Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Effects of OMACOR® in patients with a cardiac sodium channel gene SCN5A mutation, one variant of the congenital long-QT syndrome

Investigational product:	Omacor® capsule
Study Design:	National, multicenter, single-arm, open-label, proof of concept study
Protocol number: **EudraCT Number:**	**V00067 CA 201 1A** 2009-011819-20
Phase of development:	Phase II
Date of first enrolment:	October 7, 2009
Date of last completed:	May 25, 2010
Coordinating investigator:	Prof. Antoine LEENHARDT, MD, PhD Hôpital Lariboisière – Service de Cardiologie 75475 Paris cedex – France Phone: 01 49 95 82 23 / Fax: 01.49.95.82.06
Sponsor Representatives for study report:	Clinical Study Monitor: E. Coppel (05.34.50.62.08) Clinical Study Manager: T. Clavel (05.63.71.39.84) Statistician: S. Roye (05.62.24.27.49)
Date of report:	25 November 2011

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: Omacor®	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:** Eicosapentaenoic acid (EPA) ethyl ester + Docosahexaenoic acid (DHA) ethyl ester	**Vol.: .....Page: .....**	

Title of study:	Effects of OMACOR® in patients with a cardiac sodium channel gene SCN5A mutation, one variant of the congenital long-QT syndrome. A proof of concept study	
Coordinating Investigator:	Prof. Antoine Leenhardt, MD, PhD	
Study centres:	- Cardiology Unit, Lariboisière hospital, Paris (Prof. Antoine Leenhardt), - Cardiology Unit, Pasteur private hospital, Toulouse (Serge Boveda, MD)	
Publication (reference):	No publication was written.	
Studied period: **date of first enrolment:** **date of last completed:**	8 months October 7, 2009 May 25, 2010	**Phase of development: II**
Objectives:	The primary objective was to assess the effect of Omacor® on the electrocardiographic QTc Fridericia (QTc_F) interval in LQT3 patients (cardiac sodium channel gene SCN5A mutation leading to congenital long-QT syndrome) The secondary objectives were to assess the effect of Omacor® on: The T wave morphology, The standard ECG parameters (RR interval, QRS complex, PR interval), The relationship between the QTc_F interval and the erythrocyte cellular membrane and cheek cells concentration in Poly-Unsaturated Fatty Acids (PUFAs). The safety assessment consisted in adverse events (AE) report, analysis of ICD events, biochemistry and haematology investigations, global physical examination and vitals signs measurements.	
Methodology:	National, multicenter, single-arm, open-label, proof-of-concept study over 6 weeks of treatment in LQT3 patients with implantable cardioverter defibrillator (ICD) Number of visits: There were 5 visits: a Selection Visit performed between Day-14 and Day1, an Inclusion Visit on Day1, a Follow-up Visit (change of dosage) on Day3, a End of Treatment Visit on Day42±2 and an End of Study Visit on Day70±2.	
Number of patients:	Six patients (5 females and 1 male) were included and completed the study.	
Diagnosis and main criteria for inclusion:	- Patient having signed a written informed consent, - Male or female gender, aged from 18 to 60 years, - LQT3 syndrome genotype confirmed in medical file, - QTc interval ≥ 470 ms, - With an ICD, - Patient able to understand the protocol and to come to the clinic visits, compliant during the study (according to the investigator's opinion) and registered with a social security or health insurance system. - For women of child bearing potential: Use of an efficient contraceptive for at least 2 months before the study and one month after the end of the study, Negative urine pregnancy test.	

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Test product:	Omacor® (Pierre Fabre Médicament),
Dose:	During the first 2 days: 4 capsules per day (2 caps in the morning and 2 caps in the evening), then during the 40 following days: 1 capsule per day.
Mode of administration:	Oral route, preferably during a meal
Batch number:	PC20090412, Expiry date: 11/2011
Duration of treatment:	42 days (6 weeks)
Criteria for evaluation:	**Efficacy:** The primary criterion was defined as the modification of the QT interval corrected for heart rate using the Fridericia correction (QTc_F) after 6 weeks of treatment. The secondary criteria were: - Modification in T wave morphology, assessed on the ECG, - Modifications in RR interval, QRS complex and PR interval (measured from the beginning of the P wave to the beginning of the QRS complex), assessed on the ECG, - Correlation between the QTc_F interval change and the erythrocyte cellular membrane and cheek cells concentration in PUFAs change. **Safety:** - Adverse events (AE), - Number of arrhythmic events recorded by the ICD (analysis of ICD recording), - Physical examination, - Haematology and biochemistry investigations, - Vital signs (blood pressure and heart rate).
Statistical methods:	Efficacy data were considered individually and only descriptive statistics were provided. Assessments of the safety were descriptive.

Summary - Conclusions:

Efficacy results:

In this study, Omacor® did not induce any significant modification of QT interval duration.

Patients undergoing this study were LQT3 syndrome classified but complete analysis of genotype demonstrated that they all had the same mutation A5369G ; this mutation do not induce appearance or increase in cardiac persistent sodium current.

Safety results:

During the study, no death, no SAE and no premature withdrawal occurred.

All TEAEs were mild or moderate in severity. Overall, there were 11 TEAE reported in 5/6 patients. The most frequent was gastrointestinal disorders (4/11 TEAE) reported in 3 patients. Only these 4 TEAE were considered related to study drug in the investigator's opinion, they all resolved, 2 with corrective treatment and 2 spontaneously.

All abnormal laboratory results were considered not clinically significant by the investigator, except increase of bilirubin and/or hepatic enzymes in 2 patients.

No shock was delivered by ICD during the study course, and all vital signs measurements (blood pressure and heart rate) were judged not clinically significant.

No unexpected adverse reactions and/or safety findings were observed.

Conclusion:

In LQT3 patients without cardiac persistent sodium current, Omacor® did not lengthen nor shorten QT interval duration.

Date of report: 25 November 2011