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:	Minimum effective dose-finding study of BF2.649, in patients with moderate to severe Obstructive Sleep Apnea, experiencing Excessive Daytime Sleepiness (EDS) despite regular use of nCPAP, and patients having refused this therapy. Randomized, double blind study with BF2.649 (5-, 10-, 20-, 40- mg/d), or placebo.	
International Coordinating investigator	Prof Patrick Lévy, MD CHU, BP217, 38043 Grenoble Cedex 9, France	
Study centre(s):	19 centers: 7 in Tunisia, 2 in Argentina, 2 in Chile, 8 in France	
Publication (reference):	None	
Study period (years):	Date of first patient enrolled: October 22nd, 2010 Date of last patient completed: December 2nd, 2011	Phase of development: IIb
Objectives:	To define the minimum effective dose of BF2.649 between 5 mg, 10 mg, 20 mg, 40 mg or placebo in reducing the excessive daytime sleepiness of Obstructive Sleep Apnea patients	
Methodology:	This study consisted of a 1- to 2-week washout period, followed by a 2-week double-blind treatment period and a 1-week washout phase. After the first washout, patients who fulfilled selection criteria were randomized between 5 balanced treatment groups : placebo, BF2.649 5 mg OD, BF2.649 10 mg OD, BF2.649 20 mg OD, BF2.649 40 mg OD. Randomization was also balanced between patients receiving nCPAP and patients who did not.	
Number of patients/subjects (planned and analyzed):	Planned: 110 (10 per center; 22 per each treatment group) Analyzed: Extended Intent-to-Treat Set (EIT): 116 Intent-to-Treat Set (IT): 115 Per Protocol Set (PP): 110 Safety Set : 115 (IT Set)	

Name of sponsor / Company: Bioprojet	Individual Study Table Referring to Part of the Dossier	*(For National Authority use only)*
Name of finished product: Pitolisant	Volume: {x/x}	
Name of active ingredient: BF2.649	Pages:	

Diagnosis and main criteria for inclusion:	Inclusion criteria: Outpatients ≥ 21 years old; having been submitted to nCPAP therapy for a minimum period of 3 months, and still complaining of Excessive Daytime Sleepiness (EDS) despite the efforts made beforehand to obtain an efficient nCPAP therapy on EDS (group A) or patients with an OSA diagnosis confirmed by polysomnography and complaining of excessive daytime sleepiness, but refusing to be treated by nCPAP (group B); diagnosis of OSA confirmed by polysomnography or polygraphy (6 Channels) at the inclusion visit or during the last 6 months (under nCPAP therapy for patients of group A); Apnea-Hypopnea Index (AHI) ≥ 15 at the time of diagnosis; nCPAP ≥ 4 hours / day (compliance checked on the clock-time counter of the CPAP machine); Epworth score ≥ 11; BMI ≤ 40 kg/m²; Female patients of child-bearing potential using a medically accepted method of birth control, (i.e. oral contraceptives of normal average dosage ≥ 0.05 mg ethinyl-oestradiol) agreeing to continue this method throughout the study, and during the month following treatment discontinuation, being negative to the serum pregnancy test performed at the screening visit and visit V3; patients having agreed not to modify their lifestyle throughout the study (food habits, activity, and sleep habits); patients having signed the informed consent form. Non inclusion criteria: Chronic severe insomnia (but not due to OSA) in accordance with the International Classification of Sleep Disorders (ICSD 2005); Co-existing narcolepsy (ICSD 2005), judged on clinical criteria; sleep debt not due to OSA (according to physician's judgment); Non respiratory sleep fragmentation (restless legs syndrome…); Hypoventilation (severe COPD, important pulmonary fibrosis, chronic breathing insufficiency…); Surgery, mandibular orthosis; Shift work – Professional drivers; Refusal from the patient to stop any current therapy for excessive daytime sleepiness, or predictable risks for the patient to stop the therapy; Psychiatric disease; Current or recent (within one year) history of drugs, alcohol, narcotic, or other substance abuse or dependence; Severe co-morbid medical, or biological condition that may jeopardize the study participation, at the discretion of the investigator; Any significant serious abnormality of the cardiovascular system, e.g. recent myocardial infarction, angina, hypertension or dysrhythmias (within the previous 6 months), Electrocardiogram Bazett's corrected QT interval higher than 450 ms, history of left ventricular hypertrophy or mitral valve prolapse; Positive β HCG pregnant test or breast-feeding women; Women with child-bearing potential and no efficient birth-control method; Patient unable to understand the study protocol; Suspected or known hypersensitivity to study medication; use of prohibited treatments; Participation in another study, or being in a follow-up period in another study; Positive serology tests (optional) – HCV – HBsAg and HIV
Test product:	BF2.649 (pitolisant)
Dose:	5-, 10-, 20-, 40- mg/d
Mode of administration:	Per os
Batch number:	CPM7476 (5 mg), CPM7477 (10 mg), CPM7478 (20 mg), ID2020 (40 mg)
Duration of treatment:	14 days
Reference therapy:	Placebo
Dose:	NA

