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)	Isabelle Arnulf, M.D. CHU Pitié Salpétrière 75013 Paris, France	
Study centre(s): 32	Neurologists, hospitals, multinational sites. France: 20 centers Spain: 12 centers	
Publication (reference):	None	
Study period (Jan 2010 – August 2012):	Date of first enrolled patient: 07 January 2010 Date of last inclusion: 20 July 2011 Date of last completed visit: 09 August 2012	Phase of development: III
Objectives:	<u>Primary Objective</u> <u>To compare the efficacy of BF2.649 over placebo (Double-Blind Phase)</u> <u>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, inpatients 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) – To assess Quality of Life of Patients reported in Parkinson disease	

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	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 diaryafter 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: 268 ITT: 233 Safety Set : 235	Open-label extension phase Analyzed: Full Analysis Set (FAS): 187 ITT: 168 Safety Set : 168
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 UPDRS (Unified Parkinson disease Rating Scale), fluctuator and non-	

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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 $\geq$ 12
- Patients having a health Insurance Coverage (according to local regulatory requirements)
- Patients having signed an informed consent before any specific study procedures.

<u>Non inclusion criteria</u>:

- 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 $\geq$ 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 conduct or contra-indicate the study treatments or put patients at risk

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	– 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: E1243, E1246, E1308, E1316, E1327, E1362, E1375 (Active treatments and placebo were manufactured according to random code list. No distinction was performed regarding the final batch number). Open label extension phase: E1266, E1273, E1284, E1289, E1306, E1330, E1349, E1363, E1378, E1385, E1390	
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.	
Duration of treatment:	Comparative phase: 12 weeks of BF2.649 treatment or placebo followed by	

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	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 (ESS = 3 or ESS 10) was also provided. Δ ≤ **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 recorded3 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 Blood Laboratory tests modifications	

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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 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 ESS = 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 parametric ANCOVA with treatment factor adjusted for baseline. In the open label extension period, any changes from baseline were	

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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), 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

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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 CGIof Change (CGI-C) was used to document the perceived change inthe 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 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.

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SUMMARY – CONCLUSIONS:

Efficacy Results :

Among the 268 patients screened to take part in this study, 235 were included and randomized and received the investigational product at least once. Two patients (2103 and 2115) were excluded from the efficacy analyses as they did not have data available concerning the main efficacy criteria. The ITT population for the double-blind phase was therefore comprised of 233 patients. A total of 194 patients completed the double-blind phase. Of these, 187 patients were included in to the open-label extension phase, 168 of whom complied with the definintion of the ITT population with 135 patients completing the study. The mean age of patients at inclusion was 65 years the majority of which were male (78.6%). The mean duration of PD at baseline was longer in the BF2.649 group at 7.5 years(SD: 2.6) than in the placebo group at 5.8 years (SD: 2.6). According to clinical examination, the general condition of 94.8% of the patients was found normal at baseline. The ECG results of all of thepatients were normal. However, 23.8% and 27.5% of patients had abnormal haematology in the placebo and the BF2.649 group, respectively. Concerning blood biochemistry, 50.0% and 54.4% of patients had abnormal results in the placebo and the BF2.649 group, respectively.

Treatment compliance was better during the double-blind phase at 99.6% than the extension phase at 81.1%. The maximum dose of 20 mg/day of BF2.649 received by patients was 81.8% and 82.6% in the double-blind and open-label extension phase, respectively.

Efficacy criteria were analyzed in the blind-study 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 byEDS. 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 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 scoreof patients in the placebo group. The change in the mean patient ESS score between baseline (V2)
and V6 was determined and compared between patients from the placebo and the BF2.649 group.

