SYNOPSIS

Name of sponsor / Company: **BIOPROJET**	Individual Study Table Referring to Part of the Dossier	*(For National Authority use only)*
Name of finished product: **BF2.649**	Volume: {x/x}	
Name of active ingredient: **Pitolisant**	Pages:	
Title of the study:	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 I")	
Investigators: **(or Coordinating investigator)**	Prof. Dr med. Claudio L. Bassetti Professore di Neurologia, Universitätsspital, Zürich Ospedale Civico, Via Tesserete 46, 6903 Lugano Tel.: +41 91 811 6257, Fax: +41 91 811 6219 E-mail : claudio.bassetti@eoc.ch	
Study centre(s):	Countries: France (13 sites) , Germany (9 sites), Hungary (4 sites), The Netherlands (1site) and Switzerland (4 sites), Out of 31 selected investigational sites, 24 were active and recruited patients.	
Publication (reference):	No publication.	
Study period (years):	Date of first patient enrolled: 26 MAY 2009 Date of last patient completed: 30 JUN 2010	Phase of development: III
Objectives:	1. 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 and to modafinil by objective and subjective measurements including ESS, MWT, Sustained Attention to Response Task (SART), Clinical Global Impression of Change and Severity for EDS and cataplexy, quality of life questionnaire (EQ-5D), patient's global opinion, sleep diaries, physical examination including vital signs, laboratory tests, ECGs and adverse reactions 2. Investigate the response to withdrawal of BF2.649 after 8 weeks daily medication and one week of placebo.	

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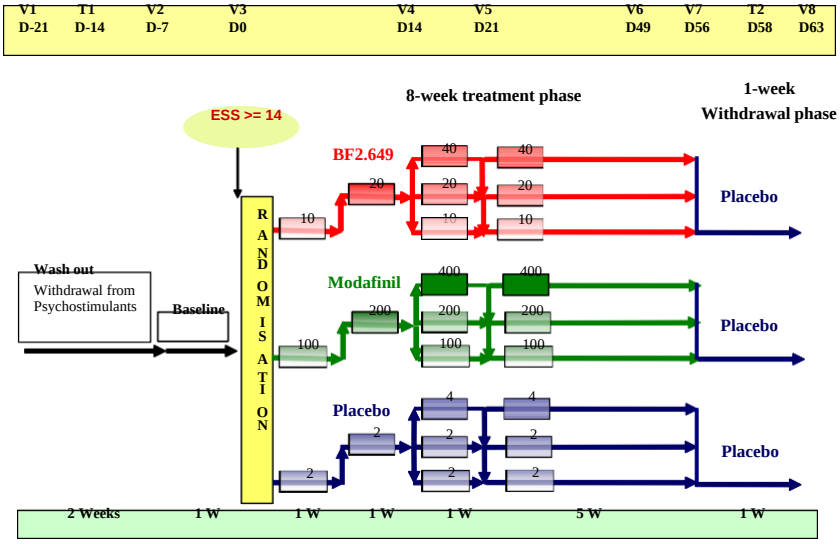
Methodology:	This was a prospective, randomized, double-blind study, placebo-controlled, parallel-group, multi-center trial assessing the effects of BF2.649 in the treatment of excessive daytime sleepiness (EDS) in narcoleptic patients with or without cataplexy. Enrolled patients using psychostimulants discontinued treatments for EDS (modafinil, amphetamine, and amphetamine-like CNS stimulants, methylphenidate or any other medications used for the treatment of EDS) during a period of a least 14 days (from D-21 to D-7, see figure 1) prior to the baseline visit (V2). If no stimulants were used, patients entered the baseline period (V2) without delay. If patients had been taking stable doses of authorized anticataplectic or purported anticataplectic treatment for at least 1 month prior to the screening visit, they were allowed to continue to receive such treatments at the constant dose during the wash-out period; once the wash-out period was complete, no modification of dose was allowed throughout the trial period. The baseline period lasted 7 days. During this baseline period, the patients were not allowed to take any prohibited treatments. After the baseline period at V3, patients continuing to meet all inclusion criteria including ESS ≥ 14/24 were randomly assigned to one of three treatment groups: Group 1: BF2.649 group Group 2: Modafinil group Group 3: Placebo group The total treatment period was 8 weeks. 

