SYNOPSIS

Name of sponsor / Company: Bioprojet	Individual Study Table Referring to Part of the Dossier	*(For National Authority use only)*
Name of finished product: **Name of active ingredient:** BF2.649	Volume: {x/x} Pages:	
Title of the study:	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 (**Harmony II**)	
Investigators: **(or Coordinating investigator)**	Professor Claudio BASSETTI (coordinator) Neurology Department, UniversitätsSpital Zürich Neurologische Klinik und Poliklinik Frauenklinikstrasse 26, CH 8091 Zürich Tel.: +41 43 255 5503, Fax: +41 43 255 4649	
Study centre(s):	Multi-centre study, 27 centres in 4 European countries: France (13), Germany (9), Hungary (4), The Netherlands (1)	
Publication (reference):	None	
Study period (years):	Date of first patient enrolled: 15 October 2009 Date of last patient completed: 28 June 2010	Phase of development: II
Objectives:	Main objective: To evaluate and compare the efficacy and safety of escalating doses of BF2.649 and BF2.649 add on modafinil on cataplexy attacks. Secondary objectives: To evaluate the additive/synergistic effect and safety 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.	
Methodology:	Prospective, randomized, double-blind, parallel-group, multi-center study	
Number of patients/subjects (planned and analyzed):	Planned: 40 (20 patients per group) Analyzed: Full Analysis Set (FAS): 14 (9 in BF + PL group and 5 in BF + MD group) Safety Set : 14 (9 in BF + PL group and 5 in BF + MD group)	

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Diagnosis and main criteria for inclusion:	Inclusion criteria: patients aged 18 years and over, suffering from narcolepsy with cataplexy (according to International Classification of Sleep Disorders 2) for more than 3 months, not taking any treatment for EDS and cataplexy for more than 3 months, with at least 5 partial or total cataplexy attacks per week during a 14-day baseline period and Epworth Sleepiness Scale (ESS) score≥ 14/24 at the end of baseline period (V2). Non inclusion criteria: use of BF2.649 or any previous investigational drugs within 30-day period prior to initial screening visit (V1), patient unable or unwilling to temporarily discontinue non authorized drugs or substances, current or recent (within one year) history of a substance abuse or dependence disorder including alcohol abuse as defined in DSM-IV, significant serious abnormality of the cardiovascular illness (i.e: recent myocardial infarction), severe hepatic impairment, severe renal impairment, psychiatric and neurological disorders, prior severe adverse reactions to CNS stimulants, known hypersensitivity to the tested treatment including active substance and inactive excipients, other active clinically significant illness, congenital galactosemia, glucose-galactose malabsorption or lactase deficiency.	
Test product:	BF2.649 / Placebo of modafinil	
Dose:	10, 20 or 40 mg per day (dose titration)	
Mode of administration:	Per os	
Batch number:	31 89 401 / MA111048 and MA111092	
Duration of treatment:	8 weeks	
Reference therapy:	BF2.649 / modafinil combination	
Dose:	BF2.649: 10, 20 or 40 mg per day (dose titration) Modafinil: 200 mg/d	
Mode of administration:	Per os	
Batch number:	31 89 401 / M0076	
Criteria for evaluation:	Efficacy: Primary endpoint = Change from baseline in weekly cataplexy attacks number. Secondary endpoints = daytime somnolence (Epworth Sleepiness Scale); duration and severity of each cataplexy attack; number and duration of diurnal involuntary sleepattacks 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; Maintenance of Wakefulness Test; Sustained Attention to Response Task; 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. Pharmacokinetics: plasma concentration of BF2.649 and its main metabolite BF2.951	

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	Safety: Adverse events; cardiovascular safety; blood laboratory tests	
Statistical methods:	For the main efficacy criterion: Main Confirmatory test: The significance of the association of BF2.649 and modafinil compared with BF2.649 and placebo of modafinil was assessed by a test of Analysis of Covariance on Final NCC adjusted for baseline corresponding NCC_0. Analysis of Covariance was conducted according to a Mixed Linear Model taking into accountCenter heterogeneity. For the secondary efficacy criteria: A descriptive analysis for each response variable was performed for each treatment group separately. Treatment comparisons were performed via ANCOVA, where baseline adjustement on associated baseline values was conducted where appropriate. For MWT and SART, the significance of treatment difference was tested according to non- parametric test (e.g. Mann-Whitney Test or Median Score Test), as from previous studies, the measured endpoint could not be considered as distributed according to a normal distribution.	

