Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

V0251 ORAL SUSPENSION EFFICACY AND TOLERANCE IN VESTIBULAR NEURITIS. A RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED STUDY.

Investigational product: V0251/ Acetyl-L-leucine / granule for oral route 8 g/Day

Study Design: Multicenter, international, randomized double-blind placebo controlled study of V0251 in parallel groups.

Protocol number: V00251 ST 201 1A
Phase of development: II/ Clinical phase

Date of first enrolment: 17 May 2011
Date of last completed: 30 April 2012

Co-ordinators: Prof. Bernard FRAYSSE, Pôle Céphalique et Odontologique, Hôpital Purpan, Pavillon Dieulafoy, Place du Docteur Baylac - 31059 Toulouse cedex 9, France
Prof. Daniele NUTI, Azienda Ospedaliera Universitaria Senese, Viale Bracci 1 - 53100 Siena, Italy

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Date of report: 09 July 2013

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: **NA**	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **Acetyl-L-leucine**	**Vol.: .....Page: .....**	

Title of study:	V0251 oral suspension efficacy and tolerance in vestibular neuritis. A randomized double-blind placebo controlled study.	
Co-ordinating board:	Prof. Bernard Fraysse, Pôle Céphalique et Odontologique, Hôpital Purpan, Pavillon Dieulafoy, Place du Docteur Baylac - 31059 Toulouse cedex 9, France Prof. Daniele Nuti,Azienda Ospedaliera Universitaria Senese, Viale Bracci 1, 53100 Siena, Italy	
Study centres:	Specialists in neurotology conducted the study in different centers	
Studied period :	Date of first enrolment*:* 17 May 2011 Date of last completed: 30 April 2012	**Phase of development:** **II**
Objectives: **Primary** **Secondary**	**<u>Primary objective:</u>** To determine the efficacy of 8 g oral administration of acetyl-L-leucine during 14 days on vertigo symptoms relief in patient suffering from acute vestibular neuritis. **<u>Secondary objectives:</u>** - To determine the efficacy of 8 g oral administration of acetyl-L-leucine during 14 days on central vestibular compensation in patient suffering from acute vestibular neuritis. - To determine the tolerance of 8 g oral administration of acetyl-L-leucine during 14 days in patient suffering from acute vestibular neuritis.	
Methodology:	Multicenter, international, randomized, double-blind, placebo-controlled, parallel groups study. Inclusion visit and baseline evaluation (V1, Day 1), inpatient period visit (V2, from day 2 up to 5), assessment visit (V3, Day 7), end of treatment visit (V4, Day 14), end-of-study visit (V5, Day 28)/ withdrawal visit.	
Number of patients (planned and analyzed):	Based on data on acute vestibular syndrome published in the literature, 64 patients per group (total of 128 patients) was needed to show an expected mean difference between groups in VSS-SF of 3.0 ± 6.0 with a risk alpha of 5% and a risk beta of 20%. In order to minimize the number of patients receiving placebo, a randomization 1:2 was to be applied, leading to 48 patients in the placebo group and 96 patients in the active treatment group (total of 144 patients). Assuming 15% withdrawal, the number of patients expected was 56 patients in the placebo group and 112 patients in the active treatment group (total of 168 patients). Due to premature study discontinuation because of lack of recruitment, only 76 patients were randomized (26 patients in the placebo group and 50 patients in the active treatment group).	
Diagnosis and main criteria for inclusion:	Were eligible subjects who meet the following criteria: - Age 18 to 80 years, inclusive. - Acute vestibular neuritis - Onset of vestibular neuritis less than 48 hours before randomization. - Diagnosis confirmed by bithermal caloric test showing a lack of responsiveness or a hypo responsiveness of the affected ear (*i.e.* asymmetry between the two sides less than 50±5% as measured with the Jongkee's formula) performed as soon as possible within 3 days from the inclusion visit.	

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Test product, **Dose,** **Mode of administration,** **Batch number:**	V0251, 8 g acetyl-L-leucine per day, Oral route, Batch Nr SB0785 and batch Nr SB0801
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo, 8 g of granules for oral suspension per day, Oral route, Batch Nr SB0786 and batch Nr SB0802
Duration of treatment:	Study duration: 28 days (4 weeks) +/- 3 days Duration of treatment: 14 days, from Day 1 to Day 14 Duration of hospitalization: 2-5 days (patients discharged upon investigator's judgment).
Criteria for evaluation: **Efficacy:**	**<u>Primary assessment criteria</u>** **Vertigo symptoms:** - Vertigo Symptom Scale – Short Form (VSS-SF) - Verbal Rating Scale (VRS) **<u>Secondary assessment criteria</u>** - VSS-SF subscores - VRS subscores - Dizziness Handicap Inventory scale (DHI) - Horizontal spontaneous nystagmus - Horizontal gaze-evoked nystagmus - Head shaking test - Head impulse test - Bithermal caloric test
Safety:	**<u>Tolerability evaluation:</u>** - Recording of adverse events - Assessment of global tolerance
Statistical methods:	**<u>Statistical analysis:</u>** Main judgment criteria were intergroup differences in VSS-SF and VRS on Day 7 analyzed by Mixed Model for Repeated Measures (MMRM) in Modified FAS using data collected on Day 1 (baseline), Day 2 and Day 7.

