Pierre Fabre Médicament
Represented by: Institut de Recherche Pierre Fabre
45, Place Abel Gance
F-92100 Boulogne

1. TITLE PAGE

ABBREVIATED CLINICAL STUDY REPORT

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure

Investigational product: F373280 (Panthenyl-ester of DHA)

Study Design: International, multicentre, randomised, double-blind, placebo-controlled study.

EudraCT number: **2012-003487-48**

Protocol number: F373280 CA 2 01

Phase of development: Phase IIa

Date of first enrolment: 20 May 2013

Date of last completed: 03 Apr 2017

Coordinating Investigator(s): **Professor Savina NODARI,** Section of Cardiovascular Diseases, University Medical School and Spedali Civili Hospital of Brescia, Piazzale Spedali Civili, 1 - 25123 - BRESCIA, ITALY
Phone: +39 030 3996 587, +39 030 393849
E-mail: savinanodari@gmail.com; nodari@med.unibs.it

Sponsor Representative(s): for study report: **Karim KEDDAD, MD, PhD** Head of Medical Unit
Institut de Recherche Pierre Fabre, BP 13562, 3 avenue Hubert Curien, 31035 TOULOUSE - France
Phone: +33 5 34 50 61 69

Date of report: **15 November 2017**

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: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

Title of study:	Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure	
Coordinating Investigator:	Professor Savina NODARI Department of Clinical and Surgical Specialities, Radiological Science and Public Health – Section of Cardiovascular Diseases – University Medical School and Spedali Civili Hospital of Brescia Brescia, Italy	
Study centre(s):	International, multicentre (4 active countries – Spain, Italy, Hungary, Czech Republic) 39 centres)	
Publication (reference):	Not yet published	
Studied period *(years, months …)***:** **(date of first enrolment)** **(date of last completed)**	3 years, 11 months 20 May 2013 03 April 2017	**Phase of development:** **Phase IIa**
Objectives: **Primary:**	To assess the efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion (ECV) in patients with persistent atrial fibrillation (AF) and chronic heart failure.	
Secondary:	The secondary objectives of the study were: • To evaluate the efficacy of F373280 on the efficiency of direct ECV; • To evaluate the effect of F373280 on echocardiographic parameters; • To evaluate the safety and tolerability of F373280.	
Methodology:	International, multicentre, randomised, double-blind, placebo-controlled study in two parallel groups. Nine visits were originally planned for the study and the planned treatment duration was 24 weeks. Following a substantial protocol amendment (22 Oct 2014), Visits 5 and 8 were cancelled to reduce the constraints of patient follow-up. Transtelephonic ECG monitor (TTEM) data were transmitted weekly from Week 6 to Week 8 (instead of being transmitted daily) and every two days from Week 9 to Week 24. After a 1 to 4-week run-in period without study treatment, a total of 152 patients were planned to be randomised into one of the following treatment groups: F373280 (1 g) or placebo for 24 weeks. Following a substantial protocol amendment (28 Sep 2016), a maximum of 135 patients were to be included in the study. CHF patients with persistent AF and requiring an ECV were included in order to assess the time to first documented recurrence of AF (or emergence of atrial flutter, amendment, 22 Oct 2014) since cardioversion. During the study, patients were scheduled for a clinical visit every 4 or 8 weeks (with an additional visit 7 days after Visit 3) in order to ensure close medical monitoring and to assess efficacy and safety parameters.	
Number of patients (planned and analysed):	It was planned to randomise a total of 152 patients; due to early stop of recruitment 157 patients were screened, and a total of 135 patients were randomised.	
	***F373280 CA 2 01* – synopsis page 1/7**	