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The score decreased by -4.30 (SD: 5.55) and -3.36 (SD: 4.89) 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 higher percentage of 'responders' (61.9%) than the BF2.649 group (51.7%), though this result was not statistically significant. The decrease in the mean ESS score between baseline and V6 indicated that the 5 mg and 20 mg dose of BF2.649 (decreasing ESS score by -1.86, SD: 6.09 and -3.09; SD: 4.60, respectively) was less effective at reducing EDS that the placebo (decreasing ESS score by -4.30; SD: 5.55) with only the 10 mg strength of the study drug (decreasing ESS score by -4.42; SD: 5.44) effecting an equivalent reduction in EDS. Therefore the placebo seemed more effective at reducing EDS than the 5 mg and 20 mg strength of BF2.649. As 81.8% 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 but was not statistically significant difference between the groups. However, the mean decrease in ESS score for the 10 mg of study drug at V4 and V5 was -6.05 (SD: 5.21) and at V5 was -5.08 (SD: 4.66), respectively, in comparison to -3.10 (SD: 4.94) and -3.65 (SD: 5.26), respectively. These results were descriptive only. The number of 'responders' remained higher in the placebo group than the BF2.649 group at V4 and V5.

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. However, at V3 patients in the placebo group had a statistically significant reduction in the mean duration of sleepiness or sleepy episodes when compared to the BF2.649 group (p value 0.05). This affect was not observed at any other visit. 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 little

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change in score for either group and there was no significant 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 and baseline and V4 patients in the BF2.649 group showed a statistically significant difference in comparison to patients in the placebo group (p values of 0.037 and 0.01, respectively) 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. This questionnaire examined 7 different sub-categories or aspects of patient life which are impacted by PD. The PDQ-39 questionnaire assesses the effect of PD on patient mobility, activities of daily living (ADL), emotional well-being, the stigma associated with PD, the social support required by patients, their cognition abilities along with their communication abilitiesand any associated bodily discomfort. 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. Themean 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

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treatment. There was no statistical difference between the two groups. However, as data was available for only one patient 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 and the BF2.649 group at baseline. At each visit the patient was re-assessed and was placed into one of the following categories 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse' and 'much worse'. 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 effectivethan the placebo.

The *BDI score*, which assesses the symptoms of depression in patients, was analyzed for both the placebo and the BF2.649 group at baseline and all the patients, in both groups, were assigned into the 'mildly depressed' category. 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)* is a self-reported questionnaire which examined whether patients suffered from SOS (yes or no question). The questionnaire also assessed the frequency of sleep attacks which could be reported as one of the following 'every day', '2-4 times per week', '2-4 times per month' and 'rarely' and whether the patient felt sleep prior to suddenly fallen asleep which was scored as 'yes', 'no' or 'sometimes'. 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. 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

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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. These points should not be ignored when assessing the results from the open-label extension phase of the study.

Concerning the *patient diaries* the mean number of sleep attacks decreased by -0.69 (SD: 1.39), sleepiness or sleepy episodes decreased by -1.41 (SD: 1.77) and the mean duration of sleepiness or sleepy episodes decreased by -49.21 (SD: 106.72) between baseline and V12 suggesting that over a longer period of time BF2.649 may be effective at reducing diurnal sleep episodes.

The mean FSS fluctuated throughout the open-label extension phase of the study with an overall decrease of -0.24 (SD: 2.27) between baseline and V12.

Between baseline and V12 the *UPDRS part I* mean patient score decreased by -0.17 (SD: 1.80), the *part II* mean patient score increased by 0.95 (SD: 3.53), the *part III* mean patient score increased by 0.33 (SD: 7.92), the *part IV* mean patient score decreased by -0.09 (SD: 1.64) and the *total score* decreased by -0.17 (SD: 1.80).

The mean patient *AES scale* score increased very slightly (0.32, SD: 8.17) between baseline and V12 indicating that even over a longer period of time BF2.649 did not reduce patient apathy.

The PDQ-39 questionnaires were assessed and a slight increase in mean patient score was observed between baseline and V12 for the ADL and communications sub-categories of 0.17 (SD: 3.71) and 0.03 (SD: 2.42), respectively. Otherwise the mean patient score for the sub-categories mobility, emotional well-being, stigma, social support and bodily discomfort decreased betweenbaseline and V12 as follows; -0.09 (SD: 6.31), -0.44 (SD: 3.87), -0.72 (SD: 2.71), -0.11 (SD: 1.87) -
1.69 (SD: 2.77) and -0.31 (SD: 2.42), respectively.