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	At V4, doses were adjusted for each patient according to the assessment of investigators on the basis of efficacy and tolerance according to the following scheme: a. Patients not sufficiently improved in their symptoms and with a good tolerance took an increased dose ('high' dose; corresponding to 40 mg of BF2.649 or 400 mg of modafinil) for the following 7 days. b. Patients for whom the optimal dose level was estimated as reached continued at the same dose ('middle' dose; corresponding to 20 mg of BF2.649 or 200 mg of modafinil) for the following 7 days. c. Patients took a reduced dose ('low' dose; corresponding to 10 mg of BF2.649 or 100 mg of modafinil) for the following 7 days if the Investigator considered that tolerance was not good. At V5 (D21), a second dose adjustment may have been performed. No increase in dose was allowed at this visit and no changes in dose were allowed after this visit up to the endof the treatment phase. Based on the tolerance of the product at V5, the Investigator may have reduced the dose one level (i.e. treatment of patients on the 'high' dose could be reduced to the "middle' dose while treatment of patients on the 'middle' dose could be reduced to the 'low' dose). Patients then continued at their assigned stable dose for an additional 5 weeks. At V6 (D49), after the stable dose phase, a control visit was carried out. Thereafter, no dosage change was allowed until the end of the treatment period. Treatment was stopped at V7. During the 1-week withdrawal phase up to the final study visit (V8), all subjects received placebo.	
Number of patients/subjects (planned and analyzed):	Selected : 110 patients EIT population: 95 patients (placebo:30, BF2.649: 32; modafinil: 33) IT analysis: 94 patients (placebo: 30; BF2.649: 31; modafinil: 33) PP analysis: 79 patients (placebo: 25; BF2.649: 26; modafinil: 28)	

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Diagnosis and main criteria for inclusion:	Main inclusion criteria: 1) ≥18 years old 2) Narcolepsy with or without cataplexy 3) Free of drugs or had discontinued psychostimulants for at least 14 days at the start of baseline period. Patients with severe cataplexy were permitted to remain on their anticataplectic or purported anticataplectic medications at stable doses, except for tricyclic antidepressants. The authorized anticataplectic/purported anticataplectic treatment had to be administrated for at least 1 month prior to the trial, and these doses could not be changed throughout the trial (from V1 to V8). 4) Epworth Sleepiness Scale (ESS) score ≥ 14/24 during the baseline period Main non-inclusion criteria: 1) Use of BF2.649, modafinil or any previous investigational drugs within a 30-day period prior to the initial screening visit (V1). 2) Narcoleptic patients without cataplexy could not have had other conditions that could have been the primary causes of EDS 3) Current or recent (within one year) history of a substance abuse or dependencedisorder including alcohol abuse, as defined in the DSM-IV. 4) Psychiatric and neurological disorders 5) Prior severe adverse reactions to CNS stimulants. 6) Inability to continue daily activities safely without the use of treatment against EDS. 7) Cardiovascular disease, severe hepatic impairment, severe renal impairment, significant abnormality in the physical examination or clinical laboratory results, any clinically significant illness that would interfere with the completion of the study by the subject.	
Test product: Dose: Mode of administration: Batch number:	BF2.649 (Pitolisant) 10 to 40 mg per day Oral Batch 073 (10 mg) – Batch 072 (20 mg) Final product batch number (BF2.649, placebo and modafinil) : CLI 5817	
Duration of treatment:	56 days	
Reference therapy: Dose: Mode of administration: Batch number:	Modafinil 100 to 400 mg Oral Batch 075 (100 mg) - Final product batch number : CLI 5817	
Batch number:	Placebo Batch 071 - Final product batch number : CLI 5817	

