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Title of Study :

Phase II, N=1 repeated crossover, double-blind, randomized versus placebo, multicenter pilot study evaluating the efficacy of SIMVAstatin on L-Dopa-induced DYSkinesias in Parkinson's disease patients

Investigators :

Coordinator investigators :
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Number total of investigators : 9

Study centre(s) :

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Publication (reference)

In preparation

Studied period (years) : - date of first enrolment : 15/10/2009 - date of last completed : 23/06/2010	Phase of development : II

Objectives :

Main objective :

To compare the efficacy of simvastatin at a fixed dose of 40 mg daily versus placebo in combination with L-DOPA in the treatment of L-DOPA-induced dyskinesias (DDI) in Parkinson's disease, as measured by improvement in dyskinesias without worsening of motor status and by a 7-point symptom scale assessing subjective discomfort (reported by the patient) caused by dyskinesias in the week preceding each visit.

Secondary Objectives :

- To compare the effect of simvastatin (at a fixed dose of 40mg per day) versus placebo in combination with L-DOPA on the duration of ON periods (with or without bothersome dyskinesias for the patient) and OFF periods based on logbooks completed by patients in the 3 days preceding each visit.
- Compare the effect of simvastatin (at a fixed dose of 40 mg per day) versus placebo on clinical symptoms, particularly motor symptoms of Parkinson's disease as measured by UPDRS Part III in the week preceding the visit.
- To compare the effect of simvastatin (40mg daily) versus placebo on dyskinesias presented by the patient during assessment visits, as measured by the AIMS scale.

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- Evaluate the clinical safety and tolerability of simvastatin (fixed dose 40mg daily) versus placebo administered orally in parkinsonian patients treated with L-DOPA

Methodology :

National, multicentric, exploratory, Phase II, translational research, proof-of-concept clinical trial using N=1, repeated crossover, double-blind, randomized versus placebo study design, evaluating the efficacy of SIMVAstatin on L-DOPA-induced DYSkinesias in Parkinson's disease patients treated with levodopa. The treatment phase consists of 3 cross-over series. Each cross-over lasts a total of 28 days: 4 days wash-out on placebo, 10 days (+2 days) treatment with simvastatin/placebo, 4 days wash-out on placebo and 10 days (+2 days) treatment with placebo/simvastatin. The number of cross-overs was set at 3. This is the minimum number recommended for this type of design.
Two groups of patients were compared: dyskinetic patients treated with levodopa and exposed to simvastatin (group A) and dyskinetic patients treated with levodopa and exposed to placebo (group B).

Number of patients (planned and analysed) :

- Number of patients planned : 10
- Number of patients analysed : 10

Diagnosis and main criteria for inclusion :

Medical condition : Idiopathic Parkinson's disease

Inclusion criteria :

- Men or women, over 30 and under 80 years old
- Clinical diagnosis of idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria, responsive to treatment with L-dopa
- Able to complete assessment questionnaires and logbook after individual training
- Presenting at least moderately disabling dyskinesias according to UPDRS categorization (UPDRS IV item 33 > 1)
- Hoehn and Yahr stage < 5 in “OFF” condition
- Patients on stable-dose anti-parkinsonian therapy combining, in addition to L-DOPA, dopaminergic agonists, COMT inhibitors, selegiline and anti-cholinergics for at least 1 month prior to inclusion, and presumed to remain stable for the duration of the trial.
- Patients with stable pacing parameters for 3 months and expected to remain stable for the duration of the study
- With stable doses of antiparkinsonian treatment for at least 1 month prior to study inclusion and for the duration of the trial
- For women of childbearing potential, use of effective contraception for at least 1 month prior to inclusion.
- Able to understand the protocol, having given consent and able to complete the assessments required for the study
- Affiliated with a social security scheme

Exclusion criteria :

- Secondary or atypical parkinsonian syndromes (AMS, PSP, ...)
- Significant neurological conditions other than Parkinson’s disease (PD)
- History within the last 30 days or presence of a clinically significant systemic disease other than Parkinson’s disease that compromises patient follow-up in the study, as advised by the investigator (i.e. psychiatric conditions (including hallucinatory or psychotic symptoms in the

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last 3 months), hematological, renal, hepatic, endocrinological, neurological conditions other than Parkinson's disease, cardiovascular or requiring statin therapy within 3 months of the screening visit or malignant disease)

