SYNOPSIS

Name of sponsor/Company: Bioprojet Name of finished product: BF2.649 Name of active ingredient: Pitolisant	Individual Study Table Referring to Part of the Dossier Volume: {x/x} Pages:	*(For National Authority use only)*
Title of the study:	Randomized, Multicenter, 12-Week, Double-blind, Placebo-Controlled, Study to Assess the Efficacy and Safety of BF2.649 in Excessive Daytime Sleepiness (EDS) in Parkinson disease, followed by a 9-month Open-Label Extension Phase.	
Investigators: (or Coordinating investigator)	Karla Maria Eggert, M.D. Klinik für Neurologie, Universitätsklinikum Rudolf-Bultmann-Strasse 8 35039 Marburg, Germany	
Study centre(s): 30	Neurologists, hospitals, multinational sites. Germany: 12 centers Sweden: 8 centers Czech Republic: 10 centers	
Publication (reference):	None	
Study period (March 2010 – August 2012):	Date of first enrolled patient: 10 March 2010 Date of last inclusion: 04 August 2011 Date of last completed visit: 10 August 2012	Phase of development: III
Objectives:	<u>Primary Objective</u> <u>To compare the efficacy of BF2.649 over placebo (Double-Blind Phase) and assess the long</u> term efficacy (Open-Label Extension Phase) of BF2.649 in the improvement of excessive daytime sleepiness, as measured by the change from baseline (V2) in the Epworth Sleepiness Scale (ESS) scores at Week 12 and confirm the long-term efficacy at Week 53, in patients diagnosed with Parkinson's disease <u>Secondary Objectives</u> – To evaluate diurnal somnolence and sleep episodes number and duration as reported in the patients' sleep diaries – To assess the evolution of the Fatigue Severity Scale Scores (FSS) – To evaluate the evolution of the Unified Parkinson disease Rating Scale (UPDRS)	

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	– To assess Quality of Life of Patients reported in Parkinson disease Questionnaire (PDQ-39) – To assess dopamine agonists dosage modification – To assess the evolution of the Clinical Global Impression on EDS as measured by the CGI scale scores. – To assess patients' depression as measured by the Beck Depression Inventory (BDI) score – To assess Patients' Apathy as measured by the Apathy Evaluation Scale (AES) To assess patient's sleep as measured by the Sudden Onset Sleep Scale (SOS) – To assess the product withdrawal effect at W13 and W54 by collecting the changes in signs and symptoms (increased appetite, increased sleepiness, excitability, changes in mood) and by assessing the modification of ESS, AES, FSS, PDQ-39, CGI , BDI and sleep diary after one week of product withdrawal. <u>Safety Objectives</u> To assess the safety of BF2.649 on a short term period (12-week double blind phase) and on a long-term period (40 weeks open label extension phase)	
Methodology:	Prospective, pivotal, multicenter, double-blind placebo controlled, randomized (ratio 2 BF2.649:1 placebo) 12-week study, comparing BF2.649 over placebo in two parallel groups followed by an optional 9-month open-label extension phase with BF2.649	
Number of patients/subjects (planned and analyzed):	Planned: 246 patients Double-blind phase Analyzed: Full Analysis Set: 273 ITT: 231 Safety Set : 231	Open-label extension phase Analyzed: Full Analysis Set (FAS): 135 ITT: 121 Safety Set : 121
Diagnosis and main criteria for inclusion:	<u>Inclusion criteria</u>: – Outpatients, male or female, aged 30 years and older – Patients with a documented history of Parkinson's disease according to	

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- UPDRS (Unified Parkinson disease Rating Scale), fluctuator and non-fluctuator patients, Hoehn and Yahr score < 5
- Patients stabilized on optimal antiparkinsonian treatments unmodified for 4 weeks prior to study entry
- Patients presenting an Excessive Daytime Sleepiness as indicated by an Epworth Scale Score ≥ 12
- Patients having a health Insurance Coverage (according to local regulatory requirements)
- Patients having signed an informed consent before any specific study procedures.

