their parents) and the investigator (or his/her deputy) will allow to record all adverse events having occurred since the latest visit (AE recorded at visit V8), and to fill in the withdrawal symptoms questionnaire and ascertain that the treatment discontinuation is well tolerated.

5.2.10. V8 – End of study visit or Start of Open-Label after 1 week of placebo wash out (Day 63 ± 2 days) / Premature withdrawal visit (Double blind phase)

The premature withdrawal patients from the study should be followed by a visit performed within a maximum of 5 days after the last dose of study drug.
A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,
A physical examination including vital signs shall be carried out,
12-lead ECG recording with calculation and control of QTcF,
A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick), (only for premature withdrawal patient),
The following questionnaires should be performed:
- PDSS,
- CASS,
- CDI,
- C-SSRS,
- Ullanlinna narcolepsy scale, (only for premature withdrawal patient),
- CGI-C on EDS and on cataplexy,
- Patient's Global Opinion on the effect of investigational treatment if able to express himself. If not will be reported either by parents or teachers, (only for premature withdrawal patient),
- Retrieval of sleep diary and check by the investigator,

-Withdrawal symptoms questionnaires.

The treatment pack bring back from previous visit by patient is checked by investigator for the compliance.

Patients willing to continue the study in the prolonged open label period will receive a new pack of investigational treatment and will start an escalating dose treatment. Week 1 at 5 mg/day then week 2 at 10 mg/day. Those patients will receive one sleep diary which have to be filled out daily during the 7 days prior to the next visit. Patients not willing to continue in the study will be followed under usual practice.

When a patient has already performed the visit V8, the follow up control visits will be scheduled and an end of study visit should be planned as soon as the BF2.649 (pitolisant) is commercialized in children from 6 to 17 years included or as soon as the patient reaches 18 years and it has at its disposal the commercialized treatment in adult.

5.2.11. V9- Dose adjustment visit (Day 77± 2 days)

A complete interrogation including occurred of possible adverse events and concomitant medication used will be done and recorded,

A physical examination including vital signs shall be carried out,

12-lead ECG recording with calculation and control of QTcF,

The following questionnaires should be performed:

- PDSS,
- CGI-C on EDS and on cataplexy,
- CDI,
- C-SSRS,
- Patient's Global Opinion on the effect of investigational treatment if able to express himself. If not will be reported either by parents or teachers,
- Retrieval of sleep diary. (Sleep diary will be filled out daily during the 7 days prior to the next visit) and delivery of one other.

Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the investigator's prescription patients for whom the optimal dose level is estimated will continue at the same dose or if not sufficiently improved in their symptoms, and with a good tolerance, will increase to a higher dose or the level dose will be reduced based on the tolerance to the product. Dose allocation: either 5, 10, 20 or placebo in the morning during 7 days.

The treatment pack bring back from previous visit by patient is checked by investigator for the compliance. Investigator will remind patient to bring back the investigational treatment packs at the next visit.

5.2.12. T2- Telephone contact at D98 (± 1 day)

This phone call between patients (or their parents) and the investigator (or his/her deputy) will allow to record all adverse events having occurred since the latest visit (AE recorded at visit V10).

The investigator should assess the efficacy and tolerance and the dose of treatment should be adjusted accordingly, when applicable.

In opinion of investigator, the dose could be re-adjusted according the effectiveness/tolerability of treatment to patient.

In case of need, it is to plan a visit on site within the week following phone contact for obtaining new bottles of treatment with the corresponding dose.

The other doses decrease, from 40 to 20 and 10 to 5 mg, in agreement with investigator don't need a visit. The bottles contain a suitable number of tablets to decrease the dose.

5.2.13. V10- Dose adjustment visit (Day 84± 2 days)

Idem to the visit V9.

Investigational treatment allocation: the dose of pitolisant will be individually adjusted according to the investigator's prescription.

A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),

Dose allocation: either 5, 10, 15, 20, 30 or 40 mg/day or placebo in the morning during 28 days.

Patients with a weight less than 40 kg could be treated with a maximum daily dose up to 20 mg.

5.2.14. V11- Dose adjustment visit (Day 112± 7 days)

Idem to the visit V9.

Dose allocation: either 5, 10, 15, 20, 30 or 40 mg/day or placebo in the morning during 3-month.

Patients with a weight less than 40 kg could be treated with a maximum daily dose up to 20 mg.

5.2.15. V12- Dose adjustment visit (Day 196± 7 days)

Idem to the visit V11.

Dose allocation: either 5, 10, 15, 20, 30 or 40 mg/day or placebo in the morning during 6-month.

Patients with a weight less than 40 kg could be treated with a maximum daily dose up to 20 mg.

5.2.16. V13- Dose adjustment visit (Day 364± 7 days)

Idem to the visit V12.

A blood sample will be taken for routine haematological and biochemical test (including β-HCG pregnancy test for pubescent female) and semi-quantitative urinalysis (dipstick),

Dose allocation: either 5, 10, 15, 20, 30 or 40 mg/day or placebo in the morning during 6-month.

Patients with a weight less than 40 kg could be treated with a maximum daily dose up to 20 mg.

All subsequent visits are performed each 6 months as V13.

The investigator should instruct each patient to report any subsequent event(s) that the patient or his personal physician believes might reasonably be related to participation of this study.

In case of occurrence of adverse event or in case of unresolved adverse event, the investigator should schedule an additional follow-up in order to follow any adverse events until they are resolved. Thereafter, the patient will be discharged from the study.

