Synopsis

NAME OF COMPANY BIOPROJET 9, rue Rameau 75002 Paris **NAME OF FINISHED PRODUCT** BF2.649 **NAME OF ACTIVE INGREDIENT** NA	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE OF STUDY: Randomized, dose-finding study of BF2.649 5, 10, 20 and 40 mg/d in comparison to placebo in excessive daytime sleepiness in Parkinson's disease patients.

INVESTIGATOR/COORDINATOR:

France: Dr Isabelle Arnulf
Germany: Dr. Jen Carsten MÖLLER

STUDY CENTER(S):

Eighteen (18) centers in France and Germany.

PUBLICATION (REFERENCE):

Not applicable.

STUDIED PERIOD:

First Patient First Visit: 27 OCT 2007
Last Patient Last Visit: 09 JAN 2009

PHASE OF DEVELOPMENT: Phase IIb

OBJECTIVES:

The primary objective of this study was to determine the minimum effective dose (MED) of BF2.649 (5, 10, 20 or 40 mg/d over placebo) on the reduction of Excessive Daytime Sleepiness (EDS) in Parkinson's disease (PD) patients. The Epworth Sleepiness Scale scores (ESS) changes on the 4-week treatment period (from V2 to V4) were compared between treatment groups.

The secondary objectives were to compare between treatment groups from V2 to V4:

- the mean number of daytime sleep or sleepiness episodes
- the total duration of nocturnal sleep time
- the Sudden Onset of Sleep (SOS)
- the changes in the scores of the Unified Parkinson's Disease Rating Scale (UPDRS) total score, motor score and activities daily living score
- the levodopa or dopamine agonist dosage changes initiated by the investigator
- the changes in the Clinical Global Impression Scale (CGI-S).

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METHODOLOGY:

This is a prospective, pivotal, multicenter, double-blind, parallel, randomized 4-week treatment study, comparing four doses of BF2.649 5, 10, 20 or 40mg/d versus placebo in 5 parallel balanced groups.

This study was designed with 4 visits:

- Selection visit (V1) without treatment: from V1(D-7 to D-14) to V2 (D0)
- V2 (D0): Each patient was randomly assigned to one of the 4 dosage levels of BF2.649 or to placebo (it means assigned to one of the 5 treatment groups)
- V3 (D14): patients received the bottle labelled "Period 2"
- V4 (D28): no treatment disposition.

BF2.649 and placebo were provided to the patients in identical capsules dosed at 0, 5, 10, 20 and 40mg. After randomization, the patient was taken one capsule once a day (in the morning, before or during breakfast) of the randomized treatment. The duration of therapy was 28 days.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Total number of patients planned: 100

Total number of patients included: 135

Total number of patients analyzed: 107

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION:

Subjects who met all of the following inclusion criteria were eligible to participate in this study:

Adult outpatients of both sex older or equal to 18 years old with confirmed diagnosis of idiopathic PD defined by

- UKPD Society Brain Bank clinical diagnostic criteria
- Historical knowledge of positive response to levodopa or dopamine agonist test

Severity of PD

- Hoehn and Yahr < 5
- Fluctuator and non fluctuator patients

Stable treatment of PD for at least 4 weeks and 8 weeks for dopamine agonist

Excessive Daytime Sleepiness (EDS): Epworth scale ≥ 13

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Patients having accepted to participate in the study and signed the informed consent form

Patient with health insurance

Female patients with childbearing potential using a medically accepted method of birth control, agreeing to continue this method for the duration of the study and to be negative to serum pregnancy test performed at the screening visit

Patients accepting and having sufficient support (in the opinion of the investigator) to comply with the study requirements (tests, self- administered diaries completion, drug compliance, scheduled visits, car driving restriction if deemed necessary by the investigator…) and to maintain during the study their usual lifestyle (i.e. circadian rhythm, caffeine consumption, nocturnal sleep duration)

None psychostimulant treatment intake for 2 weeks (at V2).