SUMMARY – CONCLUSIONS:

Efficacy:

Overall, 15 patients diagnosed with narcolepsy with cataplexy were screened and 14 were randomized, 9 in the BF2.649 alone group and 5 in the BF2.649/modafinil combination group. Demographic and baseline narcoleptic characteristics were similar between groups. The two groups were also comparable for significant medical history.

The mean compliance was more than 95% in the 2 groups.

Circulating levels of BF2.649/BP2.951 in human serum showed a significant exposure of subjects receiving BF2.649 per os (Table 9) and no apparent clearcut modification when associated with modafinil.

BF2.649 alone decreased the weekly number of cataplexy episodes by 56% in patients suffering from a large number of crises per week. When co-administered with modafinil, this effect was even slightly superior (71% decrease) despite a higher attack frequency (Table 7) and a higher BMI at baseline in this group.

Daytime somnolence assessed with ESS score was reduced with BF2.649. This effect was enhanced when BF2.649 was associated with modafinil (Table 8). However the number of patients whom ESS was normalized at the end of treatment was 3 out of 9 in the group BF2.649 and placebo, and 1 out of 5 patients in the group BF2.649 and modafinil. An improvement of the wakefulness maintenance tests at the end of treatment in comparison with baseline was observed in both groups for the SART and, in a marked manner, for the MWT in the group BF2.649 + modafinil.

Among the workable results, we can observe the CGI-C for EDS and cataplexy.

Comparisons between the two groups were not statistically significant, maybe due to the too small number of patients included, smaller than initially planned.

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Safety:

All patients of the BF2.649 alone group completed the 8-week treatment period, 2 of them (22.2%) with a stable dose of 20 mg/d and 7 (77.8%) with a stable dose of 40 mg/d during five weeks. Three patients (60.0%) of the BF2.649/modafinil group completed the study with a stable dose of 40 mg/d. The remaining two patients of this group (40.0%) prematurely discontinued the trial after 2 and 3 weeks of treatment, before stable dose could have been determined.

Treatment with BF2.649 either with or without modafinil was well tolerated. Half of patients experienced at least one AE, but these AEs were mild or moderate, none was serious, and all patients recovered. AEs occurred generally during the first 14 days of treatment. The most frequent reported preferred term was "headache".

Two patients (14.3%) prematurely discontinued the trial drug, both in the BF2.649/modafinil group, due to non serious mild to moderate AEs that occurred between 8 and 10 days after treatment onset. Study drug was stopped 14 and 21 days after initiation and both patients recovered.

Five AE (abnormal behaviour, sleep attacks, dyssomnia, headache, hunger), some of which likely related to the investigational treatment were reported in 3 patients (21.4%; 1 patient in BF2.649/modafinil combination group and 2 patients in BF2.649 alone group). They all recovered, either spontaneously, or after dose decrease or permanent discontinuation.

There were no clinically relevant changes in vital signs (blood pressure and pulse rate), biochemistry and haematology measurements between baseline and end of treatment in both groups. ECG did not show any relevant change in both groups.

Conclusion:

Despite the low number of patients, this "proof of concept" study suggested the potential of Pitolisant as an anticataplectic agent and confirmed its effect on EDS; it also suggested the feasibility of associating Pitolisant and Modafinil, two drugs with distinct mechanisms of action. Safety results were in line with those reported in previous studies and did not reveal any new concern.

Date of report: 04 October 2011

N° EudraCT: 2008-007845-29