5.2.17. Early withdrawal visit (Open label phase)

The premature withdrawal patients from the study should be followed by a visit performed within a maximum of 5 days after the last dose of study drug.

Tests and exams are applied as V13 with no dispensation.

Patients will be followed under usual practice after their study discontinuation.

5.2.18. Phone visits during the COVID-19 pandemic

During the COVID-19 pandemic, while patients are unable to attend any visit in the investigative sites and to limit the risk for the patient to spread/acquire the infection, special measures are put in place to maintain the participants in the study. During that period and until return to normal situation at sites, study visits at can be replaced by phone visits.

The investigator should assess during these calls the efficacy and tolerance and the dose of treatment should be adjusted accordingly, when applicable.

Direct shipment of study treatment from the site, or hospital pharmacy, to the patient's home is allowed via a courier with the full documentation of shipment and receipt by the patient/parents.

Patients will return all medication at his/her subsequent site visit. Diaries to be documented daily are sent to the patient with the study treatment.

5.3. PATIENT WITHDRAWAL CRITERIA

5.3.1. Criteria to withdraw subject from the trial treatment

In accordance with the Declaration of Helsinki, patients will be free to withdraw from the study at any time if they wish to do so, for any reason specified or unspecified.

Before the final scheduled study visit the investigator have the responsibility and the right to interrupt the patient participation. Out of emergency cases (listed below), the investigator will have to contact the sponsor or his representative before the application of his decision.

- Voluntary withdrawal of patient consent, or loss to follow-up, or inability to remain under medical observation
- Severe depression indicated by Childhood Depression Inventory (CDI ≥ 16) or suicidal risk with a positive Columbia-Suicide Severity Rating Scale (C-SSRS).
- Non-compliance or major deviation from the protocol
- Appearance of a Serious Adverse Event (SAE) or any other situation where, in the opinion of the investigator, continuation of the study would not be in the interest of the subject.

Should any of the patients be withdrawn from the study, the reason for withdrawal has to be recorded in the CRF for all withdrawn patients.

5.3.2. Type and timing of data to be collected from withdrawn patients

When a patient is prematurely withdrawn from the study before the *"End of study visit" V8*, the investigator has to perform a complete visit, within a maximum of 5 days after the last dose of study drug. This will also apply for open label phase.

5.3.3. The follow -up for withdrawn patients

The investigator should make every effort to contact the prematurely withdrawn patient and to identify the reason why he fails to attend the visit and to determinate his health status. In case of adverse event no recovered at the time of study withdrawal, the investigator will have to plan a follow-up visit in order to complete the adverse events evolution.

5.4. STUDY DISCONTINUATION CRITERIA

5.4.1. Criteria for terminating the trial

Bioprojet reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons, and reasons related to protection of patients. In all cases the Ethics Committee (IRB/IEC) and Health Authorities should be informed.

Possible reason for the study termination can include but are not limited to:

- The discovery of an unexpected, significant or unacceptable risk to patients enrolled in the study
- A decision on the part of Bioprojet to suspend or discontinue the development of the investigational product
- Request of the relevant regulatory agency

If the study is prematurely discontinued, enrolled patients should be called for an "end of study" visit"

5.4.2. Criteria for terminating site

Bioprojet reserves the right to terminate the study at a given centre at any time after the study initiation if:

- ICH GCP regulations are not observed
- The protocol is violated without justification
- The data generated are of poor quality
- Changes in personnel or facilities adversely affect performance of the study (e.g. low rate of inclusion).

6. SAFETY ASSESSMENT AND REPORTING

6.1. DESCRIPTION OF SAFETY PARAMETERS

6.1.1. Vital signs

Vital signs including systolic and diastolic blood pressures, heart rate and body weight will be measured at each visit. Measurements will be recorded in the CRF.

6.1.2. Physical examination

A complete physical examination (including the height at screening only) will be performed at screening visit (V1, or V0 when applicable) and at each visit for the purpose to observe the child's overall appearance, general health, and behavior. The examination includes cardiovascular, respiratory, abdominal, neurological, locomotive and dermatologic systems. Any significant abnormalities should be recorded in the CRF.

6.1.3. Electrocardiogram (ECG)

ECG will be performed at the screening visit (V1), at each subsequent visit from V2 to V8 for the double blind phase, and all visits of the open-label period, using the internationally recognized 12-lead ECG recording which includes date, time, initials of the technician/nurse, initials of the investigator or its deputy, at least 2 complexes for each lead and a single lead run. The corresponding source data will consist of the Cardiograph paper print-outs that should be kept in the file and a copy provided to Bioprojet. Main ECG parameters including heart rate, sinusal rhythm PR, QRS, and Fridericia's corrected QTc interval ($QTcF = QT/\sqrt[3]{(60/HR)}$) QTc interval will be analyzed and should be recorded.
All ECGs will be reviewed a posteriori by a central reviewer.

6.1.4. Blood Laboratory tests and Urinalysis

A full laboratory test should be performed at screening visit (V1), at the end of the double blind treatment (V7 or at early withdrawal visit), and at during open-label period at V10, V13, then every 6-month. All laboratory tests will be performed according to the Good Laboratory Practice by site-dependent Laboratory and tests data should be analyzed, reported and duly signed by its responsible. The results of laboratory tests as paper print outs should be reviewed and assessed (dated and signed) by the investigator at the next visit and reported in the specific form of the CRF.