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Main criteria for evaluation:	Efficacy: • Sleepiness in patients assessed evaluated at baseline and main endpoint using the Epworth Sleepiness Scale (ESS) questionnaire • Subjective evaluation of narcolepsy symptoms according to patient diaries • Maintenance of Wakefulness Test (MWT) and Sustained Attention to Response Task (SART) performed a total of four times at the inclusion visit (V3) and at the endpoint visit (V7 or the last on-study visit) • Severity of EDS measured by investigator using the Clinical Global Impression of Severity (CGI-S) at V2 and V3 • The frequency and severity of cataplexy were assessed before and at the end of treatment by the analysis of sleep diaries and in using the Clinical Global Impression of Change (CGI-C). • Quality of life measured using the European Quality of life questionnaire (EQ-5D) • Patient-rated global effect of treatment at V4, V5, V6, V7 and V8 • Sleep quality and narcolepsy symptoms based on sleep diary analysis: occurrence of abnormalities after treatment compared to baseline, including number of cataplexy attacks, number of hallucinations, number of sleep paralysis episodes, number and duration of diurnal sleepiness and sleep episodes, number and duration of nocturnal awakenings, duration of nocturnal sleep Safety: • Adverse and unexpected events, emergent or not, reported during the study (frequency, severity, relationship to study drug, incidence and occurrence) • Change of vital signs parameters (heart rate, blood pressure, body weight) from baseline values • Physical examination: abnormalities in each system class and change from baseline • ECG parameters: comparison between end-of-treatment period and baseline • Laboratory abnormalities • BDI $_{13}$ questionnaire • Questionnaire of amphetaùine like withdrawal syndrome during (DSM IV) and at the end of the weaning period were established at the end of the treatment period • Overall safety assessment by the Investigator	
Statistical methods:	Populations analyzed **EIT population:** all randomized patients, regardless if treatment was initiated and irrespective of their outcome. **IT population:** all randomized patients having taken at least one dose of drug and provided at least one value after baseline. **PP population:** all patients in the IT population who completed the study until at least V6, (i.e. having one value at V6 or V7) and without any major protocol deviation related to primary endpoint.	

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Demographics

Summarized for the IT Population. Groups were compared using a two-sided Student's t-test for quantitative variables Fisher's exact test for qualitative variables.

First primary efficacy criterion (EDS):

This primary analysis was the comparison, using a linear mixed effect model, of the difference in ESS at end of study between the pitolisant group and the placebo group, adjusted for ESS at baseline and using treatment and center as fixed and random effects, respectively. The ESS score at the end of study (ESSFINAL) was calculated as the summary mean of V6 and V7 visits values or as the ESS at the last visit for premature withdrawals (ESS*). The ESS* score was associated with the summary mean of the two last observation carried forward values, however, if no post-baseline value was available, then as ESSFINAL = ESSBL. As an alternative endpoint ESSMEAN was also calculated as the average of the non-missing available values of ESS during post-baseline (i.e. ESSV4, ESSV5, ESSV6, ESSV7, and/or ESS*).The main confirmatory analysis was conducted using a linear mixed effects model adjusted according to the ESSBL, with TREATMENT as a fixed effect and CENTER as a random effect.

By designating ESS final values of placebo, BF2.649 and modafinil adjusted for baseline by PL, BF, MD < respectively, we conducted a stepdown scheme starting with a first superiority test (H_{01}: PL = BF, H_{11}: BF < placebo). At the only condition that H_{01} was rejected, we conducted a second non-inferiority test (H_{02}: BF > MD+NI, H_{12}: BF < MD+NI), NI defined as the pre-determined non-Inferiority margin fixed to 2.

Secondary efficacy criteria:

A descriptive analysis for each response variable was performed for each treatment group separately. Two-way comparisons between treatment groups were planned via ANCOVA, with baseline adjustment according to associated baseline values where appropriate. Parameters involving duration of time, standard survival analysis were planned with adjustment according to baseline values where appropriate. For MWT and SART, the significance of treatment difference was tested using a Mann-Whitney test because previous studies showed that the measured endpoint is not normally distributed. The clinical relevance of the difference between a) placebo and BF2.649 and b) BF2.649 and modafinil was tested by calculating the proportion of patients for which the increase of the measured endpoint from V3 to V7 exceeded a pre-determined Minimum Clinical Relevance. The absolute risk difference (and 95%CI) was estimated.
Regarding cataplexy, we studied the significance of the differences between placebo, BF2.649 and modafinil, by comparing the geometric mean of the daily rate of cataplexy between the three treatments, and testing the ratio by a T-test on log-transformed values. We considered the population of patients having experienced at least one cataplexy episode during baseline or treatment periods (EXP). As these periods were short to estimate a low rate, for patients characterized by no episode during baseline or treatment periods, we imputed the daily rate by the worst case value defined by the reciprocal of thenumber of days of exposure, considered as the worst case estimate of the daily rate. We successively studied the mean cataplexy ratio and tested the significance of the effect of BF/placebo, modafinil/placebo and BF/modafinil. We repeated this analysis both on IT and EXP selection bases.

Several secondary analysis using a simple ANCOVA without a CENTER effect were computed:
1) ESSFINAL adjusted according to ESSBL,
2) ESSFINAL not adjusted according to ESSBL,
3) Relative difference between ESSFINAL and ESSBL (ESSFINAL – ESSBL/ESSBL),
4) ESSMEAN

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Statistical methods:	An unadjusted responder rate was calculated, where a patient was considered a responder if ESSFINAL did not exceed 10. Additional secondary analysis conducted with responder rate were as follows: 1) ESSBL adjusted odds ratio (OR) with CENTER as a random effect using logistic regression 2) CENTER adjusted OR using logistic regression 3) ESSBL adjusted Absolute Risk Difference (ARD) with CENTER as a random effect using Poisson regression 4) ESSBL adjusted ARD with CENTER as a random effect using Ordinary Least Squares The Inter-patient baseline variable may have had an effect on the studied endpoint: BMI, Gender, Age, and Illness duration. These four variables were entered in a stepwise model to identify, in a first stage, significant predictors of the studied endpoint without consideration of the treatment effect. In the second step, any significant predictors identified in the first step were added to the main analysis to test the treatment effect (i.e. LME with ESSBL as covariates, TREATMENT as a fixed effect, and CENTER as a random effect).	
	<u>Safety:</u> All statistical analyses for the safety evaluation were conducted for the IT population. A descriptive analysis was performed by treatment group. Specifically, AEs were classified by time of occurrence, intensity/seriousness level, relationship to treatment, andrecovery status. Patients were included, regardless if they withdrew from the trial or not. If an AE was reported with different intensities at the same visit, only the highest intensity was taken into account. Both number of events and number of patients experiencing at least one event were computed. Change from baseline were imputed for vital signs parameters (heart rate, blood pressure, body weight), physical exam and blood laboratory values (including abnormalities), cardiovascular safety, ECG parameters, sleep quality and narcolepsy symptoms. Intra-individual changes for ECG and blood laboratorytest parameters were provided and compared between treatment groups. Sleep quality and narcolepsy symptoms based on sleep diary analysis: occurrence of abnormalities after treatment compared to baseline: number of cataplexy attacks, number of hallucinations, number of sleep paralysis episodes, number and duration of diurnal sleepiness and sleep episodes, number and duration of nocturnal awakenings, duration of nocturnal sleep Patients also filled Beck Depression Inventory (BDI-SF 13 items) at each endpoint to be able to check patient's mood and eliminate any severe depression or risk of suicide. Finally, patients answered a questionnaire on withdrawal symptoms (DSM-IV) after one week of placebo wash out, at the end of the study, during the last visit. A withdrawal syndrome is defined by the presence of dysphoria and of at least two other evaluated symptoms.	

SUMMARY – CONCLUSIONS:

This first Phase III study of pitolisant in narcolepsy confirms the data previously obtained in both a faithful model of the disease (the orexin -/- mouse) and in two previous POC studies: the drug significantly reduces the two major symptoms of thedisease i.e. diurnal sleepiness and cataplexy (the latter experienced by 25 patients treated by BF2.649, 27 patients treated by modafinil, and 24 patients treated by placebo).

The main endpoint was the Epworth Sleepiness Scale score measuring EDS and, when compared to placebo, improvement at the end of treatment elicited by BF2.649 was significantly superior to that in the placebo group ($P < 0.05$), whatever the

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statistical method used (linear mixed effect model, adjusted for ESSBL and using treatment, center as fixed and random effects respectively). These results were confirmed by using linear mixed effect model without accounting for center effect. The changes in ESS were, for placebo: -3.4, for BF2.649: -5.8 and for modafinil: -6.9. i.e. a difference of 2.4 units with placebo, considered as clinically significant. The numbers of responders (ESS ≤ 10) were 13.3% (n=4) for placebo, 45.2% (n=14) for BF2.649 and 45.5% (n=15) for modafinil. Among the 31 patients treated by BF2.649, 8 had remained at a stable dose of 20 mg and the change in their ESS was – 9.1 ± 5,8; 62,5% of them being found "responders".

The values of BF2.649 and modafinil did not differ significantly. The mean change in the two active treatments was almost the same and characterized by a mean difference between both treatments of 0.09 (95%CI -2.11 to 2.30), thus the non inferiority of BF2.649 compared with modafinil failed to be demonstrated.

The analysis of results on the secondary criteria shows a decrease in cataplexy crises frequency as evaluated from the sleep diaries. The treatment groups were compared in estimating the Cataplexy ratio Rate (RR) between any two groups, defined as the ratio of their cataplexy rates, for the Exposed population, i.e. patients having at least one occurrence of cataplexy crisis at baseline or during treatment (imputation was performed for patients with no event at one of these periods). The cataplexy ratio (BF2.649 – placebo) was significantly different in favour of BF2.649 in comparison with placebo: RR (placebo, BF2.649) = 0.38, with a 95%CI [0.15, 0.93], this result found significant (p=0.034). In contrast, the cataplexy rate in the modafinil group did not differ significantly from that of the placebo group (RR=0.70; 95%CI [0.297; 1.629]; p=0.396) and tended to be less reduced than that of the BF2.649 group but this latter difference did not reach the level of significance (p=0.138). This means that BF2.649 is characterized by a significant reduction of the rate of cataplexy compared with placebo.

Except for cataplexy, the few occurrences of each parameter collected in the patient's sleep diaries did not allow any formal comparison between treatment groups. Thus, only descriptive analysis is provided. However, for some parameters, a tendency to a better result with BF2.649 in comparison to placebo was observed. In agreement, the daily rate of diurnal sleep attacks was reduced between baseline and final periods in the BF2.649 (1.83 vs 1.32) and modafinil population (1.71 vs 1.32)whereas corresponding values in the placebo population were 1.52 vs 1.46. Among the secondary narcolepsy symptoms, hallucinations were reported by 39 patients; compared to baseline, the number of hallucinations was reduced by 80% at the end of BF2.649 treatment, by ~50 % at the end of modafinil treatment and not modified at the end of placebo treatment.

The results of the objective tests on wakefulness and attention represented by the MWT and the SART showed a difference of response between baseline and the end of treatment for the active drugs. Treatment with either BF2.649 or modafinil increases sleep latency in the MWT whereas it decreases in the placebo group.These results are statistically significant in the Intent-to Treat (IT) as well as in the Per Protocol analyses when BF 2.649 is compared to placebo.

In the IT population, the values of SART NOGO and TOTAL error scores at Final and Basal were similar in the placebo group but decreased in the BF2.649 group, the difference between these two groups being significant (p=0.042 and 0.041 for the NOGO and TOTAL scores respectively); these values also decreased similarly in the modafinil group, the difference withthe BF2.649 group being not significant (p=0.780 and 0.363 for the NOGO and TOTAL scores respectively). Similarchanges was found with SART GO scores but failed to reach statistical significance. Same conclusions was reached with the PP population.

Taken together, the various analyses of the two "vigilance" tests (MWT and SART) indicated an improvement under the two active drug treatments with no significant difference between them.

After 2 weeks of treatment, the Investigators reported any improvement in EDS - in scoring the CGI-C for EDS "minimally improved", "much improved" or "very much improved"- for 13 (43.3%) patients in the placebo group, for 24 (80.0%) patients in the BF2.649 group, and for 25 (80.6%) patients in the modafinil group (p=0.002). These percentages were approximately the same at the end of treatment (p=0.053).

In the same way, the Investigators reported an improvement on cataplexy after 2 weeks of treatment, with "CGI-C for cataplexy" in 10% patients (3) in the placebo group, and 26.7% (8) patients under BF2.649, and 9.7% (3) patients under modafinil. These percentages were higher at the end of treatment: 24.0% (6) in the placebo group, 34.6% (9) in the BF2.649

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group, and 28.6% (8) in the modafinil group. If we consider only the patient population with cataplexy during the trial, at the end of treatment (at V7) the results on CGI-C Cataplexy are "improved" in 28.6 % (6) for placebo, 45.0% (9) for BF2.649 and 34.8% (8) for modafinil group.

At the end of treatment, the mean EQ-5D score was increased by 6.2 points compared to baseline in the placebo group, while it was increased of 8.5 points in the BF2.649 group and 13.9 points in the modafinil group, i.e. on average, patients had a better quality of life after treatment (EIT and PP analysis).

The patient's opinion on the effectiveness of treatment over the study showed an improvement in 14 (56%) patients in the placebo group, 21 (80.8%) patients in the BF2.649 group, and 24 (85.7%) patients in the modafinil group**.**

Safety:

Safety was evaluated on the population that received at least one dose of investigational dose (N = 94).

No death was reported. No SUSAR was reported. Five (5) SAEs occurred: 1 in the placebo group, 2 in the BF2.649 group, and 2 in the modafinil group. All SAEs were considered by the Investigator as unlikely to be related to the investigational treatment.

Fourteen (14) events reported to be severe occurred during the treatment period. Among them, six (6) were related to the study treatment: one (1) in the BF2.649 group (abdominal discomfort), and five (5) in the modafinil group (abdominal pain, abnormal behaviour, drug withdrawal symptoms, lymphadenopathy, inner ear disorder).

More than 90% of all AEs that occurred during the treatment period (TEAE) were reported as mild to moderate in intensity and overall 36% were considered by the Investigator as unrelated to investigational treatment (unlikely). Approximately 90% of all events were reported as resolved or resolving by the end of the study. There were no clinically relevant differences between event intensity and resolution across the three treatment groups. There were also no clinical relevant differences between resolution and relatedness to treatment across the three groups

The most frequent AEs reported in BF2.649-treated patients were headache (n=11), insomnia / nausea /weight increase / cold (n=2). In modafinil-treated patients they were abdominal pain / anxiety / cold (n=2), diarrhoea (n=4), dizziness (n=3), headache (n=5). In placebo-treated they were headache (n=6).

Regarding the potential for drug abuse development, no patient having received BF2.649 displayed the DSM-IV "amphetamine like withdrawal syndrome" after the end of treatment whereas 3 patients (~10%) displayed it after the end of modafinil treatment.
Finally, not only the clinical, but also the biological, and cardiac tolerances were very good.

In conclusion, BF2.649 appears to be well tolerated and the AEs reported during the study that could be related to BF2.649 are mostly benign (headache, insomnia, nausea, cold, weight increase) and were already seen in the previous phase II studies.

Conclusion:

In conclusion, BF2.649, by its reduction of Excessive Diurnal Sleepiness, its decrease in the number of cataplexy episodes, and with a good tolerability, provides an interesting benefit-risk ratio for the treatment of major narcoleptic symptoms.

Date of report: October 2018

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