SYNOPSIS

Name of sponsor / Company: Bioprojet **Name of finished product:** Pitolisant **Name of active ingredient:** BF2.649	Individual Study Table Referring to Part of the Dossier Volume: {x/x} Pages:	*(For National Authority use only)*
Title of the study:	Randomized, double-blind, placebo and comparator-controlled, parallel-group, multicenter trial assessing the effects of BF2.649 in the treatment of excessive daytime sleepiness in narcolepsy.	
International Coordinating investigator	Prof Yves Dauvilliers, MD Hôpital Gui de Chauliac, 80 avenue A. Fliche, 34295 Montpellier, France	
Study center(s):	32 centers: Argentina (2 sites), Austria (1 site), Finland (1 site), France (8 sites), Germany (4 sites), Hungary (4 sites), Italy (6 sites), Spain (6 sites).	
Publication (reference):	None	
Study period (years):	Date of first patient enrolled: October 25th, 2010 Date of last patient completed: July 24th, 2012	Phase of development: III
Objectives:	• Evaluate the efficacy and safety of BF2.649 administered until the dose of 20 mg/d after a titration period and followed by a 5-week stable dose 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 the study treatment discontinuation after an 8-week period of daily medication.	
Methodology:	After a two-week wash-out period during which the prohibited treatments (in particular, psychostimulants) were discontinued, a one-week period enabled to carry out baseline tests. Afterwards, patients who fulfilled selection criteria were randomized between 3 treatment groups: placebo, BF2.649 and modafinil. From D1 to D7, BF2.649 dose was 5mg/d and modafinil dose was 100 mg/d. From D8 to D14, doses were increased to 10 mg/d and 200 mg/d, respectively. At D15, doses could be adjusted according to individual benefit/risk ratio (5, 10 or 20 mg/d for BF2.649; 100, 200 or 400 mg/d for modafinil). At D21, an individual dose adjustment could be performed again, but no doseincrease was allowed. Thereafter, the dose remained stable for a five-week period. FromD56 to D63, all patients received placebo.	
Number of patients (planned and analyzed):	Planned: 185 (75 in each active treatment group, 35 in placebo group) Analyzed: Extended Intent-to-Treat Set (EIT): 164 patients (32 in placebo group, 67 in BF2.649 group, 65 in modafinil group) Intent-to-Treat Set (IT): 163 patients (32, 66, 65) Per Protocol Set (PP): 152 patients (30, 60, 62) Safety Set : 165 patients (33, 67, 65)	

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<tr><td>Name of sponsor / Company:
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Pages:</td><td rowspan="3">(For National Authority use only)</td></tr>
<tr><td>Name of finished product:
Pitolisant</td></tr>
<tr><td>Name of active ingredient:
BF2.649</td></tr>
<tr><td>Diagnosis and main criteria for inclusion:</td><td colspan="2">Inclusion criteria:

Males and females ≥ 18 years old; diagnosed with narcolepsy with or without cataplexy and fulfilling the International Classification of Sleep Disorders (ICSD-2) criteria; free of drugs or having discontinued any psychostimulant medications for at least 14 days at the start of baseline period (patients with severe cataplexy were allowed to remain on their anticataplectic medication at stable dose except tricyclic antidepressants; the authorized anticataplectic treatment had to be administered for at least 1 month prior to the trial and doses were to remain stable throughout the trial); ESS score ≥ 14 during the baseline period; signed and dated informed consent ; females were to be surgically sterile or 2 years postmenopausal or had to use a medically accepted effective method of birth control (i.e. oral contraceptives of normal average dosage ≥ 0.05 mg ethinyl-oestradiol, intra-uterine device, with a barrier method such as spermicides…) and to agree to continue this method for the duration of the study and be negative to serum pregnancy test performed at the screening visit; females should not be breast-feeding patient; in the opinion of the investigator, the patient had to 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) ; if indicated by investigator, the patient had to be willing to not operate a car or heavy machinery for the duration of the trial or as long as the investigator deemed clinically indicated; in addition, the patient had to agree to maintain during the study their usual behaviour which could affect their diurnal sleepiness (e.g. circadian rhythm, caffeine consumption, nocturnal sleep duration); affiliation to medical insurance system (only applicable where mandatory e.g. in France).

Non inclusion criteria:

Use of BF2.649 or any previous investigational drugs within 30-day period prior to initial screening visit (V1); narcoleptic patients without cataplexy could not have any other conditions that could be considered the primary causes of EDS (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); unability or unwilling to temporarily discontinue any nonauthorized drugs or substances; 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); any significant serious abnormality of the cardiovascular system e.g. recent myocardial infarction, angina, hypertension or dysrhythmia (within the prior 6 months), Electrocardiogram Bazett's corrected QT interval (QT x √ [HR/60]) higher than 450 ms, history of left ventricular hypertrophy or mitral valve prolapsed; severe depression (BDI_{13} ≥ 16) or with a suicidal risk (item G BDI_{13} > 0); severe Hepatic Impairment (e.g. prothrombin ratio < 50% or factor V < 50% if treatment with anti-vitamin K) or severe Renal Impairment (e.g. serum creatine greater than 2.0 mg/dL), or any other significant abnormality in the physical examination or clinical laboratory results; 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 could preclude the patient's participation and completion of this trial or comprise reliable representation of subjective symptoms; prior severe adverse reactions to CNS stimulants; known hypersensitivity to the tested treatment including active substance and excipients; inability to continue daily activities safely, without the use of treatment against EDS; other active clinically significant illness, including</td></tr>
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	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; congenital galactosemia, glucose-galactose malabsorption or lactase deficiency; participation in another study or being in a follow–up period for another study.	
Test product:	BF2.649 (pitolisant)	
Dose:	5, 10, 20 mg/d	
Mode of administration:	Per os	
Batch number:	BF2.649 5 mg: CPM7476, CPM7607, CPM7436 BF2.649 10 mg: CPM7477, 7608, 7456 BF2.649 20 mg: CPM7478, 7609, 7437	
Duration of treatment:	8 weeks	
Reference therapy:	Modafinil	
Dose:	100, 200, 400 mg/d	
Mode of administration:	Per os	
Batch number:	Modafinil 100 mg: 3/1003/A.MA, 4/1003A.MA Modafinil 200 mg: 3/1003/A.MA.200, 4/1003A.MA.200	
Reference therapy:	Placebo	
Dose:	NA	
Mode of administration:	Per os	
Batch number:	3/128/01.PB, 4/128/01.PB, CPM7723	
Criteria for evaluation:	<u>Efficacy</u>: Primary endpoint: Epworth Sleepiness Scale (ESS) scores change between the treatments groups, during an 8-week treatment period. Secondary endpoints: ESS responder rate (ESSF $\leq$ 10 or ESSF-ESSBL $\geq$ 3); Daily Cataplexy Rate; MWT; SART; CGI-Severity and CGI-Change Scales; EQ-5D; patient's global opinion; polysomnography. <u>Safety:</u> Adverse events; BDI; vital signs; 12-lead ECG parameters; laboratory blood tests (blood cells count, Na, K, Cl, GGT, ALT, AST, ALP, total bilirubin, prothrombin ratio or factor V, urea, creatinine, blood glucose, total cholesterol, triglycerides, β-HCG pregnancy test for women).	

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Statistical methods:	For the main efficacy criterion: Analysis of covariance on Final ESS (summary mean of the last two visits during treatment) adjusted for baseline (summary means of the two baseline values) with treatment considered as a fixed factor and center as a random effect Superiority test on BF2.649 compared with placebo and Non Inferiority test of BF2.649 compared with modafinil were simultaneously tested by a hierarchical procedure (stepdown approach). For the secondary efficacy criteria: logistic regression model adjusted on baseline (ESS responders), Student's t-test and geometric mean (MWT, SART), quasi-Poisson regression model (Daily Cataplexy Rate).	

SUMMARY – CONCLUSIONS:

Efficacy:

Overall, 166 patients were randomized, of whom 1 never took the study drug and was prematurely withdrawn. This patient was not taken into account for the analysis. One additional patient was excluded from the efficacy analysis as he actually did not meet the criteria for a diagnosis of narcolepsy (qualifying disease). A third patient was excluded of the IT population because of premature withdrawal after one single intake and no post baseline values but is included in the EIT population. Overall, 153 completed the study with similar proportions among groups (between 90% and 95% of patients in each group).

The three treatment groups were comparable with regard to the baseline demographic characteristics (age, weight, height, BMI, sex ratio, ethnicity; p>0.05 for each parameter).

They were also comparable regarding baseline characteristics of narcolepsy (mean time elapsed since narcolepsy start, associated symptoms, history of cataplexy) and baseline efficacy variables (ESS, MWT, SART, EQ-5D, BDI scores, CGI regarding EDS and cataplexy). Between 75% and 81% of patients in each group were cataplectic (p=0.766) but patients were in a great majority considered normal to moderately ill when cataplexy was rated with CGI scale . Mean baseline ESS score was around 18 in each group. Median baseline ESS score was comprised between 17.5 and 18.5 in each group .

The proportion of patients with a good compliance (intake of 80% to 120% of prescribed treatment) in each treatment group was 92.4% in BF2.649 group, 96.9% in placebo group and 100% in modafinil group. Compliance was not statistically significantly different between groups (p=0. 159).

To eliminate bias due to the unbalanced distribution of treatments within centers, a random re-allocation of small centers was organized for the analysis.

The primary analysis showed a significant improvement of -2.19 (95%CI [-4.17 to -0.22]; p=0.030; IT population) with BF2.649 compared to placebo (linear mixed effects model performed with adjusted ESS final scores, treatment as fixed factor and center as random effect). The non inferiority between BF2.649 and modafinil could not be concluded, the lower bound of the 95% CI of the difference being smaller than the pre-defined NI value of 2 (Difference =2.75, 95%CI [1.02 to 4.48]; p=0.002).

Similar results were observed either with sensitivity analyses, or when centers were not re-allocated. No significant covariates that may have had a potential effect on the studied endpoint were identified.

ESS responders rate was statistically significantly increased with BF2.649 in comparison to placebo (34.4% of responders with placebo versus 65.2% with BF2.649; RR=2.14; 95%CI [1.35-3.39]; p=0.001). The difference between BF2.649 and modafinil was non-significant (RR=0.87; 95%CI [0.74-1.02]; p=0.086).

The ratio of mean change in MWT (final/baseline) between BF2.649 and placebo was significant (1.46; 95%CI [1.06, 2.01]; p=0.021), whereas the difference between BF2.649 and modafinil was non-significant (0.85; 95%CI [0.66-1.09], p=0.198).

The ratio of mean change in SART NOGO error scores between BF2.649 and placebo was significant (0.77; 95%CI [0.65, 0.91]; p=0.002), whereas the difference between BF2.649 and modafinil was non-significant (1.08; 95%CI [0.93-1.26]; p=0.294).

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No significant difference was observed between groups in the Daily Cataplexy Rate (exposed population).

The EDS assessed with CGI scale improved between inclusion (V3) and endpoint (V7) visits in significantly more patients of BF2.649 and modafinil groups than placebo group whatever the population dataset (36.7% in placebo group, 72.1% in BF2.649 group and 77.8% in modafinil group; p = 0.001; IT population).

The cataplexy assessed with the CGI scale improved between inclusion (V3) and endpoint (V7) visits in more patients of BF2.649 and modafinil groups than placebo group, even if non significant (35.7% in placebo group, 59.6% in BF2.649 group and 54.2% in modafinil group; p =0.075; IT population).

There was no statistically significant difference between groups in the evolution of each of the five dimensions of the EQ-5D questionnaire (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) between inclusion (V3) and endpoint visits (V7). Treatment with BF2.649 or modafinil did not impair the sleep parameters.

Safety:

Among the 166 patients who were randomized in this study, one was prematurely withdrawn after inclusion visit and did not take any study drug (patient 25004). This patient was excluded from the safety analysis.

Among the other patients who took at least one dose of study drug (safety population), 12 prematurely definitely discontinued the study treatment: 2 in the placebo group, 7 in the BF2.649 group and 3 in the modafinil group. All the remaining patients (n=153) completed the study treatment period: 31 (93.9%) in the placebo group, 60 (89.6%) in the BF2.649 group and 62 (95.4%) in the modafinil group.

In this study, the BF2.649 dose was limited to 20 mg/d, whereas modafinil could be titrated up to 200 or 400 mg/d, the recommended daily dose mentioned in its SPC.

At the end of the first 2-week titration period, all patients were receiving the medium dose, except one in placebo group and one in BF2.649 group (low dose). Afterwards, at any time point of the study, between 63% and 75% of patients of the BF2.649 group were taking the 20 mg/d dose and between 16% and 24% were taking the 10 mg/d dose. Two patients were maintained at the 5 mg/d dose from D14 to D56 (patients 16003 and 29024). In the modafinil group, between 66% and 79% of patients were taking the 400 mg/d dose and between 19% and 28% were taking the 200 mg/d dose. Two patients were maintained at the 100 mg/d dose from D14 to D56 (patients 05004 and 12003).

Overall, 77 patients (46.7%) reported 160 TEAEs: 12 patients (36.4%) of placebo group, 33 (49.3%) of BF2.649 group and 32 (49.2%) of modafinil group.

Twelve TEAEs (7.5%) led to treatment discontinuation: 2 in the placebo group (1 patient), 9 in the BF2.649 group (5 patients) and 1 in the modafinil group (1 patient). Eighteen TEAEs (11.2%) were severe, none in the placebo group, 13 in the BF2.649 group and 5 in the modafinil group. One third of severe TEAEs were considered possibly or likely related to the study drug in the BF2.649 group (cataplexy, somnolence, abdominal pain), whereas they were two thirds in the modafinil group (somnolence, migraine, worsening of abdominal pain).

Seven patients (4.6%) only discontinued the study drug because of AEs: 1 in placebo group (patient 32011), 5 in BF2.649 group (patients 01001, 01002, 13001, 20004, 32007) and 1 in modafinil group (patient 32006).

The most frequently reported preferred term in the BF2.649 group was headache (12.7% of TEAEs in this group), followed by dizziness (5.6%), nausea (4.2%), vomiting (4.2%), nasopharyngitis (4.7%), decreased appetite (4.2%) andinsomnia (4.2%). In the modafinil group, they were headache (10.2%) and nasopharyngitis (6.8%). In the placebo group they were headache (16.7%), insomnia (10.0%), fatigue (6.7%) and diarrhea (6.7%).

No death was reported in this study. Only one serious AE was reported; it occurred in modafinil arm (patient 29015 distal radial fracture) and was judged as unrelated to the study treatment.

Laboratory parameters were within the normal limits in almost all cases. When abnormal results were observed, they were not clinically significant or probably due to the current or concomitant diseases. No difference was observed between groups at selection and end-of-study for any parameter (p>0.05).

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No clinically significant difference was observed between groups in vital signs except the mean changes in SBP and DBP from selection to the end of study which were greater with placebo than BF2.649 or modafinil (SBP: -6.7 versus -2.4 and -0.1 mmHg, p=0.043; DBP: -5.2 versus -0.4 and -1.1 mmHg, p=0.035).

There was no statistically significant difference between groups with regard to clinical exam and ECG parameters (heart rate, PR interval, QRD interval, QT, QTc).

Mean change in BDI score was similar among groups: -1.1 ± 3 in placebo group, -1.7 ± 2.6 in BF2.649 group and -1.3 ± 2.8 in modafinil group (p=0.547).

No patient in the BF2.649 group had a DSM-IV-defined withdrawal syndrome during the withdrawal phase whereas two patients in the other groups met the criteria, one in placebo group and one in modafinil group.

Conclusion:

In conclusion, the efficacy of BF2.649, used as a flexible dosing up to 20 mg OD, on Excessive Daytime Sleepiness measured with the Epworth Sleepiness Scale in narcoleptic patients was documented in this phase III study. The non inferiority could not be concluded between BF2.649 and modafinil prescribed at daily doses recommended in its SPC. In comparison, the BF2.649 dosage was limited to 20 mg/d, which is not the maximal daily dose that can be administered. BF2.649 had a good overall clinical, cardiovascular and biological safety profile.

Date of report: V2.0, October 2018

N° EudraCT: 2010-019687-36