Pierre Fabre Médicament
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45, Place Abel Gance
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1. TITLE PAGE

CLINICAL STUDY REPORT

EFFECTS OF TANGANIL® (THREE 500 MG TABLETS TWICE DAILY) ON POSTURAL DISTURBANCES IN THE ELDERLY
Randomized, double blind, crossover, 2-way, placebo-controlled pilot study

Investigational product :	Tanganil® (L0014 CP)
Study design :	Randomized, double blind, crossover, 2-way, placebo-controlled pilot study
Protocol number :	L00014 CP 201
EudraCT number :	2007-000562-21
Phase of development :	Phase II
Date of first enrolment :	11/06/2008
Date of last patient out :	14/10/2008
Date of report :	06/10/2009
Coordinator Investigator**:**	Pr Claude JEANDEL Centre Antonin Balmès 39 av Charles Flahault 34295 MONTPELLIER Cedex 05
Sponsor Representative(s) for study report:	
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Clinical trial performed in compliance with Good Clinical Practice

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2. SYNOPSIS

<table>
<tr><td>Name of the Company :
PIERRE FABRE MEDICAMENT
45, place Abel Gance
92100 BOULOGNE (France)</td><td rowspan="3">Individual Study Table Referring to part :
of the Dossier :

Volume :
Page :</td><td rowspan="3">(FOR NATIONAL Authority Use only)</td></tr>
<tr><td>Name of finished product :
Tanganil® (L0014 CP)</td></tr>
<tr><td>Name of Active Ingredient :
Acetylleucine</td></tr>
<tr><td colspan="3">Title of Study:
Effects of TANGANIL® (three 500 mg tablets twice daily) on postural disturbances in the elderly ; randomized, double blind, crossover, 2-way, placebo-controlled pilot study.</td></tr>
<tr><td colspan="3">Coordinator Investigator:
Pr Claude JEANDEL, MD
Centre Antonin Balmès
39 av Charles Flahault
34295 MONTPELLIER Cedex 05</td></tr>
<tr><td colspan="3">Study centre(s):
Centre Antonin Balmès, 39 av Charles Flahault, 34295 MONTPELLIER Cedex 05
CHU hôpital Gui de Chauliac, 80 av Augustin Fliche, 34295 MONTPELLIER Cedex 05</td></tr>
<tr><td colspan="3">Publication (reference): not applicable</td></tr>
<tr><td>Studied period:
date of FPI: 11/06/2008
date of LPO: 14/10/2008</td><td colspan="2">Phase of development: II</td></tr>
<tr><td colspan="3">Objectives :
Primary objective:
• to assess the effects of Tanganil® on postural disturbances related to vestibular disorder without vertigo in the elderly.

Secondary objectives:
• to assess the effects of Tanganil® on patient's self-perceived handicap of dizziness.
• to assess the systemic tolerability of Tanganil®.</td></tr>
<tr><td colspan="3">Methodology :
Randomised, double blind, crossover, 2-way, placebo-controlled pilot study
with a 2 week minimum wash-out in-between period.</td></tr>
<tr><td colspan="3">Number of patients
Planned: 30 patients. Included: 2 patients.</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion :
Inclusion criteria:
• Out-patients aged over 60 years complaining of postural disturbances,
• Postural disturbances reported as "dizziness", "dysequilibrium", "unsteadiness",
• Postural disturbances with an abnormal Tinetti's test
• Ability to perform activities of daily living independently with a Katz's index of independence in Activities of Daily Living (ADL) score at 6,
• Patient with a normal neurological examination,
• Patient with a vestibular disorder without vertigo confirmed by a caloric test and/or a computerized dynamic posturography,</td></tr>
</table>

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- With a normal corrected visual acuity,
- Patient's health care covered by Social Security,
- Able to understand and sign an approved Informed Consent Form prior to study participation,
- Able to understand the protocol and to come to the control visits.

Non inclusion criteria:

*** Criteria related to pathologies**

- Genuine vertigo, ataxia,
- Extra-pyramidal or cerebellar disease,
- Mild to moderate dementia,
- Sequela of stroke,
- Foot disease interfering with balance,
- Locomotor disorders related to lower limb myopathy, disabling sarcopenia, osteoarthritis (hip, knee), peripheral neuropathy,
- Postural or postprandial hypotension, vasovagal syndrome, carotid sinus sensitivity.
- Chronic documented anaemia,
- Post-fall syndrome

*** Criteria related to the way of life**

- Heavy intake of alcohol (more than 3 glasses each day),
- Need for a gait aid (cane, walker).

*** Criteria related to treatments**

- Sedative benzodiazepine drugs introduced or modified in the 4 weeks within the inclusion visit,
- Antidepressant drugs introduced or modified in the 4 weeks within the inclusion visit,
- Myorelaxant drugs introduced or modified in the 4 weeks within the inclusion visit,
- Neuroleptic drugs introduced or modified in the 4 weeks within the inclusion visit,
- Antivertigo drugs,
- Patient with hypersensitivity to acetylleucine.
- Patient with gluten intolerance.

*** Criteria related to the population**

- Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
- Patient who is in the 1-month exclusion period of a previous study or participating to another clinical trial during this study,
- Patient who has forfeited his freedom by administrative or legal award, or who is under guardianship or who is in an emergency situation.

