Sponsored by: Pierre Fabre Médicament
Represented by: Institut de Recherche Pierre Fabre
45, Place Abel Gance
F-92654 Boulogne Cedex

1. TITLE PAGE

CLINICAL STUDY REPORT

A DOUBLE-BLIND PLACEBO CONTROLLED STUDY OF 1G, 2G, AND 4 G V0251 EFFICACY AND TOLERANCE IN VESTIBULAR NEURITIS

Investigational product: **V0251**

Protocol number: V00251 IV 201

Phase of development: **PHASE II**

EudraCT number: **2007-005054-23**

Date of first enrolment: 13/04/2008

Date of last completed: 19/04/2010

Co-ordinator(s): Professor Bernard FRAYSSE

Sponsor Representative(s) for study report:
Clinical Monitor *(*Mrs. Claire MEUNIER*)*
Statistician *(*Mrs. Marielle AGUILAR, +33 5 62 24 54 42*)*
Medical Writer *(*Miss. Victoria Pearson, Scinopsis, +33 4 94 83 90 20*)*

Date of Version: 09/09/11

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: **Not applicable (NA)**	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **L-acetylleucine**	**Vol.:.....Page:.....**	

Title of study:	A double-blind placebo controlled study of 1g, 2g and 4g V0251 efficacy and tolerance in vestibular neuritis (VN)	
Principal Investigator:	Professor Bernard FRAYSSE Pôle Céphalique et Odontologique, Hôpital Purpan, TSA 40031 – 31059, Toulouse, France	
Study centre:	Specialists in otorhinolaryngology and otoneurology in 20 centres in 7 countries: Belgium, Czech Republic, France, Germany, India, Italy and Spain.	
Publication:	None	
Studied period: **Date of first enrolment:** **Date of last completed:**	2 years and 6 days 13/04/2008 19/04/2010	**Phase of development:** Phase II

Objectives:

Preferential: To determine efficacy on central vestibular compensation of three doses versus placebo of L-acetylleucine (V0251) within 4 days of intravenous (i.v.) administration in patients hospitalised for acute VN,

Secondary:

- To determine tolerance of three doses V0251 within 4 days of i.v. administration in patients hospitalised for VN,
- to determine optimal dose (efficacy and tolerance) of V0251 within 4 days of i.v. administration in patients hospitalised for VN,
- to evaluate the primary criteria and the endpoint choices,
- to assess a dose-effect relationship.

Methodology: Multicentre, double-blind, placebo-controlled, four parallel group study.
All patients were to attend seven study visits: inclusion visit (Visit 1; Baseline (Day 1 pre-administration) and Day 1 (1 hour after 1st administration), treatment visits (Visits 1-4; Days 1-4), evaluation and ambulatory visits (Visits 5, 6 and 7 [end of study]; Days 7[±1], 14[±1] and 28[±1], respectively).

Number of patients: 120 patients were planned, with 30 patients in each of the three V0251 treatment groups (1, 2 and 4 g/day) and 30 patients in the placebo group. 109 patients were screened, 107 patients were included and randomised, and 96 patients were evaluated (25 patients in the 1 g/day V0251 group, 26 in the 2 g/day V0251 group, 22 in the 4 g/day V0251 group, and 23 patients in the placebo group). 88 patients completed the study.

Diagnosis and main criteria for inclusion: Eligible patients met the following criteria:

- patient aged above 18 years,
- patient admitted to the hospital for vertigo related to acute VN,
- VN (acute unilateral vestibulopathy) defined as:
  - acute or subacute onset of severe, prolonged rotatory vertigo, nausea and postural imbalance that began less than 48h before the inclusion visit,
  - horizontal spontaneous nystagmus with a rotational component beating toward the unaffected ear (fast phase), without evidence of central vestibular lesion,
  - Pathological Head Impulse Test (Halmagyi-Curthoys) toward the affected side,
- negative pregnancy test at inclusion for woman of child bearing potential and using an efficient contraceptive (implants, injectables, combined oral contraceptives, some intra-uterine devices or vasectomised partner related to note 3 of the Committee for Proprietary Medicinal Product [CPMP]/ International Conference on Harmonisation [ICH]/286/95) for at least 2 months before the study and one month after the end of the study,
- patient willing to participate in the study, and able to understand and sign an approved Informed Consent Form,
- patient able to understand the protocol and to attend visits,
- patient who, in the judgement of the investigator was likely to be compliant during the study,
- registered with a social security or health insurance system.