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

Diagnosis and main criteria for inclusion:	**Inclusion criteria:** (taking into account all the protocol amendments)**.** • Men or women aged 18 years or more, with: • current episodes of persistent AF (with duration between 7 days and 6 months) for whom ECV was warranted; • With previous history of documented episodes of persistent AF and ischemic or non-ischemic heart failure; • New York Heart Association (NYHA) class I or II chronic heart failure at selection and inclusion; • Left ventricular systolic dysfunction defined at selection and inclusion by left ventricular ejection fraction (LVEF) ≥ 30% and ≤ 45% or for patients with a LVEF > 45%: • An increased left ventricular end-diastolic size (diameter ≥ 60 mm and/or > 32 mm/m² and/or volume > 97 ml/m²); • And/or an increased left ventricular end-systolic size (diameter > 45 mm and/or > 25 mm/m² and/or volume > 43 ml/m²); • And/or a reduced left ventricular outflow tract velocity time integral < 15 cm; • On appropriate, stable medical treatments for heart failure; • Left atrial area (LAA) ≤ 40 cm² at selection and at inclusion;Treated or having to be treated by vitamin K antagonists (VKAs); • Patients having signed informed consent and meeting all legal and ethical requirements in biomedical research. **Non-inclusion criteria** • More than two successful cardioversions (electrical or pharmacological) in the last 6 months; • Secondary AF due to alcohol or severe valvular heart disease (grade III to IV); • NYHA class III or IV heart failure at selection or at inclusion; • Thyroid disease uncontrolled by treatment:thyroid-stimulating hormone • Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy within 6 months before selection; • Severe chronic kidney disease (creatine ≥ 25 mg/l or estimated glomerular filtration rate [GMR] < 30 ml/min) at selection; • Bradycardia (heart rate [HR] ≤ 50 beats per minute [bpm]); • Hyperkalaemia or hypokalaemia (according to the standards of local laboratories) at selection; • Cardiac surgery within 3 months before selection or planned during the study duration; • Previously ineffective pharmacological or ECV; • Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to screening), except amiodarone, dronedarone and stable doses of digoxin, betablockers, calcium antagonists; • Previously ineffective pharmacological or ECV; • Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to screening), except amiodarone, dronedarone and stable doses of digoxin, betablockers, calcium antagonists;
	***F373280 CA 2 01* – synopsis page 2/7**

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

	• Concomitant treatment with oral amiodarone or dronedarone after selection; • Concomitant treatment with intravenous amiodarone after selection; • Patient requiring a cardiac resynchronisation therapy (CRT) or having undergone CRT implantation within the last 6 months; • Treatment with any polyunsaturated fatty acid (PUFA) within the last 3 months; • Dietary supplements with omega-3 or 6 if judged by the Investigator. • Having undergone any type of ablation therapy for AF; • Anticoagulant treatment with oral anticoagulants other than VKAs
Test product, **Dose,** **Mode of administration,** **Batch number:** **Other product,** **Dose,** **Mode of administration,** **Batch number:**	F373280, soft capsules. 1 g Oral, one capsule each evening with dinner. CL0019, CL0036/A, CLB001, CLB003/1, CLB005, CLB004, CL0098 Not applicable
Duration of treatment:	24 weeks (25 if ECV postponed by 1 week)
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo soft capsules 1 g Oral, one capsule each evening with dinner. CL0020, CL006.
Criteria for evaluation:	<u>Primary efficacy criterion:</u> Time to first AF recurrence or atrial flutter emergence defined by the time to first episode of AF or atrial flutter lasting for at least 10 minutes (follow-up of 20 weeks after Visit 3 - ECV Visit). AF recurrences or atrial flutter emergences: 7-day continuous electrocardiogram (ECG; 5-leads/2 or 3 channels) ambulatory recording (Holter ECG) between Visit 3 (ECV Visit) and Visit 4 (Week 5). Then, the follow-up was documented using the TTEM: one transmission every two days from Week 9 to Week 24. For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter was assessed after Visit 3 (from Week 5). Moreover, during this TTEM period, if the patient experienced any AF or atrial flutter symptoms, it was recorded and documented using the TTEM. All ECG (Holter and TTEM) were evaluated by a Central Reading Laboratory.
	***F373280 CA 2 01* – synopsis page 3/7**

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

Secondary efficacy criteria:

During the 7-day continuous ECG monitoring:

- Number of AF episodes;
- Duration of AF episodes;

Clinical parameters:

During the whole study:

- Number of recurrences of symptomatic AF episodes;
- European Heart Rhythm Association (EHRA) score;
- Hospitalisation for cardiovascular events;
- Hospitalisation for thromboembolic stroke;
- All causes of hospitalisation;

Cardioversion:

- Assessment of spontaneous cardioversion;
- Assessment of successful cardioversion;
- Shocks distribution (1, 2 or 3 shocks);
- Number of patients needing another cardioversion after the initial ECV;

Other:

- Evolution of echocardiographic parameters (at Visit 4, 6 and 9) (left atrial diameter [mm], LAA [cm^2], left atrial volume [ml], left atrial volume/body surface area [BSA; ml/m^2], LVEF [%], left ventricular end diastolic volume/BSA [ml/m^2], left ventricular end systolic volume/BSA [ml/m^2], left ventricular end diastolic diameter [mm], left ventricular end diastolic volume [ml], left ventricular end systolic diameter [mm], left ventricular end systolic volume [ml]);
- Evolution of omega-3 index and intra erythrocyte docosahexaenoic acid (DHA; for this assessment samples were centralised).

Safety criteria:

- **Adverse events** (AEs; observed and/or spontaneously reported);
- **Vital signs**, all visits except V4(blood pressure [BP; supine and standing], HR);
- **Physical examination** (Thorough all visits except V4) (body weight, body surface area);
- **Standard 12-lead ECG**: (all visits except V4) HR (bpm), PR (ms), QRS (ms), QT (ms), QT interval using Bazett's correction formula (QTcB; ms), QT interval using Fridericia's correction formula (QTcF; ms), repolarisation patterns (ECG not centralised);
- **Haematology**: haematocrit, haemoglobin, erythrocyte count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets;
- **Biochemistry**: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma glutamyl-transferase, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), fasting glucose, total cholesterol, cholesterol (high density lipoprotein [HDL], low density lipoprotein [LDL]), triglycerides, creatine phosphokinase, fibrinogen (local laboratory);
- **Coagulation parameters**: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), international normalised ratio (INR; local laboratory), prothrombin time.

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

Statistical methods:	**Sample size:** Assuming an AF recurrence or atrial flutter emergence rate under placebo of 85% and a difference between groups of 20%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, a number of 76 randomised patients per group was necessary, using a log-rank test of survival curves. **Analysis sets:** The following analysis sets were defined: • Safety Set, composed of all randomised patients who received at least one dose of the study treatment; The final analysis of safety was done on the Safety Set; • Full Analysis Set (FAS), composed of all randomised patients having received at least one dose of the study treatment and with a successful cardioversion observed at Visit 3; a successful cardioversion was defined as either spontaneous cardioversion before Visit 3 or successful ECV performed at Visit 3 (early relapse within the observation period after ECV was considered non-successful); The final analysis of efficacy was done on the FAS. • Per Protocol (PP) Set, which consisted of all FAS patients without any major protocol deviation or other bias for primary criteria analysis. The PP Set was used for the supportive analysis of the primary efficacy criterion. **Analysis of efficacy: primary criterion:** The primary criterion was the time to first AF recurrence or atrial flutter emergence defined by the time to first episode of AF or atrial flutter lasting for at least 10 minutes during the 20-week follow-up after visit 3 (ECV visit). ***Primary analysis:*** The primary analysis, performed on the FAS, was a survival analysis using the Kaplan-Meier method and the Cox regression model. **Safety analysis:** Descriptive statistics were performed on the Safety Set *In light of the reduction of study power, and due to negative primary results, it was decided to not perform the additional and sensitivity analyses of the primary efficacy criterion, and the secondary criteria analyses. Safety data were analysed as initially planned..*
	***F373280 CA 2 01* – synopsis page 5/7**

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

Summary - Conclusions:

Of the 135 patients randomised, 71 (52.6%) patients were prematurely withdrawn from the study: 24 patients (17.8%) were prematurely withdrawn due to efficacy concerns (recurrence of persistent AF or emergence of atrial flutter). 13 patients (9.6%) were withdrawn due to safety concerns following AEs/serious AEs (SAEs). Among the remaining 36 patients (26.7%) who were withdrawn for other reasons, 11 were withdrawn due to unsuccessful ECV. The percentage of patients that were prematurely withdrawn was comparable between the F373280 group (n=34, 50.0%) and the placebo group (n=37, 55.2%) and the reasons for premature withdrawal were also similar between the two groups. A total of 64 patients (including patients with AF, 19 on F373280 and 13 on placebo) completed treatment, with a similar percentage of completers in the F373280 group (n=34, 50.0%) and the placebo group (n=30, 44.8%).