Concerning changes in anti-parkinsonian treatment by V12 of the open-label extension phase of the study less than 10% of the patients had changed treatment.

In relation to the results from *Global Clinical Impression (GCI) of EDS* very little change was observed when comparing the number of patients were placed in the ‘very much improved’, ‘much improved’ and ‘minimally improved’ categories at V8 in comparison to V12. The percent of patients placed in the ’very much improved’ category at V8 increased from 6.6% to 10.7% at V12. Otherwise the only other increase observed was in the ‘minimally worse’ category which changed from 7.2% at V8 to 10.7% at V12.

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The BDI score decreased by -0.31(SD: 2.42) between baseline and V12. This decrease did not affect the category into which the patients were placed. BF2.649 did not appear to be more efficacious over a longer period of time.

During the open-label extension phase of the study the number of patients who suddenly fell asleep (Sudden Onset of Sleep; SOS) decreased from 61.2% at the baseline to 35.5% at V12. The number of patients who fell asleep on a daily basis decreased from 47.5% at the baseline to 13.6% at V12. Similarly, the number of patients who fell asleep rarely increased from 7.5% at the baseline to 20.5% at V12. The number of patients who felt sleepy prior to SOS increased from 31.2% at the baseline to 46.4% at V12.

Safety Results :

Study drug exposure and TEAEs

The mean duration of patient exposure to study treatment during the double-blind phase was 78.0 days (SD: 32.2). The mean duration of patient exposure to the study treatment during the open-label extension phase was 325.8 days (SD: 86.8).

During the double-blind phase :

TEAEs (“all”, “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 SOCs ‘psychiatric disorders’ and ‘nervous system disorder’.

- For “psychiatric disorders” SOC : incidence was similar for both treatment arms placebo and BF2.649.(17.9%) for “all” TEAES, and lower in BF2.649 arm (9.9%) versus 15.5% in placebo, for “related” TEAEs
- For ”nervous system disorders” SOC : incidence was slightly higher in the BF2.649 arm than in the placebo for “all” TEAEs (BF2.649 : 25.2%, placebo : 23.8%) and for “related” TEAEs (BF2.649 : 11.3%, placebo : 10.7%)

Corresponding Preferred Terms were respectively insomnia, depression,for the SOC ‘psychiatric disorders’ and headache and dizziness for the SOC ‘nervous system disorders’.

The third more frequent TEAEs reported by patients were classified to the SOC ‘gastrointestinal disorders’ (placebo : 11.9% and BF2.649 : 15.2%), and were mainly nausea and vomiting.

Severe TEAEs experienced by the highest and second highest proportion of patients**,** were classified to the SOCs ‘gastrointestinal disorders’ and ‘musculoskeletal and connective tissue disorders’, respectively, with similar numbers of patients being affected in both the placebo and BF2.649 groups

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(7%).

The most pronounced difference observed during the double-blind phase between the placebo and BF2.649 groups concerned the SOCs 'gastrointestinal disorders' and 'infections and infestations' for the TEAE description 'all'. A higher proportion of patients in the BF2.649 group (15.2%) reported TEAEs classified to the SOC 'gastrointestinal disorders' than the placebo group (11.9%). Conversely, a higher proportion of patients in the placebo group (15.5%) reported TEAEs classified to the SOC 'infections and infestations' than the BF2.649 group (7.3%).

In the open label extension phase :

TEAEs ("all", "related" and "leading to treatment discontinuation") ,that were the most frequently reported by patients, were also classified to the SOCs 'psychiatric disorders' and 'nervous system disorders'.

An overview of the percentage of patients that reported TEAEs which were classified to these two SOCs for patients who were treated with BF2.649 during the double-blind period (3 months) and the open label extension phase (9 months) is given in table 23 and table 24.

An increase in the proportion of patients :

- reporting TEAEs which were classified to the SOC 'psychiatric disorders' for "all", "severe", "related" and "'leading to treatment discontinuation' TEAEs,
- reporting TEAEs which were classified to the SOC 'nervous system disorders' for the descriptions 'severe' and '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 descriptions 'all' and 'related' which were classified to the SOC 'nervous system disorders' during the open label phase in comparison to the double blind phase was also observed.

SAEs and significant adverse events No

deaths occurred during this study.

Regarding serious adverse events (SAEs), a total of 12 SAEs (concerning 9 patients) and 23 SAEs (concerning 20 patients) were declared respectively during the double-blind and the open-label extension phase.

Of the 12 SAEs declared during the double-blind phase, two of the SAEs (concerning 1 patient: 1409), were determined to be 'possibly' related to the study treatment, but the patient received

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placebo.

Of the 23 SAEs declared during the open-label, one SAE (concerning 1 patient; 1406), was determined to be 'possibly' related to the study treatment.

It was a dopaminergic psychosis (classified to the SOC psychiatric disorders), of mild intensity, which occurred 3 days after increasing patient anti-parkinsonian treatment (L-dopa/carbidopa/entacapone) from 350 mg/day to 900 mg/day. The investigator initially considered this SAE as not related to BF2.649 and decided to change the relationship 15 months later, quoting it as "possibly related". Further to this SAE, the patient BF2.649 treatment was permanently stopped, his anti parkinsonian treatment readapted once more and the patient recovered without sequelae.

BF2.649 withdrawal syndrome

Among all symptoms reported during the study drug washout periods, none of the patients reported a amphetamine-like withdrawal syndrome according to the DSM-IV-TR criteria. Furthermore, most of the symptoms reported were associated with re-emergence of sleepiness symptoms due to cessationof BF2.649 treatment, without any rebound effect.

Laboratory test, vital signs and ECG

During the double-blind phase no clinically relevant blood chemistry or haematological tests results were reported for any patient in the BF2.649 treatment group. During the open label phase, only 5 patients presented abnormal values reported as clinically relevant by the investigators, but none of them can be considered as directly related to BF2.649 administration, four being isolated and the fifth one being directly related to a pancreatic tumor which was discovered during the study.

Vital signs and ECG 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 neither on vital signs nor on ECGs, neither during the double-blind nor the open label extension phase.

Safety Discussion and Conclusion

Concerning the TEAEs that occurred during the double-blind phase the proportions of patients who experienced TEAEs from the placebo and the BF2.649 group were similar, as analyzed according to the categories described in Table 56.

While on one hand, the mean exposure of patients to BF2.649 during the OLE phase (325.2 days), was more than 4 times above the mean exposure to BF2.649 of the double blind phase (78.2 days), and, on the other hand, the number of patients receiving BF2.649 was also higher in OLE (n =187) than in the double blind phase (n = 151), it has to be noted from Table 57 that :

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- the percentage of patients experiencing at least one treatment related TEAE in this phase was lower than in the double blind (31.6 % versus 36.4 %),
- the number of treatment related TEAEs in this phase is also lower 26 % than in the double-blind phase 33.8%,
- 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 9.3% in the double blind phase versus 11.8% in the OLE phase.

CONCLUSION:

Despite a trend in the study showing a response to treatment on the primary efficacy criterion,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 (EDS 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. 235 Parkinson disease patients were randomized among which 151 received for 3 months BF2.649 at the following daily doses (5 mg, 10 mg or 20 mg) and 84 received placebo for 3 months under double blind conditions. Treatment with BF2.649 was prolonged for 187 patients for an additional duration ranging between 2 and 40 weeks (135 of them completing this part).

Referring to safety results discussion, it can easily be concluded that the safety and tolerability of BF2.649 administered at a daily dose of 20 mg (more than 70% of patients included received this dose) for a treatment duration ranging from 3 months to 12 months in Parkinson's patients were good.

Date of report: February 7th, 2014