Non inclusion criteria:

- Patients with a known diagnosis of other degenerative parkinsonian syndromes (e.g. Progressive supra-nuclear palsy, multisystemic atrophy, corticobasal degenerescence, diffuse Lewy Body Dementia)
- Patients who have shift work, chronic or occasional sleep deprivation, circadian rhythm disorders
- Patients with a severe depression indicated by Beck Depression Inventory (BDI ≥ 16) or at suicidal risk (BDI item G > 0) or depression treated for less than 8 weeks
- Patients with a cognitive impairment as indicated by a Minimental Status Examination (MMSE) score less than 25 or with mental conditions rendering them unable to understand the nature, scope, and possible consequences of the study
- Female patients who has not been using an adequate contraceptive method for the last 2 months, or is pregnant or breastfeeding, or not at least one year post-menopausal or unwilling or unable to continue contraceptive use during the study
- Patients with a recent history of alcohol or drug abuse within the last three years prior to study entry
- Patients with a concomitant condition (including clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease) making either implementation of the protocol or interpretation of the study results difficult or which could interfere with the study

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	conduct or contra-indicate the study treatments or put patients at risk – Patients with a progressively fatal disease, or life expectancy ≤ one year – Patients with a known history of long QTc syndrome (e.g., personal or family history of syncope or arrhythmia) or presenting any significant serious abnormality of the ECG (e.g. recent myocardial infarction), QTc strictly higher than 450 ms (electrocardiogram Bazett's corrected QT interval (QT / √ [60/HR]) – Patients who have received any other investigational drug (including BF2.649) within 1 month prior to study entry, or have such treatment planned during the study period – Patients unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits, and are unlikely to complete the study – Patients with suspected or known hypersensitivity to, or suspected serious adverse reaction to the study medication – Patients with galactose intolerance, lactase deficiency or glucose-galactose malabsorption – Patients taking associated treatments which are not allowed during the study course and which cannot be stopped at least 2 weeks prior to study entry	
Test product: Dose: Mode of administration: Batch number:	BF2.649 5 mg, 10 mg or 20 mg once daily *Per os,* once a day before breakfast with a glass of water Double blind phase: E1247, E1249, E1309, E1310, E1323, E1339. (Active treatments and placebo were manufactured according to random code list. No distinction was performed regarding the final batch number). Open label extension phase: E1272, E1278, E1296, E1299, E1300, E1302, E1322, E1328, E1329, E1337, E1338, E1376, E1382, E1387.	
Reference therapy	Placebo	
Dose: Mode of administration: Batch number:	Not applicable *Per os,* once a day before breakfast with a glass of water Active treatments and placebo were manufactured according to random code list. No distinction was performed regarding the final batch number.	

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Duration of treatment:	Comparative phase: 12 weeks of BF2.649 treatment or placebo followed by 1-week washout with placebo Optional extension phase: 40 weeks of BF2.649 treatment placebo followed by 1-week washout without any treatment.	
Criteria for evaluation: Safety	Efficacy: **Primary endpoint:** 12-week double blind study period and 9-months open-label extension phase: Evolution of the Epworth Sleepiness Scale scores (ESS). Comparison between the change from baseline (V2) to week 12 of ESS score and the change from baseline (V2) to the mean of all ESS scores for the open label phase. The number and percentage of responders (ΔESS = 3 or ESS ≤ 10) was also provided. **Secondary endpoints:** 12-week double blind study period and 9-month open-label extension phase: – Mean number of diurnal sleep or sleepiness episodes and their duration and frequency of sleep attacks (patient diary recorded 3 days prior to visit days) – Full UPDRS – Levodopa & dopamine agonists dosage modification – Clinical Global Impression of change (CGI) – Quality of Life PDQ39 score – Beck Depression Inventory (BDI) score – Fatigue Severity Scale (FSS) score – Apathy evaluation scale (AES) score – Sudden Onset Sleep Scale (SOS) score – Product withdrawal effect at W13 and W54 by collecting the changes in signs and symptoms (increased appetite, increased sleepiness, excitability, changes in mood) and by assessing the modification of ESS, AES, FSS, PDQ-39, CGI, BDI, SOS and sleep diary after one week of product withdrawal. Safety: Monitoring of adverse events, Physical examination, Vital signs, ECG and	