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Diagnosis and main criteria for exclusion:	The exclusion criteria for this study included: • pathologies which may affect the response to treatment or introduce ambiguity of diagnosis, such as chronic vestibular dysfunction prior to acute onset of symptoms, unilateral tinnitus during/after onset of vertigo, central vestibular (or ocular motor) dysfunction, chronic otitis or history of vestibular migraine, • non caloric hypoexcitability in the bithermal caloric test at Day 3 to ensure correct diagnosis, • exclusion criteria that ensured that patient groups for which V0251 treatment is not advisable, or is contraindicated, were not enrolled into the study. These criteria consisted of contraindication in patients with a history of hypersensitivity to acetylleucine or excipients, and a history of systemic or transtympanic administration of aminoglycosides or any other ototoxic substances.
Test product, **Dose,** **Mode of administration,** **Batch number:**	V0251 solution for i.v. use (acetyl-L-leucine 500mg/5ml vial). One i.v. administration of V0251 solution (and placebo to make up to volume), corresponding to a concentration of 0.5, 1 or 2g (at a volume of 20ml), **twice daily**, for a final daily dose of 1, 2 or 4g of V0251. Batch numbers CLP075 and SB0718.
Duration of treatment:	Four days (one injection twice daily).
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo solution (sodium chloride isotonic agent 45.00mg, water for injections-solvent Qs to 5 mL). One i.v. administration of 4 x 5ml vials placebo solution, corresponding to 20ml, **twice daily**. Batch numbers SB0540 and SB0649.
Criteria for evaluation: **Efficacy:**	**<u>Preferential criterion</u>** Change from Baseline (Day 1 pre-administration) on mean peak slow phase eye velocity of horizontal spontaneous nystagmus (in °/s) on Day 4, measured by videonystagmography (VNG), with patients looking straight ahead in complete darkness. **<u>Other criteria</u>** • Spontaneous nystagmus measured by VNG, analysis over time (Day 1, Day 2, Day 3, Day 4, Day 7, Day 14, Day 28), • change from Baseline on peak slow phase eye velocity of horizontal spontaneous nystagmus (in °/s), measured by VNG: - in complete darkness, straight ahead (max value), with horizontal gaze shifts towards, and opposite to, the affected side (mean and max values), - in the light, straight ahead, with horizontal gaze shifts towards, and opposite to, the affected side (mean and max values), • the proportion of responders, and rate of response (nystagmus improvement), over time by treatment group on Day 4, • the proportion of responders, and rate of response (grade improvement), over time by treatment group on Day 4, • the head-shaking nystagmus (HSN) test: peak slow phase eye velocity of horizontal nystagmus post rotatory head shaking nystagmus on Day 3, Day 7, Day 14 and Day 28, and time to return to initial value, • analysis over time of vertigo symptoms. Assessment on Day 1, Day 3, Day 4, Day 7, Day 14 and Day 28 as evaluated by the European Evaluation of Vertigo scale (EEV) administered by the investigator. Sub scores assessed were: - illusion of movement, - duration of illusion, - motion intolerance, - neurovegetative signs, - instability, • Fukuda test on Day 1 (baseline, before treatment), Day 3, Day 4, Day 7, Day 14, and Day 28, • displacement of subjective visual vertical (SVV) (otolithic dysfunction) on Day 1, Day 3,Day 4, Day 7, Day 14, and Day 28.