The following blood parameters should be evaluated:

- **Hematology:** Red Blood Cell Count, White Blood Cell Count including differential (absolute value), Hemoglobin, Haematocrit, Mean corpuscular volume (MCV), Platelet Count (Absolute).
- **Biochemistry Tests (Serum/plasma):** Sodium (Na), Potassium (K), Chloride (Cl), Creatinine, Alkaline phosphatases, Urea, Alanine aminotransferase (ALAT), Aspartate aminotransferase (ASAT), Gamma-glutamyltranspeptidase (GGT), Total Bilirubin, Blood glucose, triglycerides, total cholesterol, Quick Time.
- **β-hCG serum Pregnancy Test** should be performed in all pubescent female patients with child-bearing potential. The absence of pregnancy should be confirmed before entering the study.

All laboratory test results will be coded by using the 3 points scale as following:

- 0 = within the normal limits
- 1 = anomaly but no clinical significant
- 2 = anomaly clinically significant

Results of the clinical laboratory tests performed at screening will be included in the subject's CRF and considered as baseline values before the product administration.

In addition a semi-quantitative ("dipstick") analysis for pH, ketone bodies, proteins, glucose and blood should be evaluated. If any of these parameters gives a positive result, a quantitative analysis will be performed to characterize or count: crystals, casts, epithelial cells, white blood cells, red blood cells and bacteria if required by the investigator.

Follow-up of laboratory test abnormalities

The best interest of the subjects will always come before that of the trial. Abnormalities of any laboratory tests considered to represent a significant danger to the subject will lead to immediate discontinuation of the drug and the study monitor and Sponsor must be informed immediately.

In the event of abnormalities considered not to represent a danger, continuation of the drug will be allowed after discussion with the study monitor. These subjects will be followed up with appropriate medical management until they return to normal or baseline values or clinical diagnostics of undercurrent illness is confirmed. The results of all known laboratory tests required by the protocol will be held / recorded in the subject's CRFs. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator and the study monitor.

6.1.5. Adverse Events

6.1.5.1. Definitions

- Period of observation

For the purpose of this study, the period of observation extends from the time the patient gives informed consent (Visit 0) until one month after the last drug administration and until resolution of ongoing drug related adverse event. Any adverse events observed by the investigator or reported by the patient during the period of observation must be documented in the CRF.

- Adverse event

The term **Adverse Event** covers any sign, symptom, syndrome, or illness which appears or

worsens in a patient during the observation period in the clinical study, and which may impair the patient's well-being.

The term also covers laboratory findings or results of other diagnostic procedures which are considered to be clinically relevant (e.g., requiring unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

An adverse event may be:
A new illness;
The worsening of a sign or symptom of the condition under treatment, or of a concomitant illness;
An effect of the study medication;
A combination of two or more of these factors.
No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "Adverse Event."

- ***Exemption conditions***

In this study in narcoleptic patients, symptoms like hallucinations, sleep attacks and sudden onset of sleep should be considered as symptoms of the underlying condition and not as adverse event, and should only be reported as Adverse Event in case of worsening or unusual form.

- Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event is defined as any event not present prior to the initiation of the study treatments, or any event already present which worsens either in intensity, or frequency following the exposure to the study treatment.

- Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered as an Adverse Drug Reaction. The responses to a medicinal product means that a causal relationship between a medicinal product and an Adverse Event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. The causal relationship should be assessed as defined below §7.2.5.3 (assessment of causality).

- Unexpected Adverse Drug Reaction

An Adverse Reaction, the nature or severity of which is not consistent with the applicable

product information (e.g. Investigator Brochure).

- Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

A Serious Adverse Event is one that at any dose:

- Results in death;
- Is life-threatening[1];
- Requires patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity[2];
- Is a congenital anomaly/birth defect;
- Is medically important[3].

1 "Life-threatening" means that the patient was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

2 "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

3 Medical and scientific judgment should be exercised in deciding whether other adverse events may be considered serious because they jeopardize the patient, or may require intervention to prevent one of the other outcomes listed in the definition above. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List) should be used as guidance for adverse events that may be considered serious because they are medically important.

Cases involving cancer as an Adverse Event should be reported as "serious" using the criterion "medically important" if no other serious criterion is met.

Cases of overdose with an adverse event that meets one of the criteria given above should of course be reported as "serious". There is no antidote; in case of overdose, the patient has to be hospitalized in order to control his/her vital functions.

A serious adverse drug reaction is a serious adverse event which is related to the medicinal product whatever the dose.

- ***Clarification of the difference in meaning between "severe" and "serious"***

The terms "severe" and "serious" are not synonymous:

- **"severe"** is used to **describe the intensity** (severity) of a specific event, which could be rated ***mild, moderate or severe***. The event itself, however, may be of relatively

minor medical significance (such as severe headache).

- **"serious"** is **based on patient/event outcome** or action criteria usually associated with events that pose a threat to a patient's life or functioning. "Seriousness" (not severity) serves as a guide for defining regulatory reporting obligations.

6.1.5.2. Monitoring and recording of adverse events

The tolerance will be assessed by the occurrence of adverse and unexpected events, spontaneously reported by the patient or discovered during investigator's interview. The investigator or a designed member of his/her staff will probe each patient on any adverse experiences which may have occurred. The investigator should always ask the same question when conducting the verbal probe in order to ensure uniformity between patients. The investigator should ask:

- How are you doing (feeling)?

Based on the patient's response to this question, the investigator should ask additional questions relevant to the specific compliant such as:

- How severe is/was the symptom?
- How often did the symptom occur?
- How long did the symptom last?

For each unexpected or adverse effect, regardless the suspected causal relationship to study drug, the investigator have to report on the Adverse Event page(s) of the CRF the relevant information of AE including the nature, the anteriority (emergent or not), the timing of event occurrence and resolution, the frequency (intermittent or continuous), the severity, the seriousness (serious/non-serious), the relationship with the study compound, and actions taken to counteract the adverse experience. The investigator has also to pursue and obtain adequate information in order to determine the outcome of the adverse event and also to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the sponsor (see below). Follow-up of AEs is required until the event or its after-effects will be resolved or stabilized at an acceptable level with respect to the investigator opinion, even after the date of therapy discontinuation

6.1.5.3. Analysis of adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activity (MedDRA current version).

Adverse events will be individually listed per subject number, presenting System Organ Class

(SOC), preferred term, emergence, description, date and time of onset, date and time of last study drug administration before adverse event, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, the required action taken (corrective treatment, hospitalization….) required, and outcome if any.
It consists in the evaluation of the number of adverse events and in the number of subjects reporting these adverse events.

- **Treatment Emergent Adverse Events (TEAE)**

Adverse events will be classified into pre-defined standard categories according to chronological criteria:
- **Treatment Emergent AEs (TEAE):** AEs that occurred for the first time, or if present before that worsened **during the exposure to the study drug(**s).
- **Non-Treatment Emergent AEs (NTEAE):** AEs that occurred before the study drug administration.

- **Assessment of Intensity**

An assessment of the relative intensity of an adverse experience is based on the investigator's clinical judgment by using the following scale. The **maximum** intensity encountered during the evaluation period should be checked.

The assessment of intensity should be independent of the assessment of the seriousness of the AE.

- **Mild:** No significant interference with the subject's usual activities: acceptable, disappeared without residual effect
- **Moderate:** moderate interference with study the subject's usual activities.
- **Severe:** major interference with study the subject's usual activities, considered as unacceptable by the physician or required specific treatment or required discontinuation from the study.

- **Assessment of Causality**

The investigator will make judgment considering whether or not, in his opinion, the AEs are related to the study drug according to the following causal relationship assessment of suspected adverse reactions:

- **Related / likely:** Clearly related to the investigational agent / procedure, i.e. an event that follows a reasonable temporal sequence from administration of the

study intervention, follows a known or expected response pattern to the suspected intervention, that is can be confirmed by improvement on stopping and reappearance of the event after rechallenge and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- **Possibly related / Possible:** Follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- **Not related / Unlikely:** Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible (possibly related) or likely (related).

- **AE outcome**

All adverse Event outcomes should be documented at the last visit at the latest according to the following criteria:

– Ongoing *
– Resolved
– Unknown
– Recovered with sequelae **
– Recovered without sequelae
– Death related to adverse reaction
– Death not related to adverse reaction

* If an adverse event is still *ongoing* at the last visit the patient must be follow-up until the outcome can be documented without using the "ongoing" assessment.
** A description of sequelae must be provided in the CRF

6.1.5.4. Reporting Serious Adverse Event or Serious Adverse Drug Reaction

All serious adverse events (SAE) or Serious Adverse Drug Reaction (SADR), whatever the dose, the therapeutic or diagnostic reason, have to be reported **immediately (within 24 hours),** by any means to the Sponsor's defined representative:

Pharmacovigilance Responsable contact:

[redacted]

✉ Bioprojet 9, rue Rameau, 75002 PARIS, France

The investigator must inform the site monitor.

In case of SAE the investigator must complete the specific form "Serious Adverse Event" and send it within 48 hours to Bioprojet and the duplicated SAE form dully completed and signed to the monitor. After the initial report, the SAE should be promptly followed by a detailed writing report including all data allowing to document the event and notably the anonymous copies (subject identification code: treatment number and initials) from hospitalization's report and additional performed examination(s). The list of the pertinent documents deemed necessary to assess the gravity and the potential relationship is given at the end of the case report form. The investigator should also report to the monitor all elements concerning the follow-up of the serious adverse event.

For reported death, the investigators should supply the Sponsor and the IRB/IEC with any additional requested information such as autopsy reports if available and terminal medical reports.

The "Serious Adverse Event" form and the instructions on completion are provided in the investigator's study file. The "Instructions for Completing the SAE Form" give more detailed guidance on the reporting of serious adverse events, significant overdose cases, and Adverse Events initially reported as non serious that become serious.

7. STATISTICAL ANALYSIS

7.1. SUMMARY

The study is a 13-week, randomized, double-blind, placebo controlled, parallel-group, multi-center trial assessing the effects of BF2.649 (B) compared with Placebo (P) in the relief of Excessive Daytime Sleepiness (EDS): children from 6 to less than 12 years of age and adolescents from 12 to less than 18 years of age, all of them suffering from narcolepsy with or without cataplexy.

7.2. STATISTICAL METHODS

The Primary selection will be the Full Analysis Set (FAS), defined as all the randomized patients irrespective of their outcome, this analysis with the best conformity with Intent To Treat principle.

7.3. MAIN ENDPOINT

The main endpoint is the UNS measuring the quantity and intensity of symptoms if narcolepsy in particular EDS and cataplexies.

Metric properties of this scale are summarized as follows: Total scores range from 0 to 44 with higher scores denoting greater narcoleptic tendencies.

7.4. STATISTICAL INFERENCE

The significance of the active tested drug compared with placebo on the change of UNS will be assessed by Analysis of Covariance on Final UNS estimate (the summary mean of the two Final UNS measures V6 and V7) adjusted for baseline (summary mean of the two pre-treatment UNS values V1 and V2). ANCOVA will be conducted with a Mixed Linear Model taking into account centre heterogeneity.

7.5. SAMPLE SIZE DETERMINATION

By assuming a Pearson correlation coefficient of R=0.5 between pre-baseline and final values of PDSS, two pre-baseline measurements [(V1+V2)/2] and two post-baseline measurements [(V6+ V7)/2], a standardized mean difference of at least 0.5 (considered as the minimum clinically significant difference) will be detected at a two-sided 0.05 confidence level with a power of at least 0.8, when the sample size/group is at least 20 and 40 patients for control and tested drug groups, respectively.

In the last sample size calculation as detailed in section 7.7.2, a recruitment of 96 patients was decided, based on the following assumptions: a standardized mean difference of at least 0.5 (considered as the minimum clinically significant difference) will be detected at a two-sided 0.05 confidence level with a power ≥ 0.75. Since then, the main endpoint becomes the UNS measuring EDS and cataplexy instead of the PDSS. The validation of UNS provided good metric properties, but a residual variability slightly larger than PDSS. The power 0.75 was also considered risky and increased to 0.85.

Further to those changes, a recalculation of the sample size was performed on a standardized mean difference of 0.5 on the UNS (considered as the minimum clinically significant difference), a ratio 1:2, and a correlation R=0.4. Under these assumptions, and ANCOVA test at 0.05 two-sided confidence level, the probability of a significant effect will be found with a power of 0.85 when the sample size exceeds 36+72 patients for control and tested drug groups, respectively, thus a total of 108 patients.

7.6. HANDLING OF MISSING DATA

For patients terminating the trial before completion, the final value will be calculated as the

mean of the two last known values (baseline if needed).

7.7. INTERIM ANALYSIS

7.7.1. DSMB

According to ICH E9 an independent Data Safety Monitoring Board (DSMB) will regularly follow the progress of the clinical trial, monitor safety data and critical efficacy variables and be consulted concerning the opportunity of modifying the sample size (see next point), or terminate a trial for futility (see next point).

The DSMB will have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the DSMB is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The DSMB is a separate entity from an Institutional review Board (IRB) or an Independent Ethics Committee (IEC), and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines including statistics.
Operating procedures will define clearly the roles and responsibilities, the membership -with independent experts in the clinical aspects and one biostatistician -, and organization of the meetings. The procedures should also address the way to keep confidential the data analyzed, the voting rules and the control of dissemination of interim trial results within the sponsor organization.

7.7.2. Adaptive sample size to 96 patients

We based our sample size on the value of the assumed standardize mean difference and the correlation between baseline and final values (R). Over- or under-estimation or R is possible. An estimation of R will be found, blind to treatment, when at least 20 patients have completed the study (producing an 80% half interval length of R. In case where the difference between the observed R' values and the expected R is such that |R-R'|>.1 the sample size will be recalculated and discussed with the DSMB.
Initially, at least 60 patients are required to evaluate the primary endpoints (40 patients being administered pitolisant, and 20 patients receiving placebo). Besides, the analysis of sample size justified in the context of an adaptive sample size was performed on 29 enrolled patients including 27 randomized patients and among them 25 patients provided endpoints values at V6 and V7. The statistical outcomes highlighted the need for increase of the sample size. At least 96 patients (64 patients being administrated pitolisant, and 32 patients receiving placebo) should be needed for a power of at least 0.75, given the observed values of SD and baseline

correlation.

[redacted]

7.7.4. References

Lan K. Wittes J: The B-value: a tool for monitoring data . Biometrics 44:579-585, 1988

Lan K., Zucker D: Sequential monitoring of clinical trials: the role of information and Brownian Motion, Stat Med 12: 753-765, 1993

Proschan M.A., Statistical methods for monitoring Clinical Trials , J Bioph Stat, 9 (4) 599-615 (1999)

8. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

In conformity with GCP (ICH E6), the investigator should provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. Any authorized party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Each patient should consent in writing, to direct access to his/her original medical records.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. MORNITORING AND GOOD CLINICAL PRACTICE

The trial will be run with respect to the Good Clinical Practice, following the international regulations (ICH) and the European directives (EMA) or national ones.
The quality control of the study and the audit of the Good Clinical Practice could be performed by Bioprojet or delegated auditor or by an inspector of Authority Agency.

In particular, the current protocol will be submitted to the approval of the Ethics Committee and Competent Authority by BIOPROJET. The conformity of the study progress will be reviewed.
The investigator will carefully explain the participating conditions to each proposed patient. Each patient will receive a detailed and written information letter including the name of the product, a summary of its properties, the potential unexpected and adverse events, the doses to be administered, the treatment duration, the number of visits, the kind and number of scheduled exams.

The patient will be informed that he can dropout from the study whenever he wants, without any justification.

The system to attribute treatment number to patients is based on the anonymity obligation. Patients will receive a number according to their order of inclusion in the study on a site. The patients will be identified by the sponsor with: the centre number, the inclusion number.

Study progress conformity to the protocol will be controlled from the patients' selection, and all along the study. Each investigator has to allow the monitor, or sponsor's mandated representative, the access to any control of the study progress, and to any required documents to control data reported in case report forms (hospitalization file, consultation file, results of additional exams …).
The investigator will be available to the telephone for each patient whom he has included.
The anonymity respect shall be applied to the filling of the case report form as to any other archived documents considered as source data (blood tests, informed consent form…).

9.2. QUALITY CONTROL AND AUDIT

Control actions are implemented within the framework of the Quality Assurance System to check that the quality requirements of the study are respected.

The original documents generated in the course of the study will be controlled at each step of the study, both by the sponsor's representative and the investigator, in order to guarantee the accuracy of the analyzed data.

The conduct of the study may be audited by the Sponsor and/or inspected by the Competent Authorities where the study is performed. Auditors and/or inspectors should have access to any study records (CRFs, site files, trial master files…) and sources patients' medical documentation. Investigators accept the possibility to be audited / inspected and agree to dedicate necessary time to the proper conduct of the audit / inspection at their sites. It will enable to check that the study is being run in conformity to the protocol and to current rules and regulations.

9.3. MONITORING

The Monitors of Bioprojet or delegates will conduct initiation visits at each study center after approval of the study has been obtained from the Independent Ethics Committees and Competent Authorities to discuss the clinical protocol and review data collection procedures, safety monitoring and reporting procedures, and regulatory requirements.

Monitoring visits to the study centers will be conducted periodically during the study performance, in order to:

- Review the status of the study with respect to patient enrolment, occurrence of adverse events, etc.
- Ensure that the clinical investigators continue to meet their contractual, clinical and regulatory obligations with regard to protocol compliance (and compliance to protocol amendments, if applicable), adherence to regulatory and ethical requirements and the protection of the patients' rights and safety,
- Ensure the scientific integrity of the study by reviewing the integrity and completeness of the data collected on the CRFs on the basis of the raw data (refer to Declaration of Helsinki)
- Review the completeness and accuracy of the study Site Records

Source documents will be reviewed for verification of agreement with data on the CRFs. The study center guarantees direct access to source documents by designated Bioprojet personnel

or their designees and appropriate regulatory authorities. Monitoring will be conducted according to the internal Standard Operating Procedures.

The study may also be subject to a quality assurance audit by Bioprojet Corporation or its designees, as well as inspection by appropriate regulatory authorities.

It is important that the Investigator and the relevant study personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

9.4. INVESTIGATOR QUALIFICATIONS/RESPONSIBILITIES

- Level of experience in Narcolepsy disease and study procedures/testing adequate for participation in study trial
- Previous clinical research experience
- The number of narcolepsy patients that would suffice to meet the enrolment goals
- Agree to participate in an appropriate training program prior to first patient enrolled
- Be willing to comply with the scheduled follow-up visits as described in the protocol.
- Agree to obtain Informed Consent before conducting any study-specific tests or procedures
- Complete all CRFs promptly
- Be willing to spend time to complete the administrative work involved in the study
- Be willing to spend time with the Bioprojet Clinical Research Associate, monitors or delegates during the monitoring visits.
- Be willing to change hospital routine required by protocol

10. ETHICS

10.1. DECLARATION IF HELSINKI AND CONFORMITY WITH OTHER INTERNATIONAL STANDARDS

The trial will be carried out in accordance with the Declaration of Helsinki (Edinburgh, 2000) completed by Notes of Clarification to articles 29 (Washington, 2002) and 30 (Tokyo, 2004) respectively, as revised in 2008 (59th WMA General Assembly, Seoul) and 2013 (64th WMA General Assembly, Brazil). The trial will also be conducted in compliance with the protocol, the ICH Guidelines for Good Clinical Practice (ICH E6), the European directives on clinical trials (Directive 2001/20/EC), and the applicable local country laws/regulations.

10.2. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

It is the Sponsor's responsibility to obtain and maintain written approval of the final Study protocol, including the Patient Information and Informed Consent, from the appropriate Ethics Committee. It is also the Sponsor's responsibility to notify the Independent Ethics Committee (IEC) about any amendments to these documents. In case the protocol amendment changes the scope of the study or increases the risks of the study patients, the investigator should wait for approval of this amendment by the Independent Ethics Committee before implementing the protocol amendment. A copy of the written approval and the approved versions of the documents and a list of the Ethics Committee members, their titles and occupations should be obtained from the IEC. The written approval should identify the study and document the date of review.

The Sponsor should file all correspondences with the Ethics Committee. It is the Sponsor's responsibility to issue a final report and to provide it to the regulatory agencies as required by the applicable regulatory requirements.

10.3. EMERGENCY ACTIONS

Bioprojet accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the well-being of a study patient. The Investigator must give notice of any emergency deviations and justification for the deviation to the study personnel responsible at Bioprojet. The Ethics Committee will be informed as quickly as possible after the episode, in any event no later than 24 hours after the emergency, depending on local regulation.

10.4. PATIENT INFORMED CONSENT PROCEDURE

It is the responsibility of the Investigator to give each patient and to their parents (or the patient's legally authorized representative) prior to inclusion in the study, full and adequate verbal and written information about the objectives and the procedures of the study, potential risks involved, and personal and societal benefits. The patient and their parents must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled and that withdrawal from the study will not jeopardize their future medical care.

Before deciding on whether or not to participate, the patient and their parents (or their legal representative) should have sufficient time to think about the study and to discuss the study with third parties. The investigators and their staff will be available to answer questions from the subject at all times. Written Patient Information should be given to each patient (if old

enough to understand) and both parents (or their legal representative) before enrolment. Furthermore, it is the responsibility of the Investigator to obtain, in accordance with the pertinent local regulations, a signed Informed Consent form from each patient and their parents (or their legal representative) prior to performing any study-related procedures. (ICH – E11).

The Patient Information and Informed Consent form should be updated or amended whenever new important information becomes available that may be relevant to the patient and their parents (or their legal representative). Modifications to these documents must be approved by Bioprojet and by the IEC before being implemented.

10.5. AMENDING THE PROTOCOL

Any change to the study must be documented in a protocol amendment. Such protocol amendments will be made jointly by Bioprojet and the investigators. Both parties will sign the protocol amendment.

Bioprojet shall submit the protocol amendment for review by the Independent Ethics Committee if the change or deviation from the original protocol could increase the risks to the study patients or could adversely affect the validity of the investigation or the rights of the human subjects and shall obtain approval from the Independent Ethics Committees before such change or deviation is implemented.

When the change or deviation to the original protocol will eliminate or reduce the risk to the study patients, the protocol amendment will be implemented before approval has been received from the Independent Ethics Committee. In such cases, the Sponsor shall notify the Independent Ethics Committees within ten working days after implementation and shall submit the protocol amendment as soon as possible for information/favorable opinion from the Independent Ethics Committees.

If the protocol amendment is of the administrative kind, it will be sent to the Ethics Committees for information.

11. DATA HANDLING AND RECORD KEEPING

11.1. IDENTIFICATION OF ANY DATA TO BE RECORDED ON THE CRF, CONSIDERED AS SOURCE DATA

Source data are all information reported directly in the CRF and certified copies of original records of clinical findings, observations or other activities in the trial necessary for the reconstruction and evaluation of the trial. CRF should have the initial of the patient's first name (first letter) and the initial of the last name (first letter), as well as the center number, the inclusion number in the study. Source data relate to but not limited to:

- Subject identification, demographic data (age, weight, height, birth's date), general examination, medical history, last participation to a clinical trial if any,
- Narcolepsy diagnosis history and documentation of the previously performed evaluation (tests, questionnaires…) about illness
- A complete interrogation including the patient actual symptoms of narcolepsy (severity and duration), possible complication, details of concomitant treatments including any current and previous treatments of EDS and cataplexy and any other types of treatment.
- Dates and times of each visit and for drug administration, concomitant medication during the study.
- All data related to efficacy assessment: PDSS, MWT, CASS, CGI, UNS, TEA-Ch, Sleep diary, patient's global opinion on the effect of treatment (if able to express himself if not global opinion will be reported either by parents or teachers).
- All data related to safety assessment: adverse events, vital signs, ECG, results of biological tolerance.

11.2. DATA HANDLING AND RECORD KEEPING

Data management procedure will be fully detail in a separate document, data management plan. Anyway to be noticed that data bases corresponding to each study part (Double blind part on one hand and Open label part on the other hand) will be frozen separately in order to allow a fast double blind part results analysis.

Bioprojet will contract out the data capture to a CRO (Contract Research Organization).

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the Investigators, investigational sites and Ethics Committees agree to retain study-related

documents in a location that is secure and to which access can be gained if required. The following documents must be archived: the Investigator's File containing all required GCP documents, including signed Informed Consent forms and patient-related records, CRFs and Data Clarification Forms. The Investigator and the site should retain records for until at least 2 years after the last approval of the marketing application or at least 2 years after the formal discontinuation of clinical development of the investigational product. At the end of these regulatory delays, the investigator will inform Bioprojet of his intention to proceed to the destruction of archived data. If the records need to be retained after that duration, the investigator and the site will be notified by Bioprojet. These documents must be available for audit by authorized representative of Bioprojet or inspection by regulatory authorities. Bioprojet will keep in the same conditions the original CRFs and appendices (correction sheets, sheets with comments…).

Audits may be performed for quality assurance of data handling.

11.3. DATA PROTECTION AND CONFIDENTIALITY

All documents that concern the studied medication and the company's operations belonging to sponsor such as patent applications, formula, manufacturing process, basic scientific data and analysis bulletins; information supplied by the company and not previously published are considered confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in accomplishing this study and they will not use it for other purposes without written consent from sponsor.

Confidentiality of study source documents:

The information included in this document, as the investigator's brochure of the product, the CRF and the results of the present study are considered as confidential and should not be divulged, only in case of legal requirements.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. The signature of the present protocol is equivalent to a confidential agreement.

It is understood by the investigator that the information from the clinical study will be used by the company in connection with the development of the tested drug and, therefore, may be disclosed as required to other clinical investigators or to government agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with the complete test results as well as all data developed

during this study, under the form of a written document or computerized with the following software: Word or SAS under Windows, saved on CD-Rom.

The trial drug and the information in this document and in any future information supplied contain trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

All or part of the information should only be divulged, submitted for publication or claim for industrial proprietary act with the written consent of Bioprojet.

In compliance with the French law "Informatique et Liberté" of January 6th 1978 modified by the law N°94-548 of July 1er 1994 and the decree N°2005-1309 of October 20th 2005, all information relative to this study shall be declared to the "Commission Nationale de l'Informatique et des Libertés" (CNIL), all computerized data relative to this study shall be declared to the "Commission Nationale de l'Informatique et des Libertés". All data obtained in this study will be processed according to the European Regulation n°2016/679 on General Data Protection ("GDPR") and its French application MR-001.

12. REGULATORY ASPECTS

Notification/application to Relevant Competent Authorities

According to the individual country law/regulation, the study will not be initiated before it has been approved by the relevant Competent Authorities and Ethics Committee.

13. FINANCING AND STUDY INSURANCE

Bioprojet will cover the additional costs related of this study. These costs will be defined and agreed before the start of the study. A financial agreement will be made between the parties, institution, investigator and the sponsor, in accordance with each administrative procedure.
Bioprojet will contract a specific insurance policy for the coverage of the patients in conformity to the National regulation.

14. PUBLICATION POLICY

All information resulting from the study will be considered as confidential, and must not be divulged without the sponsor's prior agreement.

The study results may be published or presented by the investigator or analysis experts, in collaboration with Bioprojet, with the Bioprojet's written permission. Bioprojet may use the study results for any publication or communication, with the written agreement of the investigator, or the analysis experts if they are quoted.

15. CALENDAR FORECAST

- First patient visit is scheduled in Q1 2016.
- For each patient, the study will last 13 weeks, of which a 8-week treatment period with the investigational medical product or placebo.
- The end of study (double blind period) is expected in Q1 2022.

16. APPENDICES

Appendix 1: Ullanlinna Narcolepsy Scale (UNS)

Appendix 2: Epworth sleepiness scale adapted for children and adolescents (CASS)

Appendix 3: Paediatric Daytime Sleepiness Scale (PDSS)

Appendix 4: Childhood Depression Inventory (CDI)

Appendix 5: Clinical Global Impression (CGI)

Appendix 6: Sleep Diary

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

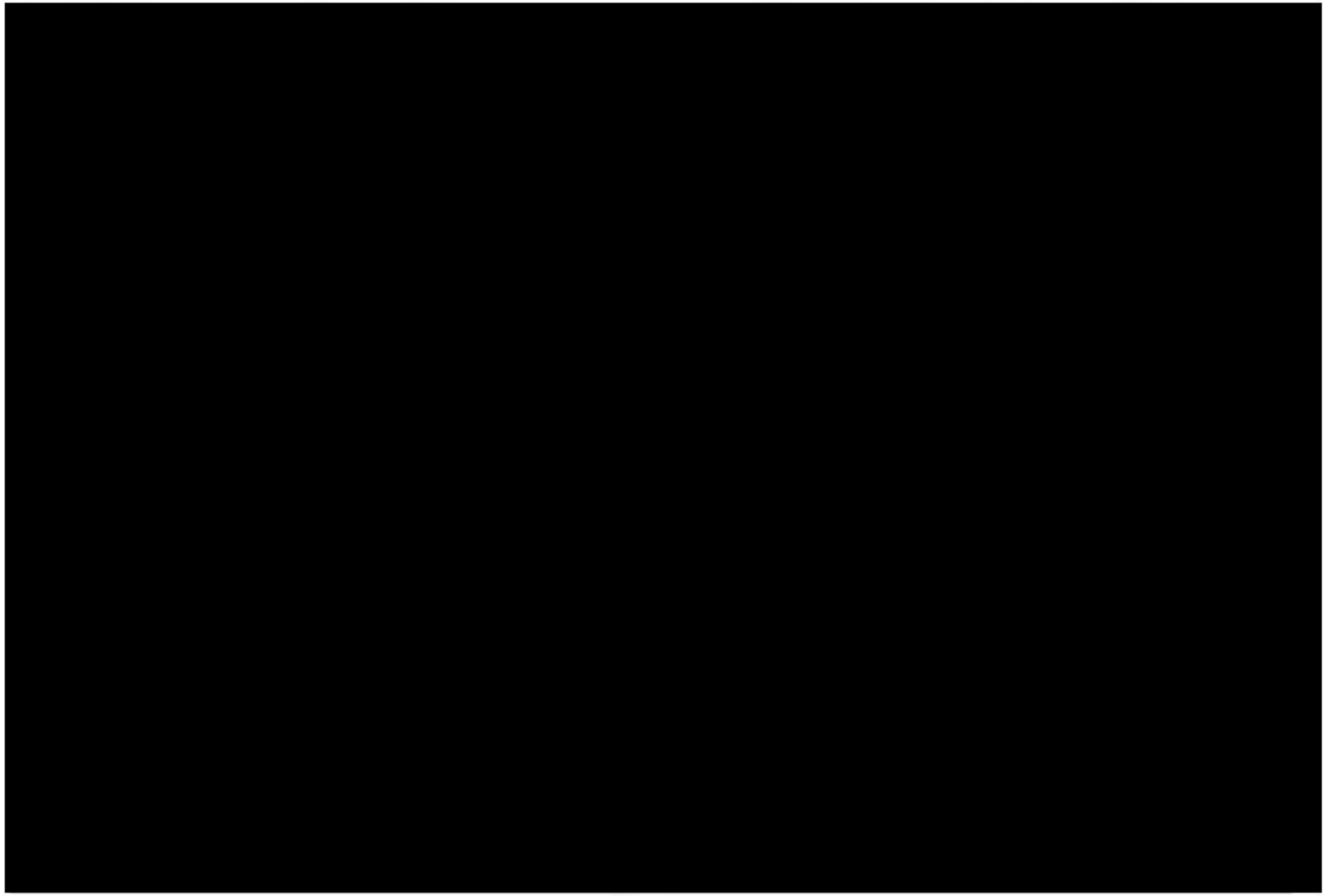
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



17. REFERENCES

1- Lin JS et al. An inverse agonist of the histamine H(3) receptor improves wakefulness in narcolepsy: studies in orexin-/- mice and patients. Neurobiol Dis 2008;30:74-83

2- Chemelli RM et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 1999;98:437-451

3- Willie et al. Distinct Narcolepsy Syndromes in Orexin Receptor-2 and Orexin Null Mice Neuron. 2003;38:715-30

4- Mochizuki T et al. Behavioral State Instability in Orexin Knock-Out Mice. J. Neurosci. 2004;24:6291-300

6- Billiard M et al. EFNS guidelines on management of Narcolepsy. Eur J Neurol 2006;13:1035-48

7- Dauvilliers Y et al. Clinical aspects and pathophysiology of narcolepsy. Clinical Neurophysiology 2003;114:2000-2017

8- Doghramji K et al, Electroencephalogr Clin Neurophysiol. 1997; 103:554-62