

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

16. APPENDICES

16.1. STUDY INFORMATION

16.1.1. Protocol and protocol amendments

Study F323280 CA 2 01

16.1. STUDY INFORMATION

16.1.1. Protocol and protocol amendments

- 16.1.1.1. Protocol and appendices (version 1: 09 November 2012)***
- 16.1.1.2. Protocol and appendices (version 2: 15 January 2013)***
- 16.1.1.3. Protocol amendment n° PA01 - local (Italy) and substantial - dated on 01 March 2013 linked to Protocol and appendices (version 3: 01 March 2013)***
- 16.1.1.4. Protocol amendment n°PA02 - General and non-substantial - dated on 28 March 2013 linked to Protocol and appendices (version 4: 28 March 2013)***
- 16.1.1.5. Protocol amendment n°PA03 - General and substantial - dated on 23 October 2013 linked to Protocol and appendices (version 5: 23 October 2013)***
- 16.1.1.6. Protocol and appendices (version 6: 02 December 2013)***
- 16.1.1.7. Protocol amendment n°PA04 - General and non-substantial - dated on 03 June 2014 linked to Protocol and appendices (version 7: 03 June 2014)***
- 16.1.1.8 Protocol amendment n°PA05 - General and substantial - dated on 22 October 2014 linked to Protocol and appendices (version 8: 22 October 2014)***
- 16.1.1.9 Protocol amendment n°PA06 - General and non-substantial - dated on 06 June 2016***
- 16.1.1.10 Protocol amendment n°PA07 - General and substantial - dated on 28 September 2016 linked to Protocol and appendices (version 9: 28 September 2016)***
- 16.1.1.11 Protocol amendment n° PA07 - Local (Italy) and non-substantial - dated on 06 December 2016 linked to Protocol and appendices (version 9: 06 December 2016)***

***16.1.1.1. Protocol and appendices
(version 1: 09 November 2012)***

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study
F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:
EudraCT Number:

F 373280 CA 2 01
2012 – 003487 - 48

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Version 1– 09 NOV 2012

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 1 – 09 NOV 2012

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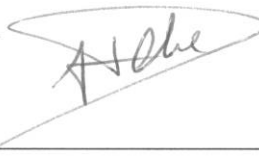
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Signature:

16 November 2012



Protocol F 373280 CA 2 01

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SIGNATURE FORM

Protocol Version 1 – 09 NOV 2012

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Country Coordinating Investigator:

"Name"

Date:

Signature: _____

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version1 – 09 NOV 2012

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 09 November 2012 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament</i> represented by the <i>Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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.	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of Atrial Fibrillation (AF) induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PUFA (PolyUnsaturated Fatty Acid) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of Atrial Fibrillation recurrence in patients with persistent Atrial Fibrillation, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2014	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 (anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (Outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35± 2 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive), 2. Patients with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted. 3. History of first documented persistent AF less than 1 year 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule)) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area $\leq 40 \text{ cm}^2$) at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 12. Having signed his/her written informed consent, 13. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 1 year 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine 25 mg/L or estimated glomerular filtration rate $< 30 \text{ mL/min}$) at selection 8. Bradycardia (HR $\leq 50 \text{ bpm}$) 9. Hyperkalemia or hypokalemia (K $> 5.5 \text{ mEq/L}$ or K $< 3.5 \text{ mEq/L}$) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration

	<p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Previous treatment with oral amiodarone within 12 months prior to inclusion 14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω3 or ω6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antithrombotic K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y₁₂ inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
Duration of Treatment:	Oral, one capsule each evening with dinner.
Reference Therapy	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Mode of Administration:	Placebo soft capsules
Evaluation Criteria:	<p>Placebo will be administered in the same conditions as the tested product.</p> <p>Oral, one capsule each evening with dinner</p> <p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of Atrial Fibrillation lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit)) <p>Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24.</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).</p> <p>Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG traces will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p> <p>During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes

	<ul style="list-style-type: none"> Duration of AF episodes <p><u>Clinical parameters:</u> During the whole study:</p> <ul style="list-style-type: none"> Number of recurrence of symptomatic AF episodes EHRA score Hospitalization for cardiovascular events Hospitalization for thromboembolic stroke All cause of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> Assessment of spontaneous cardioversion Assessment of successful cardioversion Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m², 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight), - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized). - Haematology: haematocrit, haemoglobin, RBC, WBC, differential count, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) - Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (PT)
Statistical Methods:	<p>Sample Size: Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary to achieve, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment)</p>

STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 +/-2 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (116+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2) →				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X								X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS	X	X			X	X			
ECV (3)			X						
Drug administration		← →							
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4) →		← (5) →						
TTEM (6)					← →				

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV.

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM everyday from week 6 to week 8. Then every 2 days from week 9 to week 24. In case of AF symptoms. In case of AF recurrence for at least 10 minutes and the patient does not stop the study treatment then TTEM every 4 weeks

LIST OF ABBREVIATIONS

aPTT	Activated partial thromboplastin time
AE	: Adverse event
AERP	Atrial effective refractory period
AF	: Atrial fibrillation
ALA	Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	Anti vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	Blood pressure
BSA	: Body Surface Area
CEP	Protocol evaluation committee
CHF	: Congestive heart failure
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	European heart rhythm association
EPA	Eicosapentaenoic acid
eCRF	Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine

GCP	:	Good clinical practice
GFR	:	Glomerular Filtration Rate
HBs	:	Hepatitis B antigen
HCV	:	Hepatitis C virus
HDL		High density lipoprotein
HF		Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR		International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS		Interactive voice response system
LAA		Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL		Low density lipoprotein
LOQ	:	Limit of quantification
LVEF		Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR		Mineralocorticoid receptor
MR perfusion		Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA		New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
POC		Proof of concept
PUFA	:	PolyUnsaturated fatty acid
PK	:	Pharmacokinetics
p.o.	:	Per os
PP	:	Per protocol data set
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT		Thrombin clotting time
TEAEs		Treatment emergent adverse events
TTEM		TransTelephonic ECG monitoring
VTP	:	Ventricular tachypacing

WBC White blood cells
WHO-DRUG : World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of atrial fibrillation (AF) in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the PUFAs (Polyunsaturated Fatty Acids) constitute one emerging antiarrhythmic therapy. These compounds potently address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are ALA, EPA and DHA. First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or atrial fibrillation.

The potential anti-arrhythmic effects of a PUFA was previously developed in atrial fibrillation: nicotiny ester of DHA (pro-drug based on DHA delivery) were assessed in a two-week ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of atrial fibrillation (AF) induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll assessed n-3 Polyunsaturated Fatty Acids in the prevention of atrial fibrillation recurrences after electrical cardioversion. All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct electrical cardioversion (ECV) 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion [2]. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFA on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than placebo group at one month (3.3% vs 10%; $p=0.043$), at 3 months (10% vs 25%; $p=0.004$) and at 6 months (13.3% vs 40%; $p<0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effect of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of

functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with a chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 \pm 0.33 to 1.61 \pm 0.49 and increased from 1.83 \pm 0.38 to 2.14 \pm 0.65, respectively).

The hospitalization rates for HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($P = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: 24% \pm 7% vs 29% \pm 8%, $p = 0.005$) and 1 g/d treatment groups (24% \pm 8% vs 27% \pm 8%, $P = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent atrial fibrillation and heart failure in the maintenance of sinus rhythm after electrical cardioversion.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA (docosahexaenoic acid) is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of atrial fibrillation.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