A total of 134 received at least one dose of study treatment. and were therefore included in the Safety Set: 67 patients in the F373280 group and 67 patients in the placebo group. The FAS comprised 101 patients (74.8%) who received at least one dose of the study treatment and with a successful cardioversion observed at Visit 3. The number of patients in the FAS for each treatment group was balanced: 52 patients (76.5%) in the F373280 group and 49 patients (73.1%) in the placebo group.

Overall, 12 randomised patients (8.9%) had major protocol deviations: 8 patients (11.8%) in the F373280 group and 4 patients (6.0%) in the placebo group had at least one major deviation. The majority of deviations were due to non-compliance to selection criteria or related to study treatment. Overall, 6 FAS patients (4.4%) with at least one major protocol deviation (including 3 patients [4.4%] in the F373280 group and 3 patients [4.5%] in the placebo group) were excluded from the PP Set.

In the FAS, there were more males (77.2%) than females (22.8%). The mean (standard deviation [SD]) age was 66.2 (10.9) years (ranging from 26-85 years). Physical parameters (weight, height, body mass index [BMI], BSA) were similar between treatment groups. Overall, mean (SD) LVEF was 40.5% (5.1%) and most patients (77.2%) were NYHA class II (NYHA class III and IV patients were excluded). The mean (SD) duration from heart failure diagnosis up to the selection visit was 13.8 (31.8) months, with a slightly longer duration for patients in the F373280 group (17.2 [39.2] months) compared to the placebo group. (10.1 [21.3] months). The mean (SD) duration of the current AF episode up to the selection visit was 69.5 (51.4) days and was shorter for the F373280 group compared to the placebo group (65.2 [45.0] days vs. 73.9 [57.5] days). No clinical impact was anticipated. The percentage of patients with at least one medical/surgical history was the same in both treatment groups (48 patients [71.6%]). One hundred and twenty-four patients (92.5%) were reported to have at least one concomitant disease (62 patients [92.5%] in both treatment groups). The number of patients taking at least one medication prior to first study treatment administration was similar between treatment groups (65 patients [97.0%] in the F373280 group and 64 patients [95.5%] in the placebo group). The number of patients taking at least one medication linked to study pathology prior to first study treatment administration was also similar between treatment groups (61 patients [91.0%] in the F373280 group and 63 patients [94.0%] in the placebo group).

Compliance was high in both treatment groups:. The mean (SD) compliance was 99.2% (20.5%). Only 6 patients (2 (4.0%) in F373280 group and 4 (8.3%) in placebo group) had a compliance <80% .

Efficacy results:

In the FAS, AF recurrence or atrial flutter emergence was reported in 36 patients (69.2%) in the F373280 group and 31 patients (63.3%) in the placebo group. Amongst these, 4 patients had atrial flutters, 3 patients in the F373280 group (on day 2, 4 and 104 days) and 1 patient in the placebo group (on day 7). The median time to first AF recurrence or atrial flutter emergence was 11.0 days (95% CI: 6.0, 45.0) for the F373280 group and 16.0 days (95% CI: 6.0, 141.0) for the placebo group, with a hazard ratio of 1.14 (95% CI: 0.71, 1.85). More than 40% of patients presented an AF recurrence or atrial flutter emergence in the first week following the cardioversion (using the Kaplan-Meier method, estimated probability that a patient will remain AF recurrence/atrial flutter emergence-free was 59.6% for the F373280 group and 57.1% for the placebo group at Week 1). There was no significant difference in the time to AF recurrence or atrial flutter emergence between the treatment groups (log rank test p=0.575). The results of the supportive analysis confirmed the results of the primary analysis. Mean erythrocyte DHA concentrations were higher in the F373280 group than in the placebo group at post-baseline assessments.

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: F373280	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **F373280 (Panthenyl-Ester of DHA)**	**Vol.: .....Page: .....**	

Safety results:

The total mean (SD) extent of exposure for patients was similar between treatment groups: 110.6 (66.6) days in the F373280 group and 104.7 (66.1) days in the placebo group.