- Neurosurgical intervention in the context of Parkinson's disease (i.e pallidotomy, thalamotomy, transplantation and deep brain stimulation...) in the year preceding the screening visit
- Current intake or within 3 months prior to the visit of screening associated treatment not allowed (as amantadine; taking atypical neuroleptics; antiemetic with D2 receptor antogonistic properties, such as metoclopramide, not including domperidone; budipine; riluzole; dextrometorphan; memantine)
- Drugs contraindicated in combination with statins
- Regular intake of grapefruit juice or any substance that inhibits cytochrome P450 3A4
- History of muscle disease
- Taking in the course or within 3 months prior to the statins screening visit
- Treatment with antidepressants/anxiolytics/flexible dose hypnotics in the month prior to screening visit (treatment with antidepressants/anxiolytics/hypnotics is allowed at a stable dose for the duration of study)
- Participation in another clinical trial of a tested drug within 30 days prior to the screening visit (or within 5 half-lives of the product)
- Significant impairment of cognitive functions defined by a MMSE score less than or equal to 24, and the DSMIV criteria of dementia or generally by limited mental abilities or psychiatric pathologies making the subject unable to give written consent to participate in the study or compromising their follow-up in the study
- Recent history (within the last 2 years) of drug or alcohol abuse
- Known or suspected contraindication or hypersensitivity to simvastatin (or any other drug in the same family)
- Taking a combination treatment with itraconazole, ketoconazole, erythromycin, clarithomycin, telithromycin, anti protease, nefazodone, verapamil, diltiazem, anti vitamin K, grapefruit juice
- Pregnant or breastfeeding woman
- Woman of childbearing age without effective contraception
- Patient unable to understand the protocol, not giving consent or unable to perform assessments required for the study
- Patient placed under legal safeguard

Test product, dose and mode of administration, batch number

- Lodalès®
- 40 mg/day
- Orally

Batch number : FAB09 00052-200

Duration of treatment : 30 days (3 treatment periods of 10 days each, interspersed with placebo and washout periods)
In total, treatment is divided over 12 weeks.

Reference therapy, dose and mode of administration, batch number : not applicable

Criteria for evaluation :

Efficacy : Symptomatic scale assessing the subjective discomfort caused by dyskinesia and reported by the patient in the week preceding the visit

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Safety : Adverse events, biological tests and general clinical examination

Statistical methods :

A detailed analysis plan will be defined and validated by the study's scientific advisory board.

The n=1 methodology enables us to assess the effect of a drug on an individual patient, but does not enable us to estimate the average effect in a population. For this reason, the results will be analyzed for each patient individually, and will therefore be more limited in terms of statistical analysis than comparative trials using more traditional experimental designs (parallel groups and crossover trials).
The first approach to statistical analysis will be a purely visual descriptive analysis of the data as a function of the treatment sequence within each cross-over.

For the analysis of the primary efficacy endpoint "7-point symptom scale assessing subjective discomfort caused by dyskinesias and reported by the patient in the week preceding the visit", patients will be categorized according to the difference obtained between active treatment and placebo within each cross-over pair, as follows (Nikles et al., 2000; Kent et al. 1999):

- **The "Probable Responder"** category will be defined by the fact that in the 3 consecutive cross-overs measured in the same patient, the difference in score on the 7-point symptom scale assessing subjective discomfort caused by dyskinesias between simvastatin and placebo is positive (higher score on simvastatin), whatever the magnitude of the difference observed.
- **The category of "Possible responders"** will be defined by the fact that in 2 of 3 consecutive cross overs measured in the same patient, the difference in the score of the 7-point symptomatic scale assessing subjective discomfort caused by dyskinesias between simvastatin and placebo is positive (higher score on simvastatin), whatever the amplitude of the difference observed.
- **The category of "non-responders"** will be defined by all other cases (higher score on simvastatin in only 1 cross-over or in none of the 3 cross-overs.

Secondary criteria will also be analyzed on an exploratory basis using the same responder bases.
For overall analyses, a paired Student's t-test and mixed models will be used (Guyatt et al., 1990) (alpha 5%).

The aim of this study is not to calculate a precise 1st and 2nd species risk. It is a study designed to find a signal with the product tested on dyskinesias in Parkinsonian patients.
The study will be considered "positive" if more than 70% of patients respond favorably in one of the various observed judgment criteria.

Statistical analyses will be performed by LN PHARMA using SAS System for Windows, version 9.2 or later (SAS Institute Inc., Cary, NC, USA).

Summary – Conclusions

10 patients were included and completed the study, 7 at CHU Bordeaux and 3 at CHU Toulouse.

Efficacy Results :

Primary efficacy criteria: only one patient was found to be a "possible responder". No statistically significant effect.
Secondary efficacy criteria: no criteria reached the statistical efficiency threshold
Biological variable : low (-20 to 25%, not significant) inhibition of ERK phosphorylation in B cells CD3 and CD20 not activated

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Safety Results : no SAE, 23 AE in 2 patients, 13 placebo, 10 simvastatin, 1 single with probable relationship (placebo).

Biological tolerance : no clinically significant events, no increase in muscle enzymes related to the drug tested.

Conclusion : Simvastatin at the dose of 40mg/d did not show in this trial effect on dopa-induced dyskinesias in Parkinson's disease. However, there was a low inhibition of pERK1/2 by the study product in lymphocytes suggesting too low a central dose or bioavailability.

Date of report : 2011 september, 07h