EXCLUSION:

Subjects who met any of the following exclusion criteria were not eligible for participation in this study:

1. Other degenerative parkinsonian syndromes (supra nuclear paralysis, multisystemic atrophy, corticobasal degenerescence, diffuse Lewy's Body dementia)
2. Other condition than PD that can be considered the primary cause of EDS as:
   - Previous diagnostic of severe Obstructive Sleep Apnea Syndrome (OSA) requiring Continuous Positive Airway Pressure (CPAP) according to the investigator
   - Idiopathic narcolepsy and narcolepsy secondary to structural brain lesion
   - Severe chronic alcohol consumption, shift work, chronic or occasional sleep deprivation
3. Severe depression (Beck Depression Inventory BDI ≥ 16) or with suicidal risk (item G BDI > 0) or depression treated for less than 8 weeks
4. Pregnant or breast-feeding women
5. Patients having an occupation that requires night shift
6. History of drugs, alcohol, narcotic or other substance abuse or dependence

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7. Refusal from the patient to stop any current therapy for EDS or predictable risks for the patient to stop the therapy
8. Any significant abnormality in the physical examination or clinical laboratory results e.g. liver or kidney function deficiency
9. Any significant serious abnormality of the ECG e.g. recent myocardial infarction
10. Electrocardiogram Bazett's corrected QT interval (QT x √ [60/HR]) higher than 450 ms
11. Other active clinically significant illness which could interfere with the study conduct or contra- indicate the study treatments or put patients at risk
12. Dementia with MMS ≤ 24
13. Patients taking associated treatments which are not allowed during the study course and which cannot be stopped before the inclusion visit.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

BF2.649 and placebo are presented in identical capsules dosed at 5, 10, 20 or 40 mg.

Administration route: oral, once a day, before or during breakfast, with a glass of water.

Batch number: CPM 6806 for 10 mg tablets and CPM 6807 for 20 mg tablets.

DURATION OF TREATMENT:

One to 2-week baseline without treatment: from V1 to V2.

Four-week double blind period at fixed dosage:

- At V2, patients were randomized to one of the 4 dosages of BF2.649 or placebo. The treatment was initiated the day after V2 and was prescribed for 2 weeks,
- At V3, the treatment was continued and prescribed for two more weeks,
- At V4, this was the final visit (= the end of the treatment period).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Placebo is presented in capsule.

Administration route: oral, once a day, before or during breakfast, with a glass of water.

Batch number: CPM 6805 for placebo tablets.

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CRITERIA FOR EVALUATION:

EFFICACY:

Primary criteria:

The ESS scores changes on the 4-week treatment period (from V2 to V4) were compared between treatment groups.

Secondary criteria:

- Comparison of the mean number of diurnal sleep or sleepiness episodes between treatment groups from V2 to V4
- Comparison of the total duration of nocturnal sleep time between treatment groups from V2 to V4
- Comparison of the SOS between treatment groups from V2 to V4
- Comparison of the changes in the scores of the UPDRS total score, motor score and activities daily living score between treatment groups from V2 to V4
- Description of the Levodopa or Dopamine agonist dosage changes initiated by the investigator and comparison between treatment groups from V2 to V4
- Comparison of the changes in the CGI-S between treatment groups from V2 to V4

SAFETY:

- Monitoring of Adverse Events (AE) occurring during the study from V1 to V4
- Comparison of AE occurring during the study between treatment groups from V1 to V4 (comparison by organ class, type of event, severity and relationship to the study treatment)
- Description of ECG parameters, intra-individual changes and comparison between treatment groups at V1 and V4
- Description of blood parameters, intra-individual changes and comparison between treatment groups at V1 and V4

STATISTICAL METHODS:

EFFICACY:

The primary efficacy variable was the ESS's questionnaire total score (8 items) recorded at V1, V2, V3 and V4. The confirmatory analysis essentially dealt with Dose Response (DR) drug effect statistical assessment. Linear Contrasts probably constituted the most appropriate statistical technique enabling assessment of a monotonic increase of the measured endpoint for each dose.

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ITT population constituted the only population for the main analysis. However, these analyses were carried out on the following restricted populations:

a) Patients going until the normal end of the trial (thus for which ESS values at V4 were available)
b) Patients without protocol violation (ESS baseline <13, BDI>16, MMS>24, QT>450)
c) Patients without unauthorized medications
d) Patients verifying a+b+c

Confirmatory analysis was also carried out by adjusting for age and gender.

The secondary efficacy analysis consisted in presentation of:

- Number of diurnal episodes at Visit x and change
- Number of undesired sleep episodes at Visit x and change
- The evolution of number of diurnal and undesired sleep was presented in 3 categories:
  - Increase: the number increased by 5 % since the last visit
  - Stable: the number remained the same ± 5 % since the last visit
  - Decrease: the number decreased by 5 % since the last visit
- Full UPDRS's questionnaire. The evolution of Full UPDRS's sub scores was presented in 3 categories per treatment group and per visit:
  - Increase: increase of score > 2 points since the last visit
  - Stable: same score value ± 2 points since the last visit
  - Decrease: decrease of score < 2 points since the last visit
- The evolution of the CGI-S per treatment group and per visit:
  - Increase: increase of score > 2 points since the last visit
  - Stable: same score value ± 2 points since the last visit
  - Decrease: decrease of score < 2 points since the last visit
- The changes in the dosage of Levodopa and/or dopamine agonist (INN to be provided) compared per treatment group and per visit.

Classical statistical analyses were performed with SAS® Software version 9.1.3.

To describe quantitative variables by treatment group, discrete or continuous, the following statistics were computed, unless otherwise indicated: number, mean, standard deviation (SD), minimum, maximum, median, 95% confidence interval and missing values.

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To describe qualitative variables by treatment group, the following statistics were computed, unless otherwise indicated:

- Number, percentage and missing values
- Model checking
- When conducting any parametric tests, model assumptions such as assumed distribution in response variables, heteroscedasticity of variances and normality of error terms were verified visually using scatter, residual, and normal probability plots, respectively. If model assumptions were not met, data transformations (e.g. logarithmic) were employed. Should data transformations not render the theorized distribution, then appropriate non parametric tests were executed.

All tests were two-sided at 0.05 α level.

SAFETY:

All AE recorded (from V1 to V4) during the study were analyzed, listed and coded according to MedDRA version 11.0. The proportion of subjects with AE, overall, by SOC and by PT, was tabulated for each treatment group and compared between groups using Fisher's exact test. In addition, subjects with possibly related AE, serious AE, other significant AE, AE leading to discontinuation of the study medication and laboratory abnormalities AE were also tabulated.

It was assumed that AE with missing relationship was related to study drug when summarizing the incidence of related AE and that AE with unknown severity was not counted in thefrequency table by severity.

The following frequency distributions were provided: all AE by causality, severity, seriousness, outcome (including withdrawal from treatment or from study), by SOC, by decreasing frequency and by treatment group. Any significant abnormalities possibly related to the treatment were also listed by treatment group.

SUMMARY – CONCLUSIONS

A total of 135 patients were included in the baseline phase but only 108 patients were randomized and 107 patients belonged to the ITT population (one patient didn't take the study treatment and was excluded). The demographic characteristics were comparable in the 5 groupsof patients. Patients were aged from 42 to 87 years old, with a mean age of 65.4 ± 8.5 years old (median=66.9) (p=0,542). The length of Parkinson's disease was shorter in the placebo group (4.7±3.7 years) than in the others (from 6.4±3.6 years to 9.8±6.5 years; p=0.022).

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All the patients received at least one concomitant treatment for the Parkinson's disease; the most frequent were L-Dopa (81.3%), Pramipexole (34.6%), Ropinirole (19.6%); the daily dose for these main concomitant treatments was comparable between the different groups of treatment (p=0.227, p=0.418 and p=0.594 respectively). At the inclusion visit, the ESS describing the likelihood of dozing or falling asleep of the patients was comparable between the5 treatment groups [mean=15.7±2.8, median=15.0 (p=0.280)].

EFFICACY:

On an ITT basis, a significant monotonic increasing effect of dose on efficacy was found (linear contrast p=0.0176) thus higher was the dose, better was the efficacy. By using step-down contrasts, the **MED identified dose was the 20 mg dosage, p=0.0357.** This was observed at the median values, as well as the mean values**. At this dose of 20 mg the median ESS score change was of -5** (ITT analysis; p=0.069). Gender, treatments and CGI-S at baseline visit had no significant effect on the ESS score at the final visit. The **proportion of responders defined as patients with ESS score ≤ 10 at final visit was greater in those having received 20 mg of BF2.649 (42.9%)** than in the other treatment groups (19.0% with placebo, 36.4%, 18.2% and 33.3% with respectively 5 mg, 10 mg and 40 mg of BF2.649). The proportion of responders greater in patients having received 20 mg of BF2.649 was also observed whatever the associated concomitant treatments for the Parkinson's disease (dopamine agonist or L-Dopa).