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Safety:	Adverse events (AEs), and serious AEs (SAEs), were recorded at all visits. • Laboratory investigations (haematology/biochemistry/urinalysis) were performed on Day 1 (pre-treatment) and Day 7, • physical examination was performed on Day 1 (pre-treatment) and Day 4 (end of treatment), • vital signs were assessed at each visit, performed after 5-minute rest in the supine position or sitting position (if possible).
Statistical methods:	Sample size For the peak slow phase eye velocity of horizontal spontaneous nystagmus (slow phase velocity [SPV]), a difference with placebo of 15 °/s is expected with a standard-deviation of 20 °/s. With these hypotheses and a two-sided α risk of 0.05, 30 (exactly 29) patients per group were required for a power of 80%. Efficacy • The efficacy criteria with a baseline evaluation was analysed by an analysis of covariance (ANCOVA) with the treatment group as fixed factor and the baseline as a covariate, • the efficacy criteria without a baseline evaluation were analysed by an analysis of variance (ANOVA) with the treatment group as fixed factor, • in both cases, an initial test for a dose-effect relationship was made using appropriate contrasts. If this test was statistically significant, the following procedure was applied: – test of the highest dose (4 g) versus placebo at the 0.05 level of significance; if not significant, stop, otherwise, – test of the middle dose (2 g) versus placebo at the 0.05 level of significance; if not significant, stop, otherwise, – test of the lowest dose (1 g) versus placebo at the 0.05 level of significance. This procedure kept the overall α risk at 0.05. If the test for a dose-effect relationship was not statistically significant, then the three doses were pooled and compared with placebo. These analyses were made both in the full analysis set (FAS) and VNG populations. The VNG population comprised a subset of the per protocol (PP) population defined according to baseline VNG values. The same analyses were performed on the FAS and PP populations for the other efficacy criteria. • Nystagmus improvement (in the dark with straight ahead gaze, and in the dark and in the light with gaze opposite to the affected side) was described over time by treatment group, analyzed using a Cochran-Mantel-Haenszel (CMH) test with modified ridit scores on Day 4. Time to return to the normal value (nystagmus ≤2 °/s) was described using survival curves (Kaplan-Meier method), compared between both treatment groups with the Gehan-Wilcoxon Test for the survival data. Grade improvement in the dark and in the light was described over time by treatment group, and analysed using CMH test on Day 4. Time to return to grade 0 was described using survival curves (Kaplan-Meier method), compared between both treatment groups with the Gehan-Wilcoxon Test for the survival data. Safety: • All emergent AEs (assessed at each visit) were tabulated by treatment group using the preferred terms (PTs) of Medical Dictionary for Regulatory Activities (MedDRA) dictionary grouped by System Organ Class (SOC), • for vital signs (assessed at each visit), the treatment means of raw values and absolute variations from baseline were tabulated by treatment. Changes in measures above predefined limits were tabulated by treatment and a listing of orthostatic hypotension was provided, • for the physical examination (baseline [Day 1] and Day 4 assessments) and urinalysis (baseline [Day 1] and Day 7 assessments), post trial drug administration changes that exceeded predefined limits were tabulated by treatment. Three individual data listings of clinically noteworthy abnormal laboratory values (CNALVs) were provided by dose, • concomitant treatments were presented according to the WHO-DRUG dictionary.

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Summary - Conclusions:

Demography

The mean age of patients was 50.0 years (25; 83). The mean body mass index (BMI) was 25.64 kg/m^2 (17.6; 43.2). 69.2% of patients presented with at least one medical history, in 44.9% of cases this was a surgical or medical procedure. 62.6% of patients had at least one concomitant disease, most commonly a vascular disorder (25.2%) or a metabolism/nutrition disorder (21.5%). 26.2 % patients took medication before the selection visit, (22.2%, 35.7%, 32.1% and 12.5% for the placebo and the 1, 2 and 4 g/day V0251groups, respectively), predominantly hormonal treatment (placebo group) and treatment for cardiovascular system disorders (the V0251 groups). There were a lower number of males in total (40.2%). Patient demography between groups was similar, except for a higher percentage of males in the placebo group compared with the V0251 groups, and variation in the mean baseline level of nystagmus (dark, straight ahead) between the placebo group and the 1, 2 and 4 g/day V0251 groups (15.65, 10.13, 12.76 and 10.96 °/s, respectively).

Data Set

All randomised patients were included in the FAS population: 27 in the placebo group and 28, 28, and 24 for the 1, 2, and 4 g/day V0251 groups, respectively. 11 patients were excluded from the PP data set because of major protocol deviations. Thus, the PP data set was composed of 96 patients: 23 in the placebo group and 25, 26, and 22 in the 1, 2, and 4 g/day V0251 groups, respectively. Due to the results of nystagmus measurement at baseline, a VNG population was defined for the analysis of nystagmus parameters; such a population comprised the subset of the PP population with valid VNG measurement at baseline.

Efficacy results

Preferential efficacy criterion- Primary analysis on mean peak slow wave looking straight ahead (VNG population)

Change in Nystagmus Dark Straight Ahead (Mean) at Day 4 (last observation carried forward [LOCF] approach) - Comparison between "all V0251" group and placebo (ANCOVA) [VNG]

Change of Nystagmus Dark Straight Ahead (Mean) (LOCF)	Placebo n=15	All V0251 n=46
Model Change = Baseline + Treatment Test for Baseline effect, p<0.0001 Test for Treatment effect, p=0.237		
Adjusted Change from baseline at Day 4 Least square means (LSM) (standard error [SE]) [LSM 95%CI]	-8.48 (1.24) [-11.0; -5.99]	-6.76 (0.70) [-8.17; -5.36]
Adjusted Change from baseline at Day 4, Difference between treatment groups LSM (SE) [LSM 95%CI]		1.72 (1.44) [-1.16; 4.60]
Linearity Test for linearity, p=0.918		

For this criterion, the VNG population was composed of 61 patients: 15 in the placebo group and 15, 17, and 14 in the 1, 2, and 4 g/day V0251 groups, respectively.