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	Blood Laboratory tests modifications	
Statistical methods:	For the main efficacy criterion: The primary efficacy endpoint was the Epworth Sleepiness Scale score (ESS) change from baseline (V2) between the two treatment groups, during the 12 week double blind period and the sustained improvement of ESS from baseline (V2) at week 53 in the open label extension phase. The efficacy endpoint was the change from baseline (V2) to the end of therapy visit (V6 for the double blind phase) and the change from baseline (V2) to the mean of all ESS scores for the open label phase. In the double-blind phase changes from baseline (V2) were compared at V6 between the two treatment groups (BF2.649 versus Placebo) Moreover the number and percentage of responders were provided, defined as ΔESS = 3 or ESS ≤ 10. The number of responders was compared between treatment groups using a Chi-2 or a Fisher exact test. For the secondary efficacy criteria: The same analysis that was performed for the main efficacy criterion was performed at the other assessment times. • Patient Sleep Diary: Patients were required to record in the sleep diary every morning or evening, an estimate of the following events occurred over 24 hours throughout the 3 days preceding the scheduled visit: Number of diurnal involuntary sleep attacks and episodes of severe sleepiness (sleepiness that was severe enough to prevent the carrying out of an activity), Duration of diurnal involuntary episodes of severe sleepiness, the mean daily number of sleep attacks, the mean daily number of sleepiness or sleep episodes and the mean daily duration of sleep episodes were used as a means of evaluating diurnal sleepiness. For each visit of in the acute phase, the change from baseline (V2) to each visit was compared between treatment groups using a parametric or non parametric ANCOVA with treatment factor adjusted for baseline. In the open label extension period, any changes from baseline were described at each visit. • Fatigue Severity Scale Scores (FSS) : For each visit in the acute phase, the change in total score from baseline (V2) to each visit was compared between treatment groups using a parametric or non	

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parametric ANCOVA with treatment factor adjusted for baseline. In the open label extension period, any changes from baseline were described at each visit.

- Total and sub score of Unified Parkinson's disease Rating Scale (UPDRS) :The four subscores (parts I, II, III and IV), the total UPDRS score, the Hoehn and Yahr score (part V) as well as the Schwab and England ADL score weree described at each assessment time. Changes from the baseline (V1) were calculated. For the Hoehn and Yahr score, and the Schwab and England ADL score, changes were expressed in 3 categories (improvement, no change, worsening). In the acute period, changes from the baseline were compared between treatment groups using: For quantitative parameters: a parametric or non parametric ANCOVA with treatment factor adjusted for baseline. For ordinal parameters: a Cochran-Mantel-Haenszel (CMH) test adjusted for baseline. In the open label extension period, changes from the baseline were described at each visit.
- Apathy Evaluation Scale: For each visit in the acute phase, the change in total score from baseline (V2) to each visit were compared between treatment groups using a parametric or non parametric ANCOVA with treatment factor adjusted for baseline. In the open label extension period, any changes from baseline were described at each visit.
- Levodopa or dopamine agonist dosage regimen changes: In the Levodopa or dopamine agonist users the change of dosage was analyzed according to Parkinson disease evaluation. For each visit of the acute phase, values were compared between treatment groups using a Student's t-test or a Wilcoxon rank-sum test according to the normality of the distribution. For the extension period, dosages were described at each visit.
- Clinical impression of Change: The severity of EDS was measured by the investigator using the Clinical Global Impression of Severity (CGI-S) and of Clinical Global Impression of Change (CGI-C),