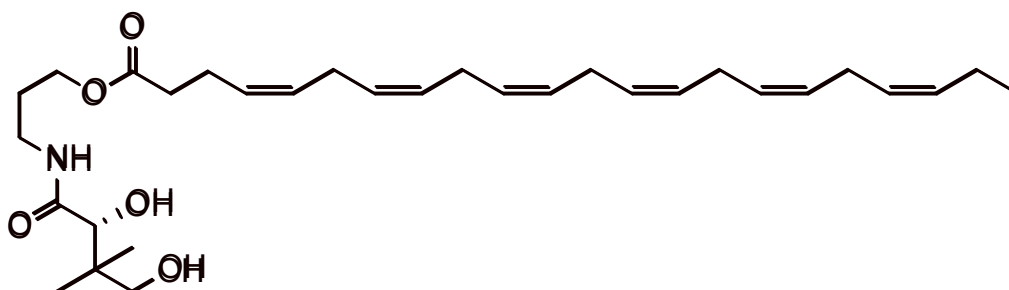
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period (AERP) were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased AERP (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $P < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the ECG intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing (VTP)-induced congestive heart failure (CHF) provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses CHF-induced AF-promotion and fibrosis in the VTP canine model. Nicotinyl ester of DHA was tested in this model, at 1g/day and 5g/day, during 4 weeks, to prevent CHF-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in atrial fibrillation duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280

similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 gm/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies , no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

6 consecutive single ascending doses were tested (0.5g, 1g, 2g, 4g, 8g and 16g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 4 were observed in the placebo group (palpitation, dizziness in standing position, 2 symptomatic orthostatic hypotensions without loss of consciousness) and 4 in the group of F373280 at the dosage of 16g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events were reported in the groups of F373280 at the dosages of 0.5g, 1g, 2g, 4g and 8g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5g to 16 g in 36 young male healthy subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding PK parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple dose

Three consecutive repeated ascending doses (1, 2 and 4g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280 5/9 TEAE were classified according the SOC in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAE have already been reported with Poly Unsaturated Fatty Acids and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** Cmax and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of atrial fibrillation (AF) induced by burst pacing [1].

Moreover, the effectiveness of PUFA has been proven in the following conditions:

- Prevention of atrial fibrillation recurrence in patients with persistent atrial fibrillation in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor®, [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($> 1/100$, $< 1/10$); uncommon ($> 1/1000$ $< 1/100$); rare ($> 1/10000$, $< 1/1000$); very rare ($< 1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations

Uncommon: gastroenteritis

- Immune system disorders:

Uncommon: hypersensitivity

- Metabolism and nutrition disorders:

Rare: hyperglycaemia

- Nervous system disorders:

Uncommon: dizziness, dysgeusia

Rare: headache

- Vascular disorders:

Very rare: hypotension

- Respiratory thoracic and mediastinal disorders:

Very rare: nasal dryness

- Gastrointestinal disorders:

Common: dyspepsia, nausea

Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper

Rare: gastrointestinal pain

Very rare: lower gastrointestinal haemorrhage

- Hepatobiliary disorders:

Rare: hepatic disorders

- Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

- General disorders and administration site conditions:

Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1g and 4g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in Atrial Fibrillation studies [2, 8]. The range of PUFAs doses tested was between 2g to 3g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in heart failure patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1g to 5g (1g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct electrical cardioversion
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of atrial fibrillation and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (AVK), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication,
- Anticoagulation with anti-vitamin K for at least 3 weeks before ECV,
- ECV in patients with stabilized INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)

- Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent atrial fibrillation and chronic heart failure.

After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 2D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit

- Visit 9 (V9): W24 (D168 ± 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent atrial fibrillation and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent atrial fibrillation with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- early persistent atrial fibrillation history (less than one year) with a duration of the current episode between 7 days to 6 months
- a moderately abnormal moderately systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- A Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of electrical cardioversion, patients should have a stable medical treatment of heart failure and should not have myocardial infarction or unstable angina or

unstable ischemic coronaropathy (assessed by coronarography or cardiac stress test or effort test within 6 months before selection).

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on anti-arrhythmics on atrial fibrillation (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be developed as a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, anti-arrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent atrial fibrillation and requiring an electrical cardioversion will be included in order to assess the time to first documented recurrence of atrial fibrillation since cardioversion.