Overall, 41 patients (61.2%) in the F373280 group and 38 patients (56.7%) in the placebo group experienced at least one treatment emergent AE (TEAE). The SOC in which TEAEs were most frequently reported was vascular disorders, reported in 25 patients (37.3%) in the F373280 group and 20 patients (29.9%) in the placebo group. In this SOC, the most frequent PT (i.e. reported in ≥10.0% of patients) was orthostatic hypotension, reported in 24 patients (35.8%) in the F373280 group and 20 patients (29.9%) in the placebo group. All other PTs were reported similarly in both treatment groups in <10.0% of patients, across all SOCs.

The number of patients with at least one related TEAE was slightly higher in the placebo group (n=4, 6.0%) than in the F373280 group (n=1, 1.5%). Related TEAEs were reported under the SOCs of gastrointestinal disorders (3 patients [4.5%]) and injury, poisoning and procedural complications (2 patients [3.0%]) in the placebo group and under the SOC of reproductive system and breast disorders (1 patient [1.5%]) in the F373280 group.

During the study, 1 death (PT: pulmonary oedema) occurred in the F373280 group. However, this death was not considered related to study treatment.

Overall, 7 TESAEs were reported in 5 patients in the F373280 group. These were Gastric ulcer perforation, Peritonitis, Cardiac failure, Atrial fibrillation, Cerebrovascular accident, Pulmonary oedema and Sick sinus syndrome. Only 1 TESAE (Ventricular tachycardia) in 1 patient was reported in the placebo group. However, none of the SAEs were considered related to study treatment. In the F373280 group, 5 TEAEs (1 in each patient) led to definitive treatment discontinuation. Two of these were TESAEs (AF and cerebrovascular accident). The other 3 TEAEs leading to study treatment discontinuation included 1 event of insomnia, 1 event of intracardiac thrombus and 1 event of cardiac failure. The investigators have considered no causality with the study treatment. At the end of study treatment, the patient with AF had not recovered, the patient with intracardiac thrombus was recovering, and the patients with insomnia or cerebrovascular accident or cardiac failure have recovered.

In the placebo group, eight patients reported nine TEAEs, leading to definitive treatment discontinuation. One of these was a TESAE (ventricular tachycardia) , The remaining TEAEs were five events of intracardiac thrombus (5 events in 5 patients), 1 event of abdominal pain upper, 1 event of abdominal distension, and 1 event of abdominal discomfort. The AEs of abdominal distension and abdominal discomfort were reported in the same patient.. Abdominal distension, abdominal discomfort and abdominal pain upper were considered related to study treatment. Of the 5 patients with intracardiac thrombus, 2 patients have recovered, 2 patients were recovering, and 1 patient had recovered.

All other events[2] had resolved by the end of study treatment. Clinically noteworthy abnormal laboratory values (CNALVs) were reported for the following parameters:

- haemoglobin levels (1 patient in the F373280 group and 1 patient in the placebo group) (low level in both patients);
- neutrophil counts (1 patient in the F373280 group and 1 patient in the placebo group) (decrease in both patients);
- platelet counts (1 patient in the F373280 group and 1 patient in the placebo group) (decrease at visits 3 and 6 in the F373280 group and then increase at the visit 9; in the placebo group, decreased at the visit 3 then increased at visit 6)
- total bilirubin concentration (1 patient in the placebo group); (high level)
- blood creatinine concentration (1 patient in the F373280 group); (high level)
- creatinine clearance rate (2 patients in the F373280 group and 1 patient in the placebo group) (increased in both groups).

Mean supine diastolic blood pressure (DBP), systolic blood pressure (SBP) and HR changes were comparable between treatment groups during the study. Overall, 1 patient was reported with 6 clinically significant ECG abnormalities in the placebo group and 5 patients were reported with 7 clinically significant ECG abnormalities in the F373280 group. The most frequently reported ECG abnormality was AF for both treatment groups.

Conclusion:

Despite an increase in the erythrocyte DHA levels at all post-baseline assessments, observed in the F373280 group, in the conditions of this study, F373280 at 1g/day did not demonstrate any benefit over placebo in preventing AF recurrence or atrial flutter emergence in patients with persistent AF and chronic heart failure. The safety results showed that treatment with F373280 was well tolerated and raised no safety concerns compared to placebo.

Date of report