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respectively. The Clinical Global Impression of Severity encompasses the severity of EDS and Global Improvement items. At V1 (baseline before the treatment), the CGI-S was rated by the investigator by using a 6-grade scale ranging from “no sign of illness”, “borderline ill”, “slightly ill”, “moderately ill”, “markedly ill”, “among the most extremely ill patients”. At each post-baseline visit (V3, V4, V5, V6 and V7), the patients’ change in EDS compared to baseline values was rated by the same investigator using Clinical Global Impression of Change (CGI-C), a 7-grade scale ranging from “very much improved”, “much improved”, “minimally improved”, “no change”, “minimally worse,” “much worse” and “very much worse”. The severity of the patients' illness was measured at baseline by the investigator using the Clinical Global Impression of Severity (CGI-S) questionnaires. At each visit, the CGI of Change (CGI-C) was used to document the perceived change in the patient illness from baseline and was compared between treatments groups at W12 and at W53 for the open labelled treated population. The CGI-C was described at each follow-up visit. In the acute phase, a CMH test was performed to analyze the association between treatment and CGI-C after adjusting for CGI-S (at V1).

- Quality of Life (PDQ39) : The change in subscores (Mobility Activities of daily living, Emotional well-being, Stigma, Social support, Cognitions, Communication, Bodily discomfort) from baseline (V2) to each visit was compared between the two treatment groups in the acute period by a parametric or non parametric ANCOVA with treatment factor adjusted for baseline. In the open label extension period, changes from baseline were described at each visit.

- Beck Depression Inventory (BDI) score : The change in BDI total score from baseline (V1) to each visit was compared in the acute phase using a parametric or non parametric ANCOVA with treatment factor adjusted for baseline. In the open label extension period, changes from baseline were described at each visit.

- Sudden Onset Sleep Scale (SOS) score : The Sudden Onset Sleep

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	Scale (SOS), a self-reported questionnaire given to patients, differentiated between sleep attacks and unintended sleep episodes. SOS items were described at each follow-up visit. In the acute phase, the treatment groups were compared using: Nominal data: a Chi-2 test or Fisher exact test Ordinal data: a CMH test.	

SUMMARY – CONCLUSIONS:

Efficacy Results :

Among the 273 patients screened to take part in this study, 231 were included and randomized and received the investigational product at least once. The ITT population for the double-blind phase was therefore comprised of 231 patients with 182 patients per protocol. A total of 198 patients completed the double-blind phase. Of these, 135 patients were included in to the open-label extension phase, 121 of whom complied with the definintion of the ITT population with 107 patients per protocol. The mean age of patients at inclusion was 64.8 years the majority of which were male (69%). The mean duration of PD at baseline was similar in the BF2.649 group at 4.7 years (SD: 3.4) and in the placebo group at 5.1 years (SD: 3.7). According to clinical examination, the general condition of 79.2% of the patients was found normal at baseline. The ECG results of the patients were 100% and 98.7% normal in the placebo and BF2.649 groups, respectively. However, 56.8.8% and 55.6% of patients had normal haematology in the placebo and the BF2.649 group, respectively. Concerning blood biochemistry, 55.4% and 48.8% of patients had normal results in the placebo and the BF2.649 group, respectively.

Treatment compliance was similar during the double-blind phase at 100.4% and during the extension phase at 99.51%. The maximum dose of 20 mg/day of BF2.649 received by patients was 81.9% and 91.0% in the double-blind and open-label extension phase, respectively.

Efficacy criteria were analyzed in the blind-study phase on the ITT population (i.e. all patients who took at least one time the study treatment) and on the ITT population only during the study extension phase.

Efficacy of BF2.649 in comparison to the placebo in the double-blind phase

The primary objective of this study was to determine whether the study drug was more effective at reducing EDS in patients with Parkinson's disease than the placebo during the double-blind phase. The effectiveness of BF2.649 at reducing excessive daytime sleepiness was determined using Epworth Scale Scores. A decrease in the ESS score indicates that the patient is less affected by EDS. The primary efficacy criterion was the assessment and comparison (non-parametric ANCOVA) of the mean patient ESS scores from patients randomly assigned to either the placebo or the

