SYNOPSIS

Name of Company: Pierre Fabre Médicament represented by IRPF	**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)*: **N-acetyl-L-leucine**	**Vol.: .....Page: .....**	

Title of study:	Effect of V0251 in acute vertigo. A randomized double-blind placebo controlled study.	
Coordinating Investigators:	Marie-Josée Esteve-Fraysse (France) - Michael Strupp (Germany) – Jose Antonio López Escámez (Spain) - Ales Hahn (Czech Republic).	
Principal Investigators:	List of Principal Investigators is available in Appendix 16.1.4.	
Study centers:	Emergency, ENT or neurology departments (in public hospital or private hospital) 6 centers in France, 9 in Germany, 12 in Spain, 9 in Hungary, 7 in Czech Republic.	
Publication (reference):	Not applicable	
Studied period *(years, months …)*: **(date of first enrolment)** **(date of last completed)**	10 months June 16, 2012 April 15, 2013	**Phase of development:** Phase II
Objectives: **Primary:**	The primary objective was to determine the efficacy of 4 g of V0251 administered by intravenous route on vertigo symptoms relief in patient presenting with an attack of acute vertigo from vestibular origin.	
Secondary:	The secondary objective was to determine the tolerance of 4 g of V0251 administered by intravenous route.	
Methodology:	This was a multicenter, double-blind, placebo-controlled, parallel groups, randomized study on patients suffering from acute vertigo attack from vestibular origin. Patients received a single injection of the study treatment (V0251 or matching placebo) at the dose of 4 g by intravenous route.	
Number of patients (planned and analyzed):	Planned: 132 randomized patients to have 120 evaluable patients Actual: 132 randomized patients (FAS: 132 / PP set: 123)	
Diagnosis and main criteria for inclusion:	The study was carried out in patients aged between 18 and 70 years included with: - Acute vertigo attack due to vestibular disorder that began within 48 hours before the inclusion, - Vertigo sensation lasting more than 20 min, - At least one vertigo symptom of strong intensity (≥ 3 on the VAS ranging 0-4) on the intensity vertigo scale at the moment of the inclusion.	

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Test product,	V0251 (N-acetyl-L-leucine) – ampoule 500 mg/5mL
Dose,	4 g N-acetyl-L-leucine in 40 mL (8 ampoules) in one single injection
Mode of administration,	Slow intravenous route (10 mL/min) (*i.e*. 40 mL administered in 4 minutes)
Batch number:	SB0842
Duration of treatment:	One single injection
Reference therapy,	Placebo
Dose,	40 mL
Mode of administration,	Slow intravenous route (10 mL/min)
Batch number:	SB0843
Other product,	Metopimazine – ampoule 10 mg/1 mL
Dose,	10 to 20 mg/day, on demand in case of intense vomiting
Mode of administration	Intramuscular or slow intravenous injection

Criteria for evaluation:

Efficacy:

Vertigo

- Intensity of 12 vertigo symptoms rated by patients on a 5-point VAS (ranging 0 (no symptoms), 1 (moderate), 2 (medium), 3 (strong) or 4 (very strong)):
  - 6 vertigo symptoms: unsteadiness (dystasia and walking unsureness), staggering, rotatory sensation, tendency to fall, lift sensation, blackout.
  - 6 trigger factors: change of position, bowing, getting-up, walking, eye movements, head movements.

A Mean Vertigo Score (VS_M) was calculated as the mean of the intensities of the 12 vertigo symptoms.

Measurements were repeated before study treatment administration and 30 min, 2 h and 4 h after study treatment administration.

- Vegetative and other concomitant symptoms rated by patients on a 5-point VAS (ranging 0 (no symptoms), 1 (moderate), 2 (medium), 3 (strong) or 4 (very strong)):
  - Nausea, vomiting, sweating, tachycardia
  - Tinnitus, impaired hearing, aural fullness, headache

A Mean Concomitant Symptom Score (CSS_M) was calculated as the mean of the intensities of the 8 vegetative and concomitant symptoms.

Measurements were repeated before study treatment administration and 30 min, 2 h and 4 h after study treatment administration.

- Overall Efficacy rated by the patient and the Investigator using a graded 5-point verbal rating scale (ranging 1 (very much improved), 2 (much improved), 3 (slightly improved), 4 (not improved) or 5 (deteriorated)): 2 hours and 4 hours after study treatment administration.

Safety:

- Sleepiness rated by patients on a 9-point scale (Karolinska Sleepiness Scale) before study treatment administration and 30 min, 2 h and 4 h after study treatment administration.
- Recording of adverse events and vital signs.

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Statistical methods:

Efficacy:

A futility analysis not pre-planned in the study protocol was performed. For this prupose, an IDMC was established by the Sponsor to assess the critical efficacy endpoints and to recommend to the Sponsor whether to continue or to stop the trial.

Primary criterion

- For the primary analysis, the VS_M change from baseline to 30 min after injection was compared between treatment groups after LOCF imputation in the FAS using rank analysis of covariance (ANCOVA) adjusted for the VS_M baseline.
- For the sensitivity analysis, the VS_M change from baseline to 30 min after injection was compared between treatment groups after LOCF imputation (i) in the FAS using a parametric ANCOVA adjusted for the VS_M baseline and (ii) in the PP data set using rank ANCOVA adjusted for the VS_M at baseline.

Secondary criteria

- The change on the VS_M to 30 min, 2 h and 4 h was compared between treatment groups after LOCF imputation (i) using rank ANCOVA adjusted for the VS_M baseline and (ii) using an MI-GEE method.
- The change on the CSS_M was analyzed according to the analysis scheme of the VS_M change.
- The two scores for the assessment of Overall Efficacy to be filled in by the patient and by the Investigator were both compared between treatment groups 30 min, 2 h, 4 h after injection after LOCF imputation (i) using Wilcoxon-Mann-Whitney test and Student test and (ii) using an MI-GEE method.
- Intake of rescue medication (metopimazin) was compared between treatment groups using a Chi-2 test or a Fisher's test if needed. The effect of the metopimazine intake after injection on the treatment effect estimated on the VS_M change at 2 h and 4 h after injection was assessed after LOCF imputation by the interaction term of the metopimazine intake effect by treatment group within an ANCOVA, which was adjusted for the VS_M baseline,

Safety

- The change on the Karolinska Sleepiness Score from baseline to 30 min, 2 h and 4 h were compared between treatment groups after LOCF imputation using ANCOVA adjusted for the score at baseline.

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Summary - Conclusions:

Acccording to results of the interim analysis, the decision to continue the trial until expected termination was taken.

Efficacy results

According to the results on the different parameters, V0251 did not evidence effect compared to placebo.

Safety results

Twenty-two (22) TEAEs were presented by 17 patients. Seven (7) of these TEAEs were considered as related TEAEs (6 in V0251 treatment group and 1 in placebo treatment group). The most frequent related TEAE was headache (3 cases with V0251). It could be noted that the number of AEs was low regarding the number of patients treated and these AEs were very common, especially taking into account the study pathology.

The only serious TEAE brain stem ischemia was reported with placebo.

No AEs led to discontinuation of the study treatment.

No sedative effect was observed on Karolinska sleepiness score.

No relevant changes from baseline were observed in vital signs. Only some orthostatic hypotensions were reported but not relevant regarding the study pathology which is commonly associated with vegetative symptoms.

Conclusion

In these study conditions no difference in efficacy parameters was observed between V0251 and placebo.

The overall safety of V0251 was good.

This study does not confirm the results from animal models of vertigo showing V0251 (N-acetyl-L-leucine) as the enantiomer supporting the full activity of N-acetyl-DL-leucine.

Date of report: December 23rd, 2013