2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table** **Referring to Module 5 of the Dossier** **Vol.: .....Page: .....**	**(For National Authority Use Only)**
Name of finished product: **DEBRUMYL**		
Name of active substance *(or ingredient)***:** **Dimethylaminoethanol pyroglutamate (DMAE-pGlu) and heptaminol chlorhydrate**		

Title of study:	Evaluation of the effect of 6 months treatment with DC158AM on fatigue in patients with Parkinson's disease. A multicentre, randomised, double-blind, placebo-controlled study in parallel groups	
Principal Investigator:	Dr Florence PORTET, UNC, CMRR du Languedoc Roussillon/ Neurologie, Hôpital Gui de Chauliac, CHU Montpellier, 80 Avenue Gaston Fliche, F - 34295 Montpellier cedex 05, France	
Study centres:	The study was conducted by hospital neurologists in 6 centres in France.	
Publication (reference):	None	
Studied period: **(date of first selection)** **(date of last completed)**	1 year and 11 months 07 August 2008 02 July 2010	**Phase of development:** Phase III
Objectives: **Primary:** **Secondary:**	To evaluate the efficacy of 6 months treatment with DC158AM on fatigue in patients with Parkinson's disease. • To evaluate changes in motor symptoms, • To evaluate the effect on cognitive functions, • To evaluate the behavioural effect, • To evaluate the effect on activities of daily living, • To evaluate the safety and tolerability of the product	
Methodology:	This was a multicentre, randomised, double-blind, placebo-controlled, parallel group study. Patients attended 4 study visits: Visit 1 (up to 4 weeks before the inclusion visit, Selection visit); Visit 2 (Baseline, Inclusion and randomisation visit); Visit 3 (Week 12 ± 2 weeks, Follow up visit) and Visit 4: (Week 24 ± 2 weeks, End of treatment visit). A phone call was scheduled at Week 26 (± 3 days). A battery of neuropsychological/functional tests and questionnaires was performed at the Visits.	
Number of patients **(planned and analysed):**	It was planned that a minimum of 120 patients were to be randomised. In all 42 patients were screened, 35 randomised and 27 completed the study (10 in the DC158AM treatment group and 17 in the placebo group).	
Diagnosis and main criteria for inclusion:	• Male or female between 45 and 80 years of age with: – an idiopathic Parkinson's disease lasting for more than 3 years, characterised by 2 of the following 3 cardinal signs (signs need to be asymmetric): resting tremor, bradykinesia and rigidity – Hoehn and Yahr stage < 4 – good response to levodopa as perceived by the patient (more than 50%) – using pharmacological therapies and/or deep brain stimulation (DBS) by electrodes – a mean score greater than 4 on the Fatigue Severity Scale (FSS) – normal or sufficiently preserved daily activities in order to exclude the diagnosis of dementia • MMSE score ≥ 24 • mastery of the French language • having given his/her written consent to take part in the study • patients covered by a social security or health insurance system	

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Test product, **Dose,** **Mode of administration,** **Batch number:**	DC158AM One ampoule contained: PGlu-DMAE 250 mg and Heptaminol 180 mg Oral solution. The content of one 5 mL ampoule taken twice a day (morning and midday) with a glass of tap water, before a meal. SB0581
Duration of treatment:	24 Weeks
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo One ampoule Oral solution. The content of one 5 mL ampoule taken twice a day (morning and midday) with a glass of tap water, before a meal. SB0580, SB0624
Duration of treatment:	24 Weeks
Statistical methods:	Efficacy *Initially planned analyses:* *Main analysis:* It had been planned that the change from baseline of the FSS score at the end of treatment would be analysed by a parametric analysis of covariance (ANCOVA) with the treatment effect and the baseline score as a covariate. If the hypothesis of normality of residuals was rejected, a rank analysis of covariance was to be performed. *Secondary analysis*: Parametric or rank analysis of covariance taking into account the stability of the treatment of the Parkinson's disease had been planned. *Performed analyses:* However, due to the early discontinuation of the study and the small number of patients included, statistical analyses were descriptive and performed only on the Full Analysis Set (FAS) composed of all randomized patients having received at least one dose of the study treatment. Safety analysis Descriptive statistics were provided summarizing AEs, vital signs and physical examination by treatment group.

Summary - Conclusions:

Demography

The median age (min; max) of the 35 patients in the FAS population was 68.36 years (51.9; 80.8): 67.51 years (54.0; 80.8) in the DC158AM group and 69.02 years (51.9; 76.5) in the placebo group. The proportion of patients in each age category was similar for both groups with 43% of all patients aged over 70 years. For the FAS population, the median body mass index was 24.91 kg/m² (19.6; 35.1), and 46% of the patients were women.

The median age at Parkinson's disease diagnosis (min; max) was 60.25 years (41.3; 75.3) in the FAS population: 59.11 years (47.5; 75.3) in the DC158AM group and 60.25 years (41.3; 72.2) in the placebo group. Median length of time (min; max) since diagnosis was 6.53 years (1.7; 14.2) in the FAS population: 6.44 years (1.7; 14.2) in the DC158AM group and 7.16 years (3.0; 13.5) in the placebo group.