Name of sponsor / Company: Bioprojet	Individual Study Table Referring to Part of the Dossier	*(For National Authority use only)*
Name of finished product: Pitolisant	Volume: {x/x}	
Name of active ingredient: BF2.649	Pages:	
Mode of administration:	Per os	
Batch number:	ID2019	
Criteria for evaluation:	Efficacy: Primary endpoint: Epworth Sleepiness Scale (ESS) scores change between the treatments groups, during 14 days. Secondary endpoints: Percentage of Epworth responders (patients in whom the absolute value of ESS is ≤ 10, or the difference corresponding to ≥ 3 between the baseline and the end of the double blind study phase); Mean number of diurnal sleep or sleepiness episodes (reported in the patients diary); CGI Scale. Safety: Adverse events, treatment-emergent or not, occurred throughout the observation period (from V1 until one week after the last visit V4); ECG parameters; Laboratory blood tests (hematology, biochemistry, βHCG, optional serological tests HIV, HCV, HBsAg) .	
Statistical methods:	For the main efficacy criterion: Linear Mixed Effects Model adjusted on baseline, treatment group and center (SD2L and superiority). For the secondary efficacy criteria: logistic regression model adjusted on baseline and treatment group (ESS responders), quasi-Poisson regression model adjusted on baseline and treatment group (DSAR), linear mixed effects model adjusted on baseline, treatment group and center (CGI-C)	
SUMMARY – CONCLUSIONS:		

Name of sponsor / Company: Bioprojet	Individual Study Table Referring to Part of the Dossier	*(For National Authority use only)*
Name of finished product: Pitolisant	Volume: {x/x}	
Name of active ingredient: BF2.649	Pages:	

Efficacy:

Overall, 116 patients were included and 110 completed the study (Figure 2). One randomized patient was not taken into account for the efficacy intent-to-treat analysis as he did not take any study treatment (Figure 3).

The five treatment groups were comparable with regard to the baseline demographic characteristics (age, weight, height, BMI, sex ratio; p>0.05 for each parameter; Table 8).

They were also comparable regarding baseline characteristics of OSA (proportion of patients receiving nCPAP, mean time elapsed since OSA start, number and duration of daytime sleep and sleepiness episodes, number of nocturnal awakening episodes, duration of sleep, ESS score, CGI-S score; Table 9). Patients had an average of 4 daytime sleep and sleepiness episodes in all groups with a mean duration comprised between 58 and 95 minutes (p=0.507). Mean total duration of sleep was 7 hours. Patients had a mean number of nocturnal awakening episodes comprised between 2 and 3.5 (p=0.595) with a mean duration between 26 and 38 minutes (p=0.882). Mean baseline ESS score was between 15 and 16 and was not statistically significantly different between groups (p=0.385).

The proportion of patients with a good compliance (intake of 80% to 120% of prescribed treatment) in each treatment group ranged from 78% (BF2.649 5 mg OD group) to 96% (placebo and BF2.649 20 mg OD groups). Compliance was not statistically significantly different between groups (p=0.313; Table 12).

The primary analysis (linear contrast performed with adjusted ESS final scores (V3) of the five treatment groups) showed that BF2.649 decreased daytime sleepiness and that its efficacy statistically significantly increased with the dose (p=0.0003; Table 14). The minimal effective dose of BF2.649 on primary endpoint was 10 mg OD. The mean difference in adjusted ESS score between BF2.649 and placebo increased proportionally with the BF2.649 dose up to 20 mg OD (Table 15): -2.74 (95%CI [-5.40; -0.08]; p=0.0218) with BF2.649 5 mg, -3.51 (95%CI [-6.15; -0.86]; p=0.0050) with BF2.649 10 mg and -5.41 (95%CI [-8.13; -2.70], p=0.0001) with BF2.649 20 mg. The mean difference between BF2.649 40 mg and placebo was also statistically significant (-4.49; (95%CI [-7.23; -1.75]; p=0.0008) but the 40 mg dose did not seem to have any additional effect over the 20 mg dose in this study.

ESS responders rate was statistically significantly increased after 2 weeks of treatment with any dose of BF2.649 in comparison to placebo and the effect seemed to increase with the BF2.649 dose up to 20 mg OD (RR=2.0 with BF2.649 20 mg and 40 mg OD versus placebo, p<0.05 each; Table 16).

DSAR was statistically significantly decreased after 2 weeks of treatment with any dose of BF2.649 except 5 mg OD in comparison to placebo (Table 16).

CGI-C score was statistically significantly decreased with BF2.649 20 mg and 40 mg OD versus placebo, with a mean difference of -0.85 with BF2.649 20 mg OD (95%CI [-1.52; -0.19], p=0.0107) and -1.23 with BF2.649 40 mg OD (95%CI [-1.91; -0.55], p=0.0005; Table 16).