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BF2.649 group. If the study drug were to induce a reduction in EDS then the mean ESS score of patients in the BF2.649 group would be expected to be significantly lower than the mean ESS score of patients in the placebo group. The change in the mean patient ESS score between baseline and V6 was determined and compared between patients from the placebo and the BF2.649 group. The score decreased by -3.76 (SD: 4.11) and -3.94 (SD: 3.89) in the placebo and the BF2.649 group, respectively. While a decrease in score indicates a reduction in EDS there was no statistically significant difference between the two groups. It must therefore be concluded that BF2.649 was not more effective at reducing EDS than the placebo. A decrease in the ESS score of a patient of > 3 points (or an ESS score of <10) categorises the patient as a 'responder' and a decrease of > 3 points is considered as clinically meaningful. As a decrease of > 3 was observed in both the placebo and the BF2.649 groups it must be acknowledged that there were patients in the placebo group who met the 'responder' definition. At V6 the placebo group contained a lower percentage of 'responders' (55.6%) than the BF2.649 group (64.8%), though this result was not statistically significant. The decrease in the mean ESS score between baseline and V6 indicated that the 20 mg (n=104) dose of BF2.649 (decreasing ESS score by -3.37, SD: 3.90) was less effective at reducing EDS that the placebo (decreasing ESS score by -3.76; SD: 4.11) with only the 5 mg (n=13) and 10 mg (n=42) strength of the study drug (decreasing ESS score by -5.70 SD: 3.47 and -4.93; SD: 3.70) respectively, effecting a higher reduction in EDS than placebo. Therefore the placebo seemed more effective at reducing EDS than the 20 mg strength of BF2.649. As 81.9% of patients in the BF2.649 group received the 20 mg strength of BF2.649 there is sufficient data to conclude that the study drug did not induce a reduction in EDS when compared to the placebo.

The analysis of the *secondary efficacy criteria* also showed that between baseline and V6, for each of the criterion, that there was no statistical difference between the placebo and the BF2.649 group and that therefore the study drug BF2.649 did not prove to be more effective than the placebo :

- When the mean patient ESS score at other times was analyzed between baseline and V3, V4 and V5 for patients in both groups the score decreased in each group and there was no statistically significant difference between the groups. The number of 'responders' was always either equivalent or very slightly greater in the placebo group than in the BF2.649 group.
- When comparing *patients diaries* results from the placebo and the BF2.649 groups there was no statistically significant difference between the baseline and V6 mean patients scores concerning the mean number of sleepiness and sleepy episodes and the mean duration of sleepiness and sleepy episodes. These results indicate that BF2.649 did not have an effect on reducing the mean number of sleep attacks, sleepiness or sleepy episodes or the mean duration of sleepiness or sleepy episodes.
- Concerning the changes in the mean *FSS score* between baseline and V6 there was no

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statiscally difference between the placebo and the BF2.649 group indicating that BF2.649 does not improve patient fatigue when compared to the placebo.

- The difference in the mean patient score for *UPDRS parts I, II, III and IV and the total score* for both the placebo and the BF2.649 group between baseline (V2) and V6 was not statistically significant difference between the two groups. This indicates that BF2.649 was not more effective than the placebo at lessening the effects of PD in terms of patient mentation, behaviour and mood. The study drug did not reduce the impact of PD on the ADL of the patient, improve their motor skills or reduce the associated complications PD therapy when compared to the placebo.
- Concerning the Hoehn and Yahr staging score of PD between baseline and V3, patients in the BF2.649 group showed a statistically significant difference in comparison to patients in the placebo group (p values of 0.008) with more patients being placed in the 'improvement' category and fewer being placed in the 'no change' and 'worsening category'. However, this effect no longer observed at V6.
- In the Schwab and England ADL score there was no significant difference between the placebo and the BF2.649 group at any point in the double-blind phase suggesting that the study drug was not more effective than the placebo.
- Concerning patient apathy as measured using the *AES scale* the mean AES score increased between the baseline and V6 for both groups but there was no statistically significant difference between the placebo and the BF2.649 group. These results suggested that patient apathy appear to worsen in both groups during the double-blind phase.
- The quality of life of patients was measured in both the placebo and the BF2.649 groups using the PDQ-39 questionnaire. The results were assessed in order to determine if BF2.649 alleviated or improved any of the previously described elements in the questionnaire. A decrease in score indicates an improvement or that PD has less of an impact upon any of the sub-categories. The mean score for each of the sub-categories decreased for patients in both the placebo and the BF2.649 group but the difference between the scores, for each sub-category, was not statistically significant. These results indicate that BF2.649 did not improve the quality of life of PD patients any more than the placebo.
- The total UPDRS score of patients who had their anti-parkinsonian treatment changed was compared at each visit to the total UPDRS of patients had no change in their anti-parkinsonian treatment. There was no statistical difference between the two groups. However, as data was available for a very low number of patients (max one patient per group) at each visit, it is difficult to conclude on the effects of changing treatment on the total UPDRS score.
- The *Global Clinical Impression (GCI) of EDS* was assessed for patients in both the placebo

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and the BF2.649 groups at baseline. The results from patients in the placebo group were then compared to results from patients in the BF2.649 group in order to determine if there was a statistically significant difference in how patients were re-partitioned between the 6 groups but each sub-category was not compared directly between groups. There was no statistically significant difference in the GCI of EDS between the two groups indicating that BF2.649 was not more effective than the placebo.

- The *BDI score*, was assessed for patients of both the placebo and the BF2.649 groups. The change between the baseline and V6 was not statistically significant different between the placebo and the BF2.649 group although the patients in the placebo group were re-assigned to the 'none or minimal depression category'. These results indicate that BF2.649 was not more effective than the placebo at reducing the symptoms of depression.
- The *Sudden Onset of Sleep (SOS)*. was assessed for patients of both the placebo and the BF2.649 groups. Analysis of these questionnaires revealed that there was no statistically significant difference between the placebo and the BF2.649 group in terms of score indicating that the study drug did not have more of an impact upon SOS than the placebo.

Efficacy of BF2.649 in the open-label extension phase of the study

All of the patients who were included into the open-label extension phase of the study received BF2.649 and consequently there were no placebo results available for comparison. The data reported in the open-label extension phase of the study was descriptive only. In general for the majority of the criteria the results trended in a direction which correlated with BF2.649 being effective over a longer period of time, specifically for the mean ESS score, which was 15.06 (SD: 2.46) at baseline (V2) and 9.72 (SD: 4.23) at week 53 (V12), corresponding to a clinically relevant mean change of -5.34 (SD: 3.74).

However, this is not a reliable interpretation of the results for a variety of different reasons. Firstly, patients who entered into the extension phase of the study were patients who had felt that their symptoms of EDS had improved during the double-blind phase (albeit this included a percentage of patients who were taking the placebo) leading to a bias in the type of population who continued on into the extension phase. Secondly, during the double-blind phase, a trend of decreasing mean patient scores for numerous secondary criteria was observed in the placebo group thereby correlating the placebo with being efficacious with the progression of time. This may imply that time rather than treatment influenced the mean patient score. Thirdly, patients who entered into the extension phase of the study and who had previously been assigned to the placebo had less exposure to the BF2.649 which may have had an impact on the results. Additionally, german health authorities didn't approve the open label extension phase and consequently, according to amendment n°2 described above, the open label phase was not conducted in germany and the open

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label phasesample size was significantly impacted. These points should not be ignored when assessing the results from the open-label extension phase of the study.

None of the other assessments performed during the open label extension phase and specifically, ESS score, patient's sleep diary, FSS, UPDRS, AES, quality of life, GCI, BDI, SOS evidenced any additional sign of efficacy from BF2.649.

Efficacy Conclusion :

Despite a trend in the study showing a response to treatment on the primary efficacy criterion, we have to conclude from the statistical analysis results that :

- BF2.649 was not more effective than the placebo on the primary efficacy criterion (ESS reduction between V6 and baseline(V2)), even at the highest dose tested in this trial i.e 20 mg daily,
- BF2.649 was also not more effective than the placebo on the secondary efficacy criteria (ESS reduction between V3, V4, V5 and baseline (V2), Number of diurnal involuntary sleep attacks and episodes of severe sleepiness, FSS, UPDRS, AES, Levodopa or dopamine agonist dosage regimen changes, CGI, Quality of life (PDQ39), BDI and SOS), even at the highest dose tested in this trial i.e 20 mg daily,
- BF2.649 did not have an effect on reducing the mean number of sleep attacks, sleepiness or sleepy episodes or the mean duration of sleepiness or sleepy episodes.

It can consequently be concluded that BF2.649 didn't have any efficacy on excessive daytime sleepiness in Parkinson's patients

Safety Results :

Study drug exposure and TEAEs

The mean duration of the double-blind phase was respectively 101.3 days (SD: 21.5) and 97.4 days (SD: 23.7) for patients in the placebo and BF2.649 group. The mean duration of patient exposure to study treatment during the double-blind phase was respectively 77.8 days (SD: 19.2) and 75.7 days (SD: 22.7) for the placebo and the BF2.649 group. The mean study duration for open-label extension phase of the study was 379.3 days (SD: 52.6) and the mean duration of patient exposure to the study treatment was 357.3 days (SD: 53.5).

In terms of overall exposure time to the study drug, patients were exposed to BF2.649 for over four times longer in the open label extension phase than in the double-blind.

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During the double-blind phase:

TEAEs ('all', 'severe', 'related' and 'leading to treatment discontinuation'), that were the most frequently reported by patients, were classified (for both the placebo and BF2.649 groups) to the following SOCs :

Corresponding Preferred Terms were :

- Parkinson's disease worsening, headache, dizziness, tremor, restless legs syndrome for the SOC 'nervous system disorders',
- Nausea, diarrhoea, dyspepsia, constipation, vomiting, abdominal discomfort for the SOC 'gastrointestinal disorders',
- Insomnia, sleep disorder, depression, abnormal dreams, disorientation, hallucination, sleep attacks, for the SOC 'psychiatric disorders',
- Fatigue, influenza like illness for the SOC 'general disorders and administration site conditions'.

Incidence of 'all', 'related' and 'leading to treatment discontinuation' TEAEs is between 1.5 and 3 times higher in the BF2.649 group than in the placebo group, while 'severe' TEAEs were only reported in the placebo group.

In the open label extension phase:

All TEAEs categories ('all', 'severe', 'related' and 'leading to patient discontinuation'), were associated with the SOCs 'musculoskeletal and connective tissue disorders', 'infections and infestations and 'nervous system disorders'.
SOC 'investigations' should not have been reported in 'severe' and 'related' and 'leading to patient withdrawal' TEAEs categories, as it was only due to non clinically significant QTcB abnormal values on ECGs which were reported as TEAEs by mistake, after study patient completion, by the investigators.

An overview of the percentage of patients that reported TEAEs which were classified to the common SOCs occurring for patients who were treated with BF2.649 during the double-blind period (3 months) and the open label extension phase (9 months) shows : The only two common SOCs were: 'psychiatric disorders' for ''related' TEAEs and ''nervous system disorders' for 'leading to treatment discontinuation' TEAEs.

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An increase in the proportion of patients reporting TEAEs which were classified to the SOC 'nervous system disorders'' for 'leading to treatment discontinuation' TEAEs,
was observed in the open-label extension period in comparison to the double blind phase. This can be partly explained, as mentioned above, by each treatment phase duration.

A decrease in the proportion of patients who experienced TEAEs for the description 'related' which was classified to the SOC 'psychiatric disorders' during the open-label phase in comparison to the double blind phase was also observed.

SAEs and significant adverse events

Two patients (8102 and 9021) died during the open-label extension phase further to the occurrence of SAEs, considered by the investigators as not related to the study treatment.

Regarding serious adverse events (SAEs), a total of 13 SAEs (concerning 9 patients) and 12 SAEs (concerning 10 patients) were declared respectively during the double-blind and the open-label extension phase.

Of the 13 SAEs declared during the double-blind phase, two SAEs (concerning 1 patient: 4504), were determined to be 'possibly' related to the study treatment, but the patient received placebo.
None of 12 SAEs declared during the open-label phase, was determined to be 'possibly' related to the study treatment.

BF2.649 withdrawal syndrome

None of the patients presented an amphetamine-like withdrawal syndrome according to the DSM-IV-TR criteria (for an overview see Table 35) since none displayed dysphoric mood.