Dementia was absent for the 35 patients in the FAS population. In all, 77% (n=27) of patients in the FAS population had a history of at least one medical or surgical procedure: 81% (n=13) in the DC158AM group and 74% (n=14) in the placebo group. Overall, 86% (n=30) of patients in the FAS population had a concomitant disease: 100% (n=16) in the DC158AM group and 74% (n=14) in the placebo group. All patients in the FAS population had received at least one previous medication.

Data Set

All randomised patients received at least one dose of the study treatment and were included in the FAS.

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Efficacy results

Primary analysis (FAS population)

Variation of FSS mean score between baseline and Week 24 (Visit 4) - FAS population

	Statistic	**DC0158 group** N=16	**Placebo group** N=19	**All** N=35
FSS mean score at baseline	n	13	19	32
	Min-Max	4.2-6.3	4.2-6.7	4.2-6.7
	Median	5.44	5.56	5.44
	Mean	5.46	5.60	5.55
	SD	0.59	0.72	0.66
FSS mean score at Week 24	n	13	19	32
	Min - Max	3.4-6.4	1.4-7.0	1.4-7.0
	Median	5.33	5.22	5.28
	Mean	5.26	5.19	5.22
	SD	0.92	1.51	1.29
Change between baseline and Week 24	Missing	3 (19%)	0 (0%)	3 (9%)
	n	13	19	32
	Min - Max	-1.2-0.8	-3.9-1.1	-3.9-1.1
	Median	-0.11	-0.11	-0.11
	Mean	-0.21	-0.41	-0.33
	SD	0.54	1.22	1.00

FAS: all randomised patients having received at least one dose of the study treatment
Baseline value was the last assessment before the first study treatment intake
A negative change means an improvement

As shown above, no differences were observed in the median values between treatment groups at Week 24. Median changes from baseline at Week 24 were -0.11 (range -3.9 to 1.1) for the 35 patients in the FAS population: -0.11 (range -1.2 to 0.8) for the DC158AM group (n=13) and -0.11 (range -3.9 to 1.1) for the placebo group (n=19). The mean reduction from baseline in FSS score observed for each treatment group was also similar. Mean changes from baseline at Week 24 were -0.33 for the 35 patients in the FAS population: -0.21 for the DC158AM group (n=13) and -0.41 for the placebo group (n=19).

Due to the small number of patients included in the study no conclusion about the primary efficacy criteria were able to be made.

Secondary criteria (FAS population)

Due to the early termination of the study and the small number of patients included, statistical analyses were descriptive in nature. Between baseline and Week 24, the Hoehn and Yahr disability scale showed that 77% (10/13) of patients in the DC0158 group and 89% (17/19) of patients in the placebo group had no change in their disability score, and for the IADL 85% (11/13) of patients in the DC0158 group reported no loss of activity compared with 74% (14/19) of patients in the placebo group. Results from the analyses of secondary efficacy criteria for both the DC0158 and placebo treatments groups were relatively variable. No consistent differences between the two group were apparent for either mean or median values. Due to the small number of patients included in the study no conclusion about the secondary efficacy criteria were able to be made.

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Safety results

Adverse events

In all, 12/16 (75%) patients in the DC0158 group, and 10/19 (53%) patients in the placebo group reported at least one AE. All patients reporting an AE had at least one treatment emergent adverse event (TEAE). In total, 6/16 (38%) patients in the DC0158 group and 2/19 (11%) patients in the placebo group had at least one AE leading to discontinuation. A total of 5/16 (31%) patients in the DC0158 group and 3/19 (16%) patients in the placebo group had at least one TEAE related to study drug. In all, 2 patients in the DC0158 group had at least one serious adverse event (SAE). No patient in the placebo group had an SAE. In the DC0158 group, the most common System Organ Class (SOC) was infections and infestations with 6/16 (38%) patients reporting at least one TEAE in this SOC. No patient in the placebo group reported a TEAE in this SOC. Of note, syphilis was recorded for one patient in the DC0158 group and counted as a TEAE but was actually a concomitant disease.

Other observations related to safety

All patients reported taking at least one concomitant treatment during the study. The total number of concomitant medications was 233 (116 in the DC0158 treatment group and 117 in the placebo group). Regarding vital signs, although some changes were observed for a few patients, no clinically significant changes were apparent in either of the treatment groups.

Conclusion

Due to the early termination of the study and insufficient number of patients in each treatment group, interpretation of results was limited and only descriptive statistics were performed. In all, 35 patients were randomised (16 patients in the DC0158 treatment group and 19 patients in the placebo group), and 27 completed the study (10 patients in the DC158AM treatment group and 17 patients in the placebo group).

On this basis, in the analysis of primary efficacy criteria, no differences were observed between treatment groups in the change from baseline of the FSS score at Week 24. Considering the analysis of secondary efficacy criteria, no consistent differences between the treatment groups were apparent for either mean or median values.

Although difficulties recruiting patients to this study meant that the number of patients in each treatment group was reduced from that originally planned, safety assessments did not identify any cause for concern.

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