There was no linearity between V0251 doses; therefore, comparison was made between the placebo group and the pooled "all V0251" group. Mean change from baseline was higher in the placebo group compared with "all V0251" group and the baseline effect was statistically significant. As seen in the above table, there was no significant difference between the placebo group and the "all V0251" group for the preferential efficacy criterion (difference between treatment groups: 1.72 ± 1.44; treatment effect p value: 0.237 – not statistically significant).

Other preferential efficacy criterion analyses Analysis over time: there was no change in pathological nystagmus at Day 1 in the V0251 group whereas there was a decrease for the placebo group. Treatment effect at Day 1 was statistically significant (p=0.0120), in the absence of a baseline effect (p=0.170), but this did not continue over time. For all following visits (Days 2, 3, 4, 7, 14 and 28), the baseline effect was significant (p values <0.0001), whereas the treatment effect was not (p values >0.05).

- In the sensitivity analysis, the unadjusted estimate of treatment effect was statistically significant (p=0.046); however, this was probably due to the different mean baseline value of nygstamus in the V0251 and placebo groups, and thus must be interpreted with precaution,
- comparison between placebo and "all V0251" groups of patients categorised according to nystagmus improvement showed no overall difference between groups (p=0.870), but there was a trend towards an increased proportion of patients that had "returned to the normal value" in the "all V0251" group compared with the placebo group,

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- survival curves over time showed a trend towards a higher rate of improvement from Days 2-28 in the "all V0251" group compared with the placebo group, even though Wilcoxon analysis showed that the treatment effect was not significant (p=0.425).

Secondary efficacy criteria

- Change in nystagmus in the dark (max) and in the light for straight ahead gaze, and with horizontal gaze shifts towards, and opposite to, the affected side showed that there was no significant difference between the placebo and "all V0251" groups from Days 2-28. Analysis using the separate V0251 treatment arms over time showed a clear increase in the rate of improvement in the 4 g/day V0251 treatment arm from Days 3-28, particularly Days 7 and 14,
- analyses of nystagmus grade improvement and normalization (FAS) at Day 4 show that although the differences between the placebo and "all V0251" groups are not significant, there is a trend towards increased grade improvement in the V0251 groups,
- the HSN (to assess vestibular imbalance compensation) (PP) and Fukuda (balance instability) (FAS) tests both resulted in gradual improvement over time for all groups, but no significant improvement for the "all V0251" group over the placebo group at Days 3, 7, 14 and 28,
- SVV deviation analysis showed no statistically significant difference between groups at all time points, even though the test for linearity was significant at Day 14 (p=0.037). However, analysis using the separate V0251 treatment arms over time showed a clear increase in the rate of improvement in the 4 g/day V0251 treatment arm from Day 3-28, particularly Days 7 and 14,
- EEV total score showed no statistically significant difference in clinical signs between placebo and the "all V0251" group at all visits, including Day 4. However, an unplanned mixed model for repeated measures (MMRM) analysis of all four treatment arms showed a trend in favour of the 4 g/day V0251 treatment group at Day 14,
- EEV3 (motion intolerance) score improvement was overall greater for the 4 g/day group in comparison to other groups at all visits. In particular, there were fewer patients with "no improvement" on Days 3 and 4 in this group than in the others. The 4 g/day V0251 treatment group was also better than other groups in terms of EEV5 (instability) score total improvement and EEV3 + EEV5 measures,
- importantly, analysis of subgroups of patients categorized by nystagmus response, showed that there was no correlation between clinical signs and VGN value.

Safety results

Patients received injections of study drug twice daily for 4 days, while hospitalised, and were then monitored for a further 24±3 days.

Adverse Events

- The percentage of patients with at least one treatment-emergent AE (TEAE) was similar between the placebo group (48.1%), the V0251 1 g/day group (50.0%), the V0251 2 g/day group (39.3%), and the V0251 4 g/day group (41.7%). Reported TEAEs in the most common SOC (Nervous System Disorders) were comparable between treatment groups. The most common TEAE Preferred Term was headache, and occurred predominantly in the placebo group (four patients) compared to the three V0251 1g/day, 2g/day, and 4 g/day groups (two, one and three patients, respectively),
- the percentage of patients with at least one study drug associated TEAE was also similar between the placebo group (33.3%), the V0251 1 g/day group (28.6%), the V0251 2 g/day group (10.7%) and the V0251 4 g/day group (29.2%). No specific AE patterns were observed with increasing dose of V0251,
- four patients had SAEs, but none of these were in the V0251 4 g/day group and none were judged to be study drug associated. Two patients who experienced stroke were judged as being inclusion diagnosis errors. Apart from these two SAEs, only one patient discontinued study drug due to a TEAE and this patient was in the placebo group.

