2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: V0191	**Referring to Module 5 of the Dossier**	
Name of active substance DMAE-pGlu (dimethylaminoethanol pyroglutamate)	**Vol.: .....Page: .....**	

Title of study:	Evaluation of the effect of 6 months treatment with V0191 on symptoms changes in patients with mild cognitive impairment. Multicenter, randomised, double-blind, placebo-controlled study in parallel groups.	
Investigators:	Prof. Bruno DUBOIS (Paris) was the coordinating investigator. See Appendix 16.1.4 for a complete list of investigators.	
Study centre(s):	57 centers in 8 countries: France (27), Monaco (1), Belgium (2), Finland (2), Spain (18), Austria (2), Croatia (3), Serbia (2)	
Publication (reference):	Publication planned for 2010	
Studied period *(years, months …)*: **(date of first enrolment) (date of last completed)**	≈ 26 months 16/10/2007 to 16/12/2009	**Phase of development:** IIb
Objectives: **Primary:**	To evaluate cognitive improvement in patients with mild cognitive impairment (MCI) of the Alzheimer's type after 6 months of treatment with V0191	
Secondary:	• To evaluate memory improvement • To evaluate the effect on activities of daily living • To evaluate the global clinical improvement perceived by the patient and assessed by the investigator • To evaluate the safety and tolerability of the product	
Methodology:	This multicenter trial was conducted using a randomized, double-blind, placebo-controlled, parallel-group design, in outpatients aged 55 to 90 years who fulfilled the criteria for MCI with an amnesic syndrome of the "hippocampal type." Patients were randomized to 1 of 2 treatment groups: 1500 mg V0191 or placebo. Six visits were planned: Visit 1, selection (2 to 4 weeks before inclusion); Visit 2, Inclusion; Visit 3, follow-up visit 1 (Week 6 ± 4 days); Visit 4, follow-up visit 2 (Week 12 ± 6 days); Visit 5, follow-up visit 3 (Week 18 ± 6 days); and Visit 6, end-of-trial visit (Week 24 ± 6 days).	
Number of patients (planned and analysed):	Planned: Minimum of 210 randomized patients. Analyzed: 241 patients.	

Diagnosis and main criteria for inclusion:	Inclusion criteria • Men or women • Aged 55 to 90 years • Progressive cognitive decline fulfilling the criteria for mild cognitive impairment: o Memory complaint, corroborated by immediate family o Amnesic syndrome of hippocampal type (isolated or associated with other cognitive disorders) with the following results obtained for the Grober and Buschke test: – Free recall ≤ 20 – Total recall ≤ 40 o Normal or sufficiently preserved daily activities in order to exclude the diagnosis of dementia o Absence of dementia (DSM-IV) • MMSE score between 24 and 30 • Global score of 0.5 on the CDR scale with: o "Memory" domain score of 0.5 or 1 o No scores > 1 • Having given his/her written consent to take part in the study • If stipulated by national regulatory requirements, patients covered by a social security or health insurance system

Exclusion criteria

Patients fulfilling the following criteria were not to be included in the study:

Criteria related to the studied disease

- Patient in whom a diagnosis of dementia was suspected or had already been made
- Presence of serious disease which may soon have become life-threatening
- Patent cerebrovascular disease with a Hachinski scale score > 4
- Patient with a progressive and/or poorly balanced psychiatric disorder according to DSM-IV, particularly:
  - Ongoing major depressive episode or recurrent depression, or bipolar disorders according to DSM-IV, and/or score ≥ 12 on the 17-point Hamilton depression scale
  - Patient with early hallucinations or cognitive fluctuations
- Patient with the following neurological disorders:
  - Epilepsy
  - Dementia irrespective of cause
  - Parkinson's disease
  - Presence of images (MRI or cranial CT scan performed during the past 12 months) suggesting vascular disease including: multiple infarction involving large blood vessels or localised single infarction (angular gyrus, thalamus, anterior cerebral artery and posterior cerebral artery region), multiple lacunae of the basal nuclei or white matter or extensive lesions of the periventricular white matter or combination of several lesions
- Patient with known vitamin B12 or folate deficiency (unless having received supplements at a stable dose for at least 6 months prior to selection) or known syphilis
- Patient with sleep apnoea syndrome