To confirm the persistent nature of atrial fibrillation, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before electrical cardioversion. According to guidelines for the management of atrial fibrillation [6], anti-vitamin K should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation, of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodary study [2], the duration of pre-treatment with PUFA before cardioversion appears to be a contributing factor in

success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of atrial fibrillation recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of atrial fibrillation recurrence occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using a more easy to carry and easy to use device, a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with atrial fibrillation [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of atrial fibrillation after cardioversion. Moreover, PUFAs at dosage of 1g and 2g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95mg/mL and 60 to 90mg/mL, respectively) (phase I study of F373280 and Salm and coll study) [16]. With regard to the rythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a dose of 1 g daily of F373280 is considered to be appropriate to be tested in this POC study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive),
2. Patient with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted.
3. History of first documented persistent AF less than 1 year
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion

Ethical /legal considerations:

12. Having signed his/her written informed consent,
13. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation),

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 1 year,

2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be check in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine 25 mg/L or estimated glomerular filtration rate < 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (K > 5.5 mEq/L or K < 3.5 mEq/L) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Previous treatment with oral amiodarone within 12 months prior to inclusion
14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO,...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENTS IDENTIFICATION

The patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

The reasons for a patient's premature withdrawal from the study may be the following:

- The patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- The Investigator's decision in the patient's interest. Particularly, if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.

- An erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion / non inclusion criteria will immediately be withdrawn and an appropriate treatment will be instored by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with anti-vitamin K for at least 3 weeks before ECV,
- Patients who will not stabilize INR between 2 and 3 on at least 3 consecutive weekly tests
- Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 week for whom a trans-oesophageal echocardiography can not be performed before ECV or for whom a trans-oesophageal echocardiography shows a thrombus in the atria.
- Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV (i.e. unsuccessful ECV) will be considered to have finished follow-up.
- An occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and uncomfortable clinical symptoms.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit, a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator

and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number,
- c) packaging batch number,
- d) the treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”.

On the treatment unit, another label will be affixed with the mention of the investigator name and patient number (completed by the investigator).

In addition, on each case, will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person.

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the *IRPF*. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion Visit and another one at Visit 6.

For each patient, the treatment number given at Visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once the patient's eligibility is confirmed, at selection visit:

- The Investigator:
 - Calls the vocal server
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the vocal server.
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 5, the Investigator will contact again the IVRS/IWRS to obtain for visit 6 the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure will be 24 weeks, with F373280 or placebo.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator, in collaboration with the Sponsor representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF, according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (Selection Visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on e-CRF. All treatments should be evaluated by the investigator at selection and their prolongation during the study or their stop should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

Anti-vitamin K should be given for at least 3 weeks before ECV and continued for the whole study duration. The anti-vitamin K used will be left to the decision of the each investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Any Polyunsaturated Fatty Acid (PUFA)
- Any anticoagulant treatment other than antivitamin K: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the case report form. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION:

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first Atrial Fibrillation recurrence is defined by the first episode of Atrial Fibrillation (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of electrical cardioversion visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM)

- Trans Telephonic ECG Monitoring (TTEM):

Thus, the follow up will be documented using the TTEM: daily transmission from visit 4 to visit 6. Then, every two days from visit 6 to visit 9.

Moreover, during this TTEM period, if patient experiences AF symptoms, it should be documented using the TTEM.

In case of AF recurrence, and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at the investigator's judgement, he/she could be maintained in the study with the treatment, in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be faxed to the site. The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. *Definition*

Number of Atrial Fibrillation episodes will consist in the assessment of episodes of AF with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.1.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the study visit 4.

8.1.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. *Duration of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episodes.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. *Clinical parameters evaluation*

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition:*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month); intermediate (1/month to almost daily); and frequent at least daily.

8.1.2.3.1.2. Schedule

This evaluation will be performed in case of symptoms evocative of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

This evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of number of AF recurrence associated with a symptom (Palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG in atrial fibrillation.

