Name of Sponsor/Company : University Hospital of Bordeaux	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product : - LEVOCARNIL - Placebo	Volume :	
Name of Active Ingredient : L-carnitine	Page :	

Title of Study :

A randomised, double blinded cross-over study comparing the efficacy of L-carnitine versus placebo in the treatment of fatigue in multiple sclerosis

Investigators :

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Study centre(s) : 7 centers

- CHU de Bordeaux Hôpital Pellegrin
- CHU de Limoges Hôpital Dupuytren
- CHU de Toulouse Hôpital Purpan
- CHU de Fort-de-France Hôpital Pierre Zobda-Quitman
- CHU de Nice Hôpital Pasteur
- CHU de Nancy Hôpital Central
- CHU de Nantes Hôpital Nord Laënnec

Publication (reference)

Presentation of results in poster format (ECTRIMS 2014, AAN 2015)

Studied period (years) : - date of first enrolment : 30/06/2010 - date of last completed : 08/07/2013	Phase of development : III

Objectives :

<u>Main objective</u> :

Evaluate the efficacy of L-cartinine on fatigue in multiple sclerosis compared to placebo.

<u>Secondary objectives</u> :

Evaluate the efficacy of L-cartinine on the multidimensional physical, cognitive and social impact of fatigue compared to placebo

Methodology :

Comparative, randomized, superiority, double-blind, multicenter clinical trial using a placebo, according to a crossover with 2 treatments compared: L-carnitine and placebo

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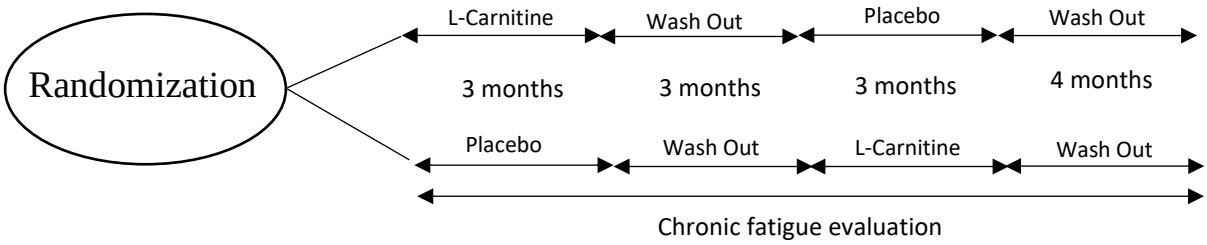

Number of patients (planned and analysed) :
- Number of patients planned : 60
- Number of patients analysed : 59

Diagnosis and main criteria for inclusion :

Inclusion criteria :
- Age ≥ 18 years old
- Patients with relapsing remitting (RR) secondary progressive (SP) or primary progressive MS on McDonald 2005 (Polman) MS diagnostic criteria, affected of fatigue for more than 3 months with global score on Modified Fatigue Impact Scale (MFIS) > 45.
- Indication of treatment of fatigue to the appreciation of the neurologist,
- Expanded Disability Status Scale (EDSS) not exceeding 6.0,
- Information and comprehensive agreement signed by patient and the investigator,
- Subject affiliated to health insurance coverage.

Exclusion criteria :
- Patients with serious unstable disease: recurrent or serious relapses, rapidly ongoing disability impairment in the preceding 6 months, serious or non stabilized depression.
- Important cognitive impairment.
- Patient who has started immunomodulatory, immunosuppressive, antidepressant or other treatment that the physician-therapist believes may interfere with fatigue assessment for less than three months or unstabilized
- Patients with a treatment of fatigue or of other condition that may interfere with fatigue evaluation to the appreciation of the neurologist.
- Patient with severe or unstabilized depressive syndrome
- Patient who received symptomatic treatment for fatigue in the last 3 months
- Energized beverage consumption or toxicomany.
- All other reasons to the opinion of the neurologist that may impair study management, especially patient compliance, neuro-psychological disorders that may input questionnaires filling.
- Patient placed under legal safeguard
- Patient participating in another clinical research trial (except with the advice of the Scientific Council)

Test product, dose and mode of administration, batch number

LEVOCARNIL : 4g/day, orally

Duration of treatment : 3 months

Reference therapy, dose and mode of administration, batch number

Placebo : NA, orally

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Criteria for evaluation :

Efficacy : global score on the Modified Fatigue Impact Scale (MFIS) to assess fatigue

Safety : collect of AE and SAE

Other(s) : Evaluation criteria for secondary objectives

- Fatigue severity scale (FSS)
- Fatigue visual analogic scale (VAS)
- Physical dimension scale of M-FIS
- SEP59 scale quality of life scale validated in daily practice to study quality of life in MS patients
- Serum levels of free carnitine and acyl-carnitine
- Exploratory criteria: impression of patient and neurologist efficacy, psychological (CES-D, EHD) and neuropsychological (SDMT, 3s PASAT) scales, gait speed, EDSS, sleep disorders (EPWORTH, BNSQ)

Statistical methods :

The main analysis was performed on an intention-to-treat. Descriptive analysis was carried out by treatment group and by group x treatment period for the endpoints.
Analysis of “treatment”, “period” and “treatment x period interaction” effects was based on a linear mixed-effects regression model.
The response variable in the variance analysis model was the overall MFIS score, and the explanatory variables were treatment group (fixed effect), treatment period (fixed effect), treatment x period interaction (fixed effect) and patient (random effect).

Summary – Conclusions

Efficacy Results :

59 patients were randomized to receive L-carnitine or placebo and 57 patients were analyzed on an intention to treat basis. The mean age was 45 years old, 74 % were women et the median EDSS was 3. At inclusion, the mean of the MFIS score was 71.3 +/- 15.5%. The compliance was good et no significant unexpected adverse events were reported. They was no diffrence in the efficacy of L-Carnitine treatment versus placebo for the main criteria MFIS score (-0.22 points, (95%CI) = [-5.80 ; 5.36], p=0.94) as well as for the secondary criteria (FSS : -0.10 points, 95%CI = [-0.45 ; 0.24], p=0.55) except for VAS fatigue : 1.43 points, 95%CI = [0.22 ; 2.65], p=0.02, in favor of placebo. There was no difference in any of the other evaluation criteria, especially the physical dimension of the MFIS score, the gait speed, psychological (CES-D, EHD) or neuropsychological (SDMT, PASAT) score, nor in quality of life between the treatment and placebo group. There was no correlation between fatigue score and serum levels of free and conjugated carnitine, and no significant efficacy in the 7 carnitine-deficient patients.

Safety Results : NA

Conclusion

In this double-blind study, L-Carnitine was no effective for the treatment of fatigue in MS patients

Date of report : 2017 september, 14th