Criteria related to previous or concomitant medication

- Patient with a known allergy to the investigational product or to one of the ingredients
- Patient with unstable hypertension (SBP > 160 mmHg and/or DBP > 95 mmHg) evaluated by the investigator, whether the patient was receiving antihypertensive treatment or not
- Patient previously treated with centrally-acting anticholinesterase or memantine, irrespective of treatment duration and date prescribed
- Patient currently treated with a product indicated for the symptomatic treatment of chronic neurosensory or cognitive pathological impairment in elderly subjects (Gingko biloba, almitrine, piracetam, etc.)
- Patient having received, during the 2 months prior to inclusion, a product indicated for the symptomatic treatment of chronic neurosensory or cognitive pathological impairment in elderly subjects (Gingko biloba, almitrine, piracetam, etc.)
- Patient receiving treatment with prohibited medication during the study period

	Criteria related to the patients • Patient with visual or hearing disorders incompatible with the conduct and/or interpretation of neuropsychological tests • Patients living in a nursing home • Patient without a reliable circle • Patient incapable of taking the investigational product as stipulated throughout the duration of the study • Patient displaying criteria for psychoactive substance abuse or dependency (according to DSM-IV) • Patient suffering from immunosuppression or insulin-dependent diabetes mellitus or diabetes mellitus not stabilised by dietary measures and/or oral hypoglycaemics, obstructive pulmonary disease, unstable asthma, recent oncological and/or haematological disorders (≤ 2 years) • History or ongoing gastrointestinal, hepatic, or renal disease, or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of medicinal products, or any other significant clinical abnormality, or any other medical or psychiatric condition which, according to the investigator, made the patient unsuitable for inclusion in the study • History of a cardiovascular event in the past 6 months, for example: vascular surgery, percutaneous coronary intervention, acute coronary syndrome (myocardial infarction with or without Q wave, unstable angina), any known arrhythmia, or planned major surgery (e.g. heart surgery or angiography with stent implantation) • Patient with severe chronic or acute disease considered by the investigator as incompatible with study implementation • Patient with a history of a disease which, according to the investigator, was liable to interfere with the study results or expose the patient to further risk • Patient who the investigator considered liable not to comply with the instructions of the protocol and/or treatment • Patient having taken part in a therapeutic trial within the past 30 days or still within a period corresponding to 5 treatment half-lives (up to the highest period) • Patient unable to understand and sign the informed consent form due to linguistic or psychiatric inability • Patient who could not be contacted in an emergency • Patient under supervision or guardianship • Non-menopausal women
Test product, **Dose,** **Mode of administration,** **Batch number:**	The test product, 1500 mg V0191, was supplied in the form of oral ampoules. V0191 was taken orally in the morning before breakfast every day for 24 weeks. Batch Numbers: SB0588, SB0616, SB0678, SB0688, SB0701, SB0732.
Other product, **Dose,** **Mode of administration,** **Batch number:**	The reference product, V0191 matching placebo, was supplied in the form of oral ampoules. Placebo was taken orally in the morning before breakfast every day for 24 weeks. Batch Numbers: SB0573, SB0735.
Duration of treatment:	24 weeks

Criteria for evaluation:	Primary efficacy criterion:
Efficacy:	The primary efficacy criterion was the comparison between the 2 groups of the percentage of patients with a decrease on the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) score of 4 points or greater compared with baseline. Secondary efficacy criteria: Comparison between the 2 groups of the mean changes from baseline on the following neuropsychological scores at weeks 12 and 24 : • Global cognitive function: ADAS-Cog • Memory: o Episodic verbal memory: California Verbal Learning Test (CVLT) o Episodic visuospatial memory: DMS48 (visual recognition memory test) and Benton visual retention test o Working memory: Category Verbal Fluency Test (Isaacs Set Test) • Executive functions: Trail Making Test A and B (TMT A&B) • Attention: Digit Symbol Substitution Test (DSST) • Global cognitive function: CDR (Clinical Dementia Rating) • Functional capacities/autonomy: Activities of Daily Living in mild cognitive impairment (ADCS-ADL/MCI) • Behaviour: Apathy Inventory (AI) • Global improvement: o Clinical Global Impression-Mild Cognitive Impairment (CGIC-MCI): global improvement evaluated by the investigator o Global improvement evaluated by the patient
Safety:	Safety endpoints: Number and percentage of patients with at least 1 adverse event (AE) occurring during treatment in the 2 treatment groups.
Statistical methods:	The Full Analysis Set (FAS) comprised all randomized patients having received at least 1 dose of study treatment. The main analysis of the primary criterion was performed on the FAS using the Cochran-Mantel-Haenszel (CMH) test stratified by country. In addition, homogeneity of the odds ratio across countries was checked using the Breslow-Day. All analyses of the secondary criteria were performed on the FAS.
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The secondary efficacy criteria were compared between treatment groups using the following tests:

- For quantitative parameters: the change from baseline was compared by an analysis of covariance (ANCOVA) with treatment effect, country effect, and baseline as a covariate. If the normality of residuals of this analysis (checked via the Shapiro-Wilk test) was rejected (at level 1%), a non parametric covariance strategy (Strokes et al., 2000) was considered: In a first step, standardised ranks for the covariate and the change from baseline in each country were to be produced. Then, residuals of the linear regression model of the change from baseline on baseline for each country was to be compared between the treatment groups using the CMH test stratifying for country.
- Categorical or ordinal parameters were compared using a CMH test adjusting for country, with modified ridit

The safety analyses were done on the safety dataset and were descriptive (number and percentage of missing values, number of observed values, frequencies and percentages [of the number of available values]).

Summary - Conclusions:

Efficacy results

The majority of patients did not have an ADAS-Cog response (defined as a decrease of 4 points or more from baseline) at Week 24 (primary endpoint). V0191 was not statistically significantly different from placebo in ADAS-Cog response at Week 24.

Response at Week 24	**V0191 1500 mg N=121**	**Placebo N=120**
No	115 (95.0%)	111 (92.5%)
Yes	6 (5.0%)	9 (7.5%)
Odds Ratio (95% CI)	0.63 (0.22, 1.81)	
p-value (Cochran-Mantel-Haenszel test adjusting for country)	0.368	
p-value (Breslow-Day test for homogeneity among countries)	0.719	

Results were similar for both the FAS and PP populations.

Safety results

A total of 54 (43.5%) patients in the V0191 treatment group and 37 (29.6%) patients in the placebo treatment group had at least 1 TEAE during the study. Of the patients with TEAES, 24 (19.4%) and 16 (12.8%) in the V0191 and placebo treatment groups, respectively, had study drug-related (as determined by the investigator) TEAEs. Ten (8.1%) patients in the V0191 treatment group and 6 (4.8%) patients in the placebo treatment group had AEs leading to discontinuation of study drug.

Eleven (8.9%) and 3 (2.4%) patients in the V0191 and placebo treatment groups, respectively, had an SAE. The investigators did not exclude a relationship to study drug for 3 of the SAEs (cardiorespiratory arrest, cardiac failure, and grand mal convulsion; V0191 treatment group). One of the later SAEs, cardiorespiratory arrest in a 78-year-old male patient, had a fatal outcome.

Patients with at least 1:	**V0191 1500 mg N=124[1]**	**Placebo N=125[1]**
	n (%)	n (%)
AE	55 (44.4)	38 (30.4)
TEAE[2]	54 (43.5)	37 (29.6)
Study drug related TEAE[3]	24 (19.4)	16 (12.8)
AE leading to discontinuation	10 (8.1)	6 (4.8)
SAE	11 (8.9)	3 (2.4)

[1] Due to IVRS mistake or dispensation error by the investigator, 8 patients (10203, 12803, 40104, 50104, 51214, 60101, 60103 and 13002) did not receive the same treatment during the study at 1 visit. Consequently, analyses of adverse events were modified (as detailed in Section 9.7.1 and in the statistical analysis plan). These patients have been considered both in the V0191 FAS data set and the placebo FAS data set. (see paragraph 10.2)

[2] TEAE defined as an event whose onset date was ≥ date of first drug intake, having been absent pre-treatment or worsened relative to pre-treatment date (before first study drug intake).

[3] Relationship with study drug other than "excluded," as determined by the investigator.

The most frequently occurring AEs were bronchitis, experienced by 2 (1.6%) patients in the V0191 treatment group and 5 (4.0%) patients in the placebo treatment group; hypertension (1 [0.8%], 5 [4.0%], urinary tract infection (2 [1.6%], 3 [2.4%]), headache (2 [1.6%], 3 [2.4%]), and diarrhea (3 [2.4%], 2 [1.6%]).

Conclusion

The current study was not able to show any statistically significant differences between V0191 and placebo at 12 or 24 weeks for the primary categorical outcome measure of 4-point change in the ADAS-Cog. Overall cognitive stability of the patient sample was evidenced by a lack of conversion from MCI to AD over the course of the study with only 5 patients converting to AD over the course of 24 weeks, among which were 4 patients on placebo.

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