8.1.2.3.3. *Number and duration of hospitalization*

- Number and duration of hospitalization for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalization for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shock distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL),

8.1.2.5.2. *. Schedule*

The measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

The measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. *Evaluation method*

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, for volume measurements, the recommended method is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. **BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA**

8.2.1. **Definition**

Because of the limited accessibility of human tissues for biopsy, red blood cell DHA contents is a marker for tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. *Collection schedule*

Blood samples will be collected for determination of red blood cells (RBC) concentrations of DHA.

Blood samples will be performed as follows:

- Visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the electronic Case Report Forms (e-CRFs).

8.2.2.2. *Technical handling*

Two blood samples will be collected containing EDTA. They will be gently shaken and centrifuged at 3000g for 15 min at room temperature, within 30 minutes after collection. Plasma and white blood cells will be discarded. Red blood cells will be stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C) within 3 weeks following collection. Analysis will be performed within 2 weeks following reception at the Analytical centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol, after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will

be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock), in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of adverse events (AEs) since the last visit will be based on the patient's spontaneous reporting, the investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The volume of blood samples complete haematology, biochemistry should not exceed 30 mL.

8.3.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *Hematocrit, haemoglobin, Red blood cells (RBC) count, white blood cells (WBC) count, WBC differential counts (% and absolute), platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate*

aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.

Blood samples will be taken in the morning, in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L,$

in women:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L] \times 0.85$

- with serum creatinine expressed as $\mu mol/l$:

$GFR (mL/min) = [(140-age) \times weight / serum\ creatinine\ in\ \mu mol/l] \times k,$ where $k = 1.23$ for men, 1.04 for women.

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patients' interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. Schedule

Vital signs will be measured at each visit.

8.3.4.2. *Technical Procedure and Parameters*

Systolic (SBP) and diastolic (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation, after at least 5 minutes in supine position and after 2 minutes in standing position by counting the beats for at least 30 seconds.

Bodyweight will be measured in patient in underwear and with the same balance at each visit.

8.3.5. **Electrocardiogram (ECG)**

8.3.5.1. *Schedule*

An electrocardiogram will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram (ECG):

The global interpretation from manual reading (normality, clinical relevance) and heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent atrial fibrillation.

8.3.6. **Coagulation parameters**

The assessment of coagulation will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV,
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV,
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by anti-vitamin K should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.3.7. Concomitant Treatments

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial can be found in section 7.

8.4. COMPLIANCE

The patient will be reminded at each visit to bring back any remaining soft capsules, blister, case (used or unused) at the following visit.

At each visit, the Investigator will record the number of supplied and remaining Soft Capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If he/she accepts to participate in the study, he/she will sign the informed consent and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and Atrial Fibrillation characteristics
- Echocardiography using a two-dimensional echocardiography.
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory (CRL). The CRL will send his/her assessment regarding the confirmation of persistent atrial fibrillation within 2 working days to the Investigator.
- The patient will enter the selection period in which anticoagulant (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will contact the IVRS/IWRS system to confirm the patient selection and order the treatment delivery and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent atrial fibrillation by the CRL during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography.
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential.

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS system.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6), in order to ensure that the INR is stable, between 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Red Blood Cell concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 ± 2 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of Adverse Events
- Concomitant treatments (authorised, disallowed)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device (Trans Telephonic ECG Monitoring) for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG

- The cardiac monitoring will be continued using a TTEM device (Trans Telephonic ECG Monitoring). The device will be given to the patient who will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 5, the investigator will contact the IVRS/IWRS to obtain another treatment unit to be dispensed at visit 6 for the last 12-week period.
- at visit 6, an echocardiography will be performed and, the red blood cell concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential

- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An adverse event is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

This includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values, which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity.

10.1.3. Reporting of Adverse Events

The records of adverse events in the electronic Case Report Form (e-CRF) describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A serious adverse event (SAE) includes, but is not necessarily restricted to any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect.

Other events such as cancer, and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough, or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdose meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure,
- preparation for routine health assessment/procedure (e.g. routine colonoscopy),
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All serious adverse events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, must be recorded by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") (see appendix 17.2) with all the available information about the event, to the Sponsor's representative:

Marlène GