PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND STUDY, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTI-CENTER TRIAL ASSESSING THE EFFECTS OF BF2.649 IN TREATMENT OF EXCESSIVE DAYTIME SLEEPINESS IN NARCOLEPSY (*HARMONY 1*)

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· Evaluate the efficacy and safety of BF2.649 administered by escalating doses and followed by 5-week stable doses in narcoleptic patients with excessive daytime sleepiness (EDS) as compared to placebo.· Evaluate the efficacy and safety of BF2.649…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sleep disturbances (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON33230

Source
ToetsingOnline

Brief title
P07-03 HARMONY1

Condition

- Sleep disturbances (incl subtypes)

Synonym
EDS - excessive daytime sleepiness, Narcolepsy

Research involving
Human

Sponsors and support

Primary sponsor: Bioprojet
Source(s) of monetary or material Support: Bioprojet;Parijs;Frankrijk

Intervention

Keyword: BF2.649, EDS, Narcolepsy

Outcome measures

Primary outcome

Subjective daytime somnolence assessed using Epworth Sleepiness Scale (ESS).

ESS will be evaluated at baseline and at endpoint corresponding to the end of 8-week double-blind phase or to the time of the last on-study visit for any subject who withdraws prior to study completion. Each ESS score corresponds to the average of 2 measures repeated after an interval of 1week. The ESS at baseline is the average of ESS at D-7 and ESS at D0; the ESS at endpoint V7 is the average of ESS at D49 and ESS at D56.

Secondary outcome

• Information reported by patients daily in electronic sleep diaries- Mean number and duration of diurnal involuntary sleep attacks and episodes of severe sleepiness- Frequency and severity of cataplexy attacks by reporting the number of total and partial cataplexy attacks.- Frequency of hallucinations, incidence of sleep paralysis.- Number and duration of nocturnal awakening and total duration of nocturnal sleep time.• Objective measures of vigilance and the ability to maintain wakefulness- Maintenance of Wakefulness Test (MWT): four sessions of 40-minute tests. - Test of Sustained Attention to Response Task

(SART).• Severity of EDS measured by the Clinical Global Impression of Change and of Severity (CGI-C and CGI-S on EDS)• Severity of cataplexy measured by the Clinical Global Impression of Change and of Severity (CGI-C and CGI-S on cataplexy)• European Quality of life questionnaire (EQ-5D)• Patient*s Global Opinion on Effect of treatment

Study description

Background summary

Excessive daytime sleepiness is a troublesome symptom which can have a major social impact upon both family and professional/school life in the course of narcolepsy. The most usual treatment is 2-4 tablets of Modafinil per day. However, its efficacy varies from patient to patient and sometimes some of its side effects, such as headache and nausea, may cause treatment to be stopped. BF 2.649 (the code name of the study drug) is a new molecule. It acts on the cerebral receptors of histamine, a major alertness circuit. Two previous clinical studies have shown in 48 narcoleptic patients that BF2.649 significantly improves daytime alertness.

Study objective

· Evaluate the efficacy and safety of BF2.649 administered by escalating doses and followed by 5-week stable doses in narcoleptic patients with excessive daytime sleepiness (EDS) as compared to placebo.
· Evaluate the efficacy and safety of BF2.649 in treatment of excessive daytime sleepiness in narcolepsy as compared to Modafinil
· Investigate the response to withdrawal of BF2.649 after 8 weeks daily medication.

Study design

This study is a 3-arm, randomized, doubleblind, placebo controlled multicenter clinical trial. The patients will be randomized in one of the following 3 groups: BF2649, Modafinil of placebo.

BF2.649, Modafinil and placebo are provided in capsules. The capsules are identical in appearance to ensure that neither the patient nor the investigator or the clinical staff knows the identity of the study medication.BF2.649 tablets at 10 and 20 mg, and Modafinil tablets at 100 mg are enclosed in

gelatin capsules; and placebo consist of identical capsules containing lactose only. Patients should take 4 capsules per day with a glass of water. They will be instructed to take capsule(s) of BF2.649, Modafinil or placebo, by oral route, 2 capsules in the morning (before or during breakfast around 8.00 a.m.) and 2 capsules at noon (before or during lunch but no later than 2.30 p.m.) in order to not disturb the nocturnal sleep. Patients should be instructed to take their doses at regular interval. Following the completion of inclusion procedures, patients will be randomized to one of three treatment groups:Group 1: BF2.649 group• BF2.649 at 10 mg/d: Patients will be instructed to take 1 capsule of BF2.649 at 10 mg and 1 capsule of placebo in the morning; 2 capsules of placebo at noon.• BF2.649 at 20 mg/d: Patients will be instructed to take 1 capsule of BF2.649 at 20 mg and 1 capsule of placebo in the morning; 2 capsules of placebo at noon.• BF2.649 at 40 mg/d: Patients will be instructed to take 2 capsules of BF2.649 at 20 mg in the morning and 2 capsules of placebo at noon.Group 2: Modafinil group• Modafinil at 100 mg/d: Patients will be instructed to take 1 capsule of Modafinil at 100 mg and 1 capsule of placebo in the morning; 2 capsules of placebo at noon.• Modafinil at 200 mg/d: Patients will be instructed to take 1 capsule of Modafinil at 100 mg and 1 capsule of placebo in the morning; 1 capsule of Modafinil 100 mg and 1 capsule of placebo at noon.• Modafinil at 400 mg/d: Patients will be instructed to take 2 capsules of Modafinil 100 mg in the morning and 2 capsules of Modafinil 100 mg at noon.Group 3: Placebo groupPatients will be instructed to take 2 capsules of placebo in the morning and 2 capsules of placebo at noon.

Intervention

From each patient blood will be collected twice: start and end of study.