At this **dose of 20 mg** the median change between the inclusion and the final visits of duration of diurnal somnolence and sleepiness episodes was reduced by 30 min compared to 15 min in the other groups; the number of diurnal somnolence and sleepiness episodes was decreased by 0.8 while the total duration of nocturnal sleep time was not changed as revealed by the data collected from the **sleep diary** (completed by the patients on the 5 days before each visit). The mean number of undesired sleep episodes decreased from 0.45 to 0.26 with 20 mg BF2.649 and the proportion of subjects with a stabilization or a decrease of undesired sleep episodes was greater among patients having received 20 mg of BF2.649: 82.8%.

Among the **secondary endpoints,** the *SOS (Sudden Sleep Onset Scale)* showed that 59.1% to 71.4% in the various groups of patients displayed this symptom at inclusion**.** At the final visit, whereas 57.1% of the placebo group patients still reported this symptom only 40%, 28.6%, 30% and 38.1% of the patients reported it in the 5mg, 10mg, 20mg and 40mg groups, respectively.

The change in full UPDRS assessing the Parkinson's disease symptomatology, between baseline and final visits didn't show any significant difference between the 5 treatment groups. However, this symptomatology was mild among the patients, all treated by antiparkinsonian drugs, and no aggravation, particularly of the motor symptoms including dyskinesia, was observed.; the proportion of patients having sleep discordance (item 41) decreased from 95.2% of patients at inclusion visit to 80.0% at final visit with 20mg of BF2.649.

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Finally, the proportion of patients with decrease of CGI-Severity was greater among those having received 20 mg of BF2.649: 42.9% compared to 27.3%-38.1% in other groups.

SAFETY:

The safety population included 107 patients among which 67 patients (62.6%) presented at least one AE during the study. The occurrence of AEs (141 in total) was comparable between the different treatment groups: 24 AEs in the placebo group versus 18 AEs, 31 AEs, 43 AEs, and 25 AEs in patients having received 5mg, 10mg, 20mg and 40 mg of BF2.649 respectively (p=0.592).
59 patients (55.1%) had at least one TEAE during the study and a total of 114 TEAEs were experienced by all patients, whatever the treatment group, and the proportions of TEAEs were comparable between the different treatment groups (p=0.172).
The most frequent TEAEs belonged to (1) nervous system disorders (26 TEAEs in 23 patients), principally Parkinson's disease and headache, (2) psychiatric disorders (21 TEAEs in 16 patients), principally insomnia and anxiety and (3) gastrointestinal disorders (18 TEAEs in 16 patients), principally nausea and upper abdominal pain.
The majority of TEAEs were classified as "mild" 50% (n=57) or "moderate" 38.6% (n=44) and their proportion was comparable between the different treatment groups in term of severity (p=0.221), seriousness (p=0.831), causality (p=0.112), or drug discontinuation (p=0.875).
Focusing on **expected TEAE**, defined as TEAE reported at least 3 times in the BF2.649 safety database whatever its relationship to the study drug, a total of 55 expected TEAEs werereported in 38 patients (35.5%) principally Parkinson's disease symptom aggravation (10 TEAEs in 9 patients), **insomnia** (8 TEAEs in 8 patients), **headache** (7 TEAEs in 6 patients) and**nausea** (6 TEAEs in 6 patients). Parkinson's disease aggravation was reported with the same incidence in all groups, including the placebo group in which was reported the only severe case,possibly related to the natural evolution of the disease.

The lab tests parameters didn't show any clinically significant change in the 5 treatment groups and results of ECG did not show any significant change and were comparable between the different treatment groups as SBP, DBP, pulse rate, physical examination and particularly no change of the QTc interval was found.
In conclusion, this study confirmed the good safety profile of BF2.649 in patients treated for Parkinson's diseases, without interference with the various antiparkinsonian drugs.

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CONCLUSION:

The study has disclosed a monotonic dose-response relationship on the primary endpoint, the ESS, i.e. on the reduction of excessive daytime sleepiness, with a MED at 20 mg. Although the tolerance was generally good, there was, however a rather large scattering of responses within patients in each group which speaks in favor of an individual dose titration regimen with 20 mg being the upper dose.

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