Laboratory test, vital signs and ECG

During the double blind phase, only 2 patients presented abnormal values (hyperglycemia) reported as clinically relevant by the investigators. But none of them can be considered as directly related to BF2.649 administration: 1 patient was in the placebo group, and the other patient presented diabetes mellitus history since 2005 with isolated abnormal glycemia.
During the open-label extension phase, the blood chemistry and haematological tests results were within normal limits for all patients.

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Vital signs parameters were fluctuating within acceptable ranges for the study population, during the entire study duration. Analysis performed did not highlight any significant BF2.649 effects on vital signs, neither during the double-blind, nor the open-label extension phase.

ECG parameters:

- during the double-blind period, there was no statistically significant different between the placebo and BF26.49 group,
- during the entire study, double-blind and open-label extension phases, 5 patients presented a TEAE as QTcB prolonged (1 during double-blind phase and 4 during open label extension phase),

  → but no value was above the threshold of 500 ms which should be the value above which QTcB abnormal value should be considered as clinically relevant, in the absence of any associated clinical signs or cardiac rhythm disorders,

  → all these abnormal values were recorded at respectively V6 and V12 after treatment completion and consequently, none should be considered as leading to study treatment discontinuation,

  → none of these abnormalities should have been considered as TEAE nor as clinically relevant, neither of severe intensity.

Safety discussion and conclusion

Concerning the TEAEs that occurred during the double-blind phase, as analyzed according to the categories described in Table 58:

- the proportions of patients who experienced TEAEs from the placebo and the BF2.649 group were similar,
- except for the description: 'at least one study treatment related TEAE', where the percentage of patients was 30.8 % in the BF2.649 group versus 18.1% in the placebo group,
- however, the percentage of patients experiencing at least one serious TEAE, was 2.5 times lower in the BF2.649 group than in the placebo one (2.5%.versus 6.9%).

While, the mean exposure of patients to BF2.649 during the OLE phase (357.3 days), was more than 4 times above the mean exposure to BF2.649 of the double blind phase (75.7 days), but, the number of patients receiving BF2.649 was lower in OLE (n =135) than in the double-blind phase (n = 159), it has to be noted from Table 58**,** that in the OLE phase:

- the percentage of patients experiencing at least one treatment related TEAE was lower than in

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the double blind phase (21.5 % versus 30.8 %),

- the number of treatment related TEAEs is also lower 24.4 %, than in the double-blind phase 36.5%,
- the number of patients experiencing at least one severe TEAE was only two times higher in the OLE phase than in the double blind phase,
- the percentage of patients with at least one TEAE leading to treatment discontinuation was 8.9% versus 7.5% in the double blind phase.

It can be concluded that the safety and tolerability of BF2.649 administered at a daily dose of 20 mg (more than 70% of patients included) for a treatment duration ranging from 9 months to 12 months in Parkinson's patients is good

CONCLUSION:

Despite a trend in the study showing a response to treatment on the primary efficacy criterion (change between V6 and baseline i.e V2), it has been concluded that BF2.649 administered at a daily dose of 20 mg daily for a 3-month duration, in Parkinson's patients did not show any better efficacy than the placebo neither on the primary efficacy criterion nor on the secondary efficacy criteria (ESS reduction between V3, V4, V5 and baseline (V2), number of diurnal involuntary sleep attacks and episodes of severe sleepiness, FSS, UPDRS, AES, Levodopa or dopamine agonist dosage regimen changes, CGI, Quality of life (PDQ39), BDI and SOS).

Anyway, this study allowed to conclude on the BF2.649 safety profile. 231 Parkinson disease patients were randomized among which 159 received for 3 months BF2.649 at the following daily doses (5 mg, 10 mg or 20 mg) and 72 received placebo for 3 months under double blind conditions. Treatment with BF2.649 was prolonged for 135 patients for an additional duration ranging between 2 and 40 weeks (122 of them completing this part).

Referring to safety results discussion in section 12, it can easily be concluded that the safety and tolerability of BF2.649 administered at a daily dose of 20 mg (more than 82% of patients included received this dose) for a treatment duration ranging from 3 months to 12 months in Parkinson's patients were good.

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