Study burden and risks

In previous studies conducted on BF2.649, the commonest undesirable events were headache (9.5%), insomnia (7.8%), nausea (4.9%) and irritability (3.7%). These effects were transient and all regressed spontaneously or when treatment stopped. There were no serious side effects connected with the treatment. As a precaution, we would ask you to contact your doctor as soon as you experience any unusual symptoms.
The following are the commonest undesirable effects encountered after taking Modafinil: nausea, headache, diarrhoea, loss of appetite, dry mouth, nervousness, anxiety, a sensation of dizziness, insomnia, arterial hypertension. Skin reactions have also been reported.
Being pregnant during this study exposes the embryo to risks of malformation. This is why women of childbearing age should use a form of contraception judged to be effective by their doctor throughout the duration of the study and for the month following the end of their participation.

Adverse experiences and drug safety• Monitoring of adverse events at each

visit: investigators rate the severity and the relationship of each adverse experience to study medication.• Cardiovascular safety: vital sign checking at each visit including blood pressure, heart rate and body weight.• Additional safety measures including 12-lead ECG and clinical laboratory tests (hematology, blood chemistry) at initial screening visit (V1) and at the end of treatment phase (V7) or at the time of the last on-study visit for any subject who withdraws prior to treatment phase completion.

Medication for the treatment of narcolepsy will be stopped during the course of the trial. The patient must not take any medication liable to alter wakefulness or sleep without the agreement of this doctor. Although the effects of the study treatment are encouraging for the treatment of narcolepsy, you must be particularly vigilant with regard to driving vehicles or using machinery throughout the duration of the study. The risks of having a road accident may be increased.

Contacts

Public
Bioprojet

9 Rue Rameau
75002 Parijs
Frankrijk
Scientific
Bioprojet

9 Rue Rameau
75002 Parijs
Frankrijk

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Males and females of any ethnic origin, 18 to 65 years of age (inclusive).
2. Both new and previously diagnosed patients with narcolepsy with or without cataplexy could be included. All patients should meet the International Classification of Sleep Disorders (ICSD-2) criteria.
3. Patients should be free of drugs or discontinue any psychostimulant medications for at least 14 days at the start of baseline period. Patients with severe cataplexy are permitted to remain on their anticataplectic medications at stable doses except tricyclic antidepressants. The authorized anticataplectic treatment should have been administrated for at least 1 month prior to the trial and these doses should not be changed throughout the trial (from V1 to V8).
4. Epworth Sleepiness Scale (ESS) score should be ³ 14/24 during the baseline period.
5. Patients have expressed a willingness to participate in and complete the study, and signed and dated informed consent prior to beginning protocol required procedures.
6. Females must be surgically sterile or 2 years postmenopausal. Females of child-bearing potential must use a medically accepted effective method of birth control, agree to continue this method for the duration of the study and be negative to serum pregnancy test performed at the screening visit. Patients using steroidal contraceptives at micro or mini doses (including oral contraceptive, skin patch, tablets and vaginal cream, intrauterine devices) should be advised of the risk of breakthrough bleeding and unintended pregnancy due to the possible reduction of effectiveness of these contraceptives during concomitant therapy with Modafinil. Alternative or additional methods of contraception are necessarily recommended during and for one month after the discontinuation of Modafinil treatment. Females should not be breast-feeding patient.
7. 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).
8. If indicated by investigator, the patient must be willing to not operate a car or heavy machinery for the duration of the trial or as long as the investigator deems clinically indicated. In addition, the patient should be willing to maintain during the study their usual behaviours which could affect their diurnal sleepiness (e.g., circadian rhythm, caffeine consumption, nocturnal sleep duration).

Exclusion criteria

1. The use of BF2.649 or any previous investigational drugs within 30-day period prior to initial screening visit (V1) for this trial.
2. In narcoleptic patients without cataplexy, they should not have 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 >= 10 per hour or and an Apnea/Hypopnea Index >= 15 per hour, periodic limbs movement (PLM) disorders as defined by a PLM arousal index (PLMAI) >=

10 per hour, shift work, chronic sleep deprivation, circadian sleep wake rhythm disorder or any other medical or neurological causes that could account for narcolepsy symptoms associated with EDS.
3. Patients who are unable or unwilling to temporarily discontinue any no-authorized drugs or substances (see Section Non-authorized treatments).
4. 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).
5. Any significant serious abnormality of the cardiovascular system e.g. recent myocardial infarction, angina, hypertension or dysrhythmias (within the prior 6 months), Electrocardiogram Bazett*s corrected QT interval (QT x Ö [HR/60]) strickly higher than 450 ms, history of left ventricular hypertrophy or mitral valve prolapse.
6. Patients with Severe hepatic Impairment (e.g. prothrombin ratio, < 50% or factor V < 50% if the patient receiving anti-vitamin K) or with Severe Renal Impairment (e.g. serum creatine greater than 2.0 mg/dl), or with any other significant abnormality in the physical examination or clinical laboratory results.
7. Psychiatric and neurological disorders, such as moderate or severe psychosis or dementia, bipolar illness, severe anxiety, clinical 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.
8. Prior severe adverse reactions to CNS stimulants.
9. Known hypersensitivity to the tested treatment including active substance and excipients.
10. The inability to continue daily activities safely without the use of treatment against EDS.
11. Other active clinically significant illness, including unstable cardiovascular, endocrine, neoplastic, gastroinstinal, hematologic, 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.
12. Any patients presenting congenital galactosemia, glucose-galactose malabsorption or lactase deficiency due to the presence of lactose in investigational treatments

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-10-2009
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BF2.649
Product type:	Medicine
Brand name:	Modafinil
Generic name:	Modiodal
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-05-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-09-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-01-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-007866-46-NL
CCMO	NL27573.058.09