Clinical Laboratory Evaluations

A few patients in each treatment group had abnormal biochemistry and/or haematology values but the incidence was similar between the placebo and V0251 groups. There was no observable dose-response relationship with study drug for any clinical laboratory parameter.

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Vital signs

Mean systolic blood pressure (SBP) decreased from baseline at each visit in all groups, except in the V0251 4 g/day group; however, there was no dose-effect pattern observed with increasing doses of V0251. An increase from baseline in mean diastolic blood pressure (DBP) was observed at each time point in the V0251 4 g/day group and also at all time-points from Day 4 in the V0251 2 g/day group. A few patients had clinically significant changes (CSC) in DBP, most notably four increases in the V0251 4 g/day group.

Concomitant treatments

Concomitant treatments started after the first administration were taken by 40.7%, 39.3%, 46.4% and 41.7% of patients in the placebo group and the 1, 2 and 4 g/day V0251 groups, respectively, mostly to treat alimentary tract/metabolism and cardiovascular system disorders. It should be noted that cardiovascular drugs were introduced for a few patients in the V0251 group, but for only one patient in the placebo group.

Conclusion

Study objectives

Preferential

This exploratory study found there was no difference between placebo and treatment groups in the preferential criterion: change from baseline in mean nystagmus straight ahead in the dark. However there was an early treatment effect at Day 1 which was statistically significant. Indeed, at this time-point, the mean value of nystagmus was decreased in the placebo group while the baseline value was maintained in the V0251 group. This unexpected result suggests an activity of V0251 on the vestibular system which needs further exploration. Moreover, trends towards greater nystagmus improvement compared with placebo were observed for the percentage of responders, "time to return to normal" value, and grade. In addition, clinical EEV score and SVV measures both showed a comparative improvement for V0251 treatment groups that persisted throughout the study, particularly for the 4 g/day V0251 treatment group, but was greatest in the early stages of treatment. These positive trends, even though not statistically significant, were observed despite the small patient number, which therefore suggests a potential interest for early V0251 treatment of VN.

Secondary

- All three doses of V0251 were well tolerated with no difference in the incidence of AEs between the placebo and the three V0251 groups. An increase in DBP was noted with V0251 4 g/day but there was no postural hypotension. Vital signs will continue to be monitored in future trials,
- With respect to the determination of optimal dose: the 1 g/day V0251 group showed improved efficacy over placebo in the EEV3 and EEV5 measures, and was also comparable to placebo for all laboratory measures and AE incidence. However, the 4 g/day V0251 group showed the greater efficacy, particularly for EEV3, EEV5, EEV3+EEV5 and SVV measures and was also well-tolerated, but with the caveat of also showing an increase in DPB. These results point to 4 g/day as being the optimal dose, provided that vital signs are closely monitored,
- There was no correlation between clinical signs and nystagmus. This, combined with the fact that the qualitative trends in favour of V0251 were rarely reflected in quantitative statistical significance, could suggest a requirement for better standardisation for nystagmus measures, or new clinical tools and scales to evaluate treatments of VN, although this is difficult to assess with an investigational study drug,
- Dose-related effects on the measures used in this study for all Cochran-Mantel-Haenszel (CMH) analyses, were not significant. None of the tests for linearity in the study were significant, with the exception of Day 14 of the SVV total score over time analysis. There were definite trends towards increased improvement in the 4 g/day group, but the EEV3 and EEV5 "total improvement" seen for the 1 g/day group, in the absence of an improvement in the 2 g/day group, also suggest, with the statistical test results, there is no linear dose-response in this dose-range for the measures used in this study.

In conclusion, no significant difference between placebo and V0251 was observed for the preferential efficacy criterion at Day 4. However, positive trends were observed for several secondary criteria, despite the small patient number. In particular, there were more responders on EEV3 and EEV5 scores for the 1 and 4 g/day V0251 group on Days 3 and 4 of treatment, which suggests an early treatment effect that may impact on recovery mechanisms. All three doses of V0251 were well tolerated with no difference in the incidence of AEs between the placebo and the three V0251 groups. Finally, it should be noted from this study that there is no correlation between nystagmus values and clinical signs, and thus future evaluations of the efficacy should be performed on clinical parameters. All these results combined with the persistent nature of both the survival rate and response improvements over placebo, and also combined with a good safety profile, show that V0251 should be further studied for this indication.

Date of report: 07 December 2016