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Efficacy results

Overall, 76 patients received at least one dose of treatment and constituted the Full Analyzed Set (FAS). The Modified Full Analysis Set (Modified FAS) was composed of patients from the FAS with positive bithermal caloric test, in order to take into account the patients presenting with vestibular neuritis only. Patients without major protocol deviations constituted the Per Protocol set (PP set). 50 patients received the test product V0251 and 26 received the placebo. The demographic characteristics of the FAS population are summarized below:

Variable	**Placebo n=26**	**V0251 n=50**	**Total n=76**
Gender			
Missing	-	-	-
Male	17 (65.4%)	28 (56%)	45 (59.2%)
Female	9 (34.6%)	22 (44%)	31 (40.8%)
Age (Years)			
Missing	-	-	-
Means (SD)	52.23 (13.64)	53.02 (15.12)	52.75 (14.54)
Min/Median/Max	26.4/54.55/77.5	21.1/53.90/80.1	21.1/54.15/80.1
Body Mass Index (kg/m^2) derived			
Missing	2	1	3
Means (SD)	27.77 (4.87)	27.12 (4.63)	27.33 (4.68)
Min/Median/Max	20.3/26.60/38.9	18.2/27.60/37.6	18.2/27.60/38.9

The descriptive statistics at baseline of VSS-SF and VRS in the FAS are summarized in the Table below:

		Placebo n=26	**V0251 n=50**	**Total n=76**
VSS-SF total score	Missing	-	-	-
	Mean (SD)	29.7 (11.6)	27.4 (11.0)	28.2 (11.2)
	[95% CI]	[25.0; 34.4]	[24.3; 30.6]	[25.6; 30.8]
	Min/Median/Max	5 / 31.5 / 60	1 / 28.0 / 49	1 / 30.0 / 60
VRS mean score	Missing	1	-	1
	Mean (SD)	2.17 (0.52)	2.30 (0.60)	2.26 (0.57)
	[95% CI]	[1.96; 2.39]	[2.13; 2.47]	[2.13; 2.39]
	Min/Median/Max	1.4 / 2.20 / 3.0	0.4 / 2.35 / 3.0	0.4 / 2.30 / 3.0

The VSS-SF and VRS score means at baseline were different between the placebo and the V0251 groups; consequently raw data could not be used and adjusted means only should be considered.

The analysis of VSS-SF and VRS change from baseline to Day 7 in the Modified FAS (main judgment criteria), showed no difference between the V0251 and the placebo groups. Results are summarized in the Table below:

		Placebo n=24	**V0251 n=37**	**Difference**
VSS-SF	LS mean (SE) [LS mean 95% CI]	-14.9 (1.55)	-15.0 (1.35)	0.2 (1.82) [-3.5;3.9]
VRS	LS mean (SE) [LS mean 95% CI]	-0.95 (0.109)	-0.94 (0.096)	-0.01 (0.135) [-0.29;0.26]

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Nevertheless, the MMRM analysis on the PP Set showed a 3.9 (2.06); 95%CI [-0.5; 8.2] points clinically relevant difference in favor of V0251 for VSS-SF change from baseline to Day 7.

In addition, a clinically relevant difference of almost 3 points was observed at Day 2 (2.8 (3.01); 95% CI [-3.2;8.9]) and Day 3 (3.6 (2.08); 95% CI [-0.6;7.8]), in favor of V0251 on the VSS-SF in the Modified FAS population. This was confirmed by the results on the FAS.

Safety results

No SAE and no death occurred during the study. No AEs led to permanent study drug discontinuation. One TEAE of diplopia led to temporary study drug discontinuation in the V0251 group.

There was a total of 45 TEAEs reported by 30 patients: 17 TEAEs in 12 patients (46.2%) receiving the placebo and 28 TEAEs in 18 patients (32.0%) receiving V0251. Overall, the relationship to study drug was considered by the investigator not excluded or unassessable for 13 TEAEs reported by 9 patients: 5 TEAEs in 2 patients (7.7%) receiving the placebo and 8 TEAEs in 7 patients (14.0%) receiving V0251. The most frequently affected SOC were nervous system and gastrointestinal disorders.

The hematology and biochemistry measurements did not give evidence of any specific abnormality. There was no clinically relevant modification of the vital signs in both groups.

Overall, there was no difference between the treatment groups regarding safety parameters.

Conclusion

Even if no difference was observed in VSS-SF and VRS from baseline to Day 7 in the Modified FAS (primary efficacy criteria) between V0251 and placebo, a clinically relevant effect of V0251 on vertigo symptoms has been evidenced at Day 2 and Day 3, suggesting a meaningful quick effect for this product designed to treat symptoms of acute vertigo. This study also demonstrated the good safety profile of V0251 given orally at 8 g per day for 14 days.

Date of report: 25 April 2013