Prospective, randomized, double-blind study, parallel-group, multi-center trial assessing the effects of escalating doses of BF2.649 and BF2.649 add on Modafinil on cataplexy in patients with narcolepsy.

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Evaluate and compare the efficacy and safety of escalating doses of BF2.649 and BF2.649 add on Modafinil on cataplexy attacks.Evaluate the additive/synergistic effect of the combination of BF2.649 and Modafinil on excessive daytime sleepiness (EDS...

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

Summary

ID

NL-OMON33083

Source
ToetsingOnline

Brief title
P07-07 Harmony II

Condition

- Sleep disturbances (incl subtypes)

Synonym
abrupt muscular weakness and EDS epiness, Cataplexy and narcolepsy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BF2.649, cataplexy, EDS, Narcolepsy

Outcome measures

Primary outcome

The primary measure of efficacy is the change from baseline in weekly cataplexy attacks.Frequency of cataplexy attacks is collected daily by reporting the number of total and partial cataplexy attacks in patient*s daily sleep diary. The number of weekly cataplexy attacks 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.

Secondary outcome

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

• Information reported by patients daily sleep diary

- Duration of each cataplexy attack

- Severity score of each cataplexy attackScore

Description of cataplexy attack

3 Patient loses posture and falls to the ground

2 Patient can maintain posture with external support, e.g. holding onto a table

1 Patient has momentary weakness, e.g. head drop or jaw opening but with

non need to hold onto an object for support

- Mean number and duration of diurnal involuntary sleep attacks and episodes of severe sleepiness

- 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 attention

- Maintenance of Wakefulness Test (MWT): four sessions of 40-minute tests.

- Test of Sustained Attention to Response Task (SART). 4 sessions of SART will be conducted in parallel with MWT

• Severity of cataplexy measured by the Clinical Global Impression of Change and of Severity (CGI-C and CGI-S on cataplexy)

• Severity of EDS measured by the Clinical Global Impression of Change and of Severity (CGI-C and CGI-S on EDS)

• European Quality of Life questionnaire (EQ-5D) • Patient*s Global Opinion on the effect of treatment

Study description

Background summary

Cataplexy and excessive daytime sleepiness are symptoms of narcolepsy which can be disabling and may impact on all aspects of life, depending on their degree of severity. Current treatment of daytime sleepiness is based on Modafinil and treatment of cataplexy is based on low-dose antidepressants and sodium oxybate. However, the efficacy of these treatments varies from one case to another and sometimes some of their 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 system that plays an important role in the

control of the sleep-waking cycle. Two preceding clinical studies on 48 narcoleptic patients demonstrated that BF2.649 significantly improved daytime alertness. In the second study, BF2.649 seemed to have an anti-cataplectic effect on a small number of patients suffering from cataplexy.

Study objective

Evaluate and compare the efficacy and safety of escalating doses of BF2.649 and BF2.649 add on Modafinil on cataplexy attacks.
Evaluate the additive/synergistic effect of the combination of BF2.649 and Modafinil on excessive daytime sleepiness (EDS), on vigilance/attention, and on changes in disease severity assessed by investigators in patients with narcolepsy.

Study design

This study is a 2-arm, randomized, doubleblind, multicenter clinical trial.
The patients will be randomized in one of the following 2 groups: BF2649 + placebo or BF2649 + Modafinil.

The capsules of Modafinil, BF2.649 and placebo are identical in appearance to ensure that neither the patient nor the investigator or the clinical staffs know the identity of the medication.BF2.649 tablets of 10mg, 20mg or 40mg and Modafinil tablets of 100 mg are enclosed in gelatin capsules; and placebo consist of identical capsules containing lactose only. Patients should take three capsules per day by oral route with a glass of water, and they should be instructed to take their doses at regular intervals.BF2.649 is concomitantly administrated with either Modafinil or placebo in blind fashion. The daily stable dose of Modafinil treatment is 100 mg twice per day (200 mg/d) by taking 1 capsule of Modafinil 100 mg in the morning (before or during breakfast around 8.0 a.m.) and 1 capsule of Modafinil 100 mg at noon (before or during lunch but no later than 2.30 p.m. in order to not disturb the nocturnal sleep).
Following the completion of inclusion procedures, patients will be randomized to one of two treatment groups:
Group 1: BF2.649 + PlaceboPatients receive in the morning one capsule of BF2.649 at daily dose of 10, 20 or 40 mg/d according to individual titration and one capsule of placebo; and at noon one capsule of placebo.
Group 2: BF2.649 + Modafinil 200 mg/dPatients receive in the morning one capsule of BF2.649 at daily dose (10, 20 or 40 mg/d) and one capsule of Modafinil 100 mg; and at noon one capsule of Modafinil 100 mg.

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; aged 18 years old and over.
2. De novo patients i.e. with newly diagnosed narcolepsy and cataplexy and not taking any treatment for EDS and cataplexy. Patients with previously diagnosed narcolepsy and cataplexy and not taking any treatment for EDS and cataplexy for more than 3 months
3. Partial or total cataplexy attacks with a frequency of at least 5 per week during a 14-day baseline period and Epworth Sleepiness Scale (ESS) score ³ 14/24 at the end of baseline period (V2).
4. The patient has expressed a willingness to participate in and complete the study, and signed and dated informed consent prior to beginning protocol required procedures.
5. 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.
6. 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).
7. 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. Patients who are unable or unwilling to temporarily discontinue non authorized drugs or substances.
3. 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).
4. Any significant abnormality in the physical examination or clinical laboratory results (e.g. liver or kidney function deficiency).
5. Any significant serious abnormality of the cardiovascular illness 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% for patients receiving anti-vitamin K medication) 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 inactive excipients.
10. Other active clinically significant illness, including unstable cardiovascular, endocrine, neoplastic, gastrointestinal, 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.
11. 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:	2
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:	06-05-2009
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	EUCTR2008-007845-29-NL
CCMO	NL27597.058.09