In summary, the minimal effective dose of BF2.649 on ESS score (primary endpoint), as well as ESS responders rate, DSAR and CGI-C (secondary endpoints) was 20 mg OD. In this study, the 40 mg OD dose did not seem to have any additional effect on most endpoints.

Name of sponsor / Company: Bioprojet	Individual Study Table Referring to Part of the Dossier	*(For National Authority use only)*
Name of finished product: Pitolisant	Volume: {x/x}	
Name of active ingredient: BF2.649	Pages:	

Safety:

In this study, after a 1- to 2-week washout period, patients were randomized to receive either placebo (n=24) or BF2.649 5 mg (n=23) or 10 mg (n=24) or 20 mg (n=23) or 40 mg (n=22) OD for two weeks. One patient allocated to the BF2.649 40 mg OD group decided to withdraw after the inclusion visit and never took the study drug. All patients of placebo and BF2.649 10 mg groups completed the 2-week treatment period. More than 90% of patients of the other groups who took at least one dose of study drug completed the active treatment phase (BF2.649 5 mg: 91.3%; BF2.649 20 mg: 95.7%; BF2.649 40 mg: 90.5%; Table 17). Five patients prematurely discontinued the study drug: 2 patients after 3 days of treatment (both in the BF2.649 5 mg group), 2 after 4 days (1 patient in the BF2.649 20 mg group and 1 patient in the BF2.649 40 mg group) and 1 after 5 days (BF2.649 40 mg group).

Overall, 55 patients (47.4%) reported a total of 116 TEAEs during the study: 45.8% of patients in the placebo group, 33.3% in the group receiving BF2.649 10 mg and between 52 and 55% in the three other BF2.649 groups (Table 18). At least 75% of TEAEs reported in each treatment group were mild to moderate (Table 21) and 23.3% only were considered likely related to the study drug (Table 19). All patients with severe TEAEs recovered except 2 in the group receiving BF2.649 20 mg OD dose and 1 in the group receiving placebo (Table 22). No TEAE considered likely related to the study drug was ongoing at the end of follow-up, i.e. one week after study drug discontinuation (Section 14, Table 42).

The most frequently reported preferred term with BF2.649 was “Headache” (20.7% of patients randomized in BF2.649 groups versus 20.8% in the placebo group), followed by “Insomnia” (13.0% of patients in BF2.649 groups versus 8.3% in the placebo group) and “Nausea” (7.6% of patients randomized in BF2.649 groups versus none in the placebo group; Table 20). The other events described in the BF2.649 groups were sporadic and reported in 1 or maximum 2 patients. Most headaches were mild to moderate (15/19 of headaches reported in the BF2.649 groups, 5/5 in the placebo group), as well as insomnia (10/12 in the BF2.649 group, 2/2 in the placebo group). All nausea were mild to moderate (Section 14, Table 40).

No serious AE (including death) was reported in this study (Table 19).

Five patients (4.3%) receiving BF2.649 experienced non serious AEs that led to treatment discontinuation (patients 01011, 03003, 09003, 09005, 09008; Tables 19 and 23): 2 in the 5 mg group, 1 in the 20 mg group and 2 in the 40 mg group. Except insomnia which was severe, all the other AEs were mild to moderate and were either considered unlikely (fever, headaches), possibly (muscle pain, nausea, enterocolitis) or likely (insomnia, headache, vertigo) related to the study drug. They all resolved with the administration of adequate treatment or after study drug discontinuation.

Laboratory parameters were within the normal limits in almost all cases (Section 14, Tables 43 and 44). When abnormal results were observed, they were most of the time not clinically significant or probably due to the current or concomitant diseases. Few cases of mild increase of triglycerides, AST/ALT and total cholesterol were described after two weeks of treatment (Section 14, Listing 1) that could be explained by concomitant disease or treatment or that were already observed before the study drug initiation. All the values returned to normal at control performed one week after the end of study treatment.

No clinically significant change was observed in vital signs (Table 24) and ECG parameters (Table 25 and Section 14, Listing 2).

Conclusion:

In conclusion, BF2.649 given at doses of 5, 10, 20, or 40 mg OD decreased daytime sleepiness assessed with ESS score and the effect statistically significantly increased with the dose (p=0.0003, Step-down Type 2 Linear Contrasts). The increase was linear up to the 20 mg OD dose. The minimal effective dose of BF2.649 on ESS score (primary endpoint), as well as ESS responders rate, DSAR and CGI-C (secondary endpoints) was 20 mg OD. The 40 mg OD dose did not seem to have any additional effect on most endpoints. BF2.649 was well tolerated in this population of patients with Obstructive Sleep Apnea and Excessive Daytime Sleepiness.

Date of report: 23 April 2013

N° EudraCT: 2010-019413-25