Test products, dose and method of administration:

Tested product

L0014 CP = Tanganil® tablet (500 mg acetylleucine).
Three tablets morning and evening, i.e. 3g acetylleucine daily.
Batch number = G00210
Expirated date = 04/2010
Oral route.

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Reference product
Placebo (tablet indistinguishable from verum form).
Three tablets morning and evening.
Batch number = SB0561
Expirated date = 01/2011
Oral route.

Duration of treatment: Two 6-week treatment periods, with a 2-week washout in-between.

Criteria for evaluation :

Efficacy :

- **Measure of subjective complaints of dizziness with a visual analogic scale**

Subjective complaints of dizziness were measured using a visual analog scale (VAS). Partients were instructed to draw a vertical line along a 10-cm horizontal line corresponding to the severity of their symptoms while sitting quietly.
One end of the line was anchored with the phrase, 'no dizziness at all,' and the other end with “as bad as it can be”.
To quantify severity of symptoms, the distance from zero ('no dizziness at all') to the mark was measured to the nearest tenth of a centimeter. A positive value indicated an increase in symptoms and a negative value indicated a decrease in symptoms.

- **Vestibular score during computerized dynamic posturography**

Computerized Dynamic Posturography provided patient’s ability to use vestibular information comparing to caloric test evaluating peripheral vestibular function.

In all cases centre of gravity was determined under four sensory conditions :

Immobile surface, immobile visual surround, eyes open.
Immobile surface, eyes closed.
Mobile surface, immobile visual surround, eyes open.
Mobile surface, eyes closed.

Each of the four conditions was performed in triplicate,giving a total of 12 tests per session.Each test lasted 20 seconds.

The following parameters were considered in the data analysis:
• Balance score (0–100%) obtained in each condition, calculated as the arithmetic mean of the three individual test scores.
• Mean overall balance score (0–100%), calculated as the arithmetic mean of the 12 individual test scores.
• Somatosensory ratio, SOM = [condition-2 score]/[condition-1 score] × 100; a measure of the patient’s ability to use somatosensory information for maintenance of balance.
• Visual ratio, VIS = [condition-4 score]/[condition-1 score] × 100; a measure of the patient’s ability to use visual information for maintenance of balance.
• Vestibular ratio, VEST = [condition-5 score]/[condition-1 score] × 100; a measure of the patient’s ability to use vestibular information for maintenance of balance.
According to the disease the vestibular score during computerized dynamic posturography had to be initially very low or even zero with an improvement in the treated group.

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- **Time measure during the "timed get up and go" test**

The timed get up and go test was a measurement of mobility. It included a number of tasks such as standing from a seating position, walking, turning, stopping, and sitting down which were all important tasks needed for a person to be independently mobile.
The normal time required to finish the test was between 7 – 10 seconds. Individuals who couldn't complete the task in that time, probably had some mobility problems, especially if they took more than 20 seconds.

Technique : patient had to do the following activities:

- Rise from sitting position,
- Walk 3 meters,
- Turn around,
- Return to chair and sit down.

Interpretation :

Patient took < 20 seconds to complete test : adequation for independent transfers and mobility.

Patient required > 30 seconds to complete test : suggestion of higher dependence and risk of falls.

Safety :
- Adverse events,
- Systemic safety (general clinical examination).

Statistical methods :

Sample size

The sample size required was based on the two efficacy criteria for which some data were available in the literature: Tinetti Balance Test (TBT) and Dizziness Handicap Inventory (DHI). The Type I error rate(α) was set at 0.05 two-sided. For both criteria, a difference between L0014 CP and its placebo of at least 15% of the baseline score was considered as clinically relevant. The sample size calculation involved also the within-subject correlation: for both criteria, the within-subject correlation coefficient was assumed to be 0.6. The baseline score of TBT was expected to be around 20 with a standard-deviation of 6.So, the expected difference between treatments was 3 with a standard-deviation of 5.4.With these assumptions,30 patients had to have a power of 83% to demonstrate a statistically significant difference. The baseline score of DHI is expected to be around 40 with a standard-deviation of 12.So, the expected difference between treatments is 6 with a standard-deviation of 11.With these assumptions,30 patients had to have a power of 82% to demonstrate a statistically significant difference.

Efficacy
Analysis of variance with the following effects: "sequence", "subject within sequence", "treatment" and "period".
Non-parametric analysis for crossover design if non-normality of residuals.
Comparison of treatments based only on data from the first period if validity of the crossover analysis not met.

Safety
Descriptive analysis of adverse events according to MedDRA dictionary.
Descriptive analysis of vital signs.

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Summary – Conclusions

Efficacy results :

2 patients were included and randomised in the study.
One of these 2 patients chose premature withdrawal couple of days after including to the trial (Visit 2 was not achieved) for personal reasons.One patient completed the trial.
The efficacy results were not possible to analyse because of lack of included and evaluable patients.

Safety results :

The analyses of adverse events at one patient who completed the study did not show any important side effects of the drug (only headache and asthenia with mild severity mentioned in CRF). Physical examination confirmed the good safety of the study drug.

Conclusion :

In this study there were included only 2 patients.
One of these two patients chose premature withdrawal for personal reasons.
This is the reason why the efficacy of treatment (Tanganil® = L0014 CP) was not assessable.
Safety was good for the unique patient who completed the trial.

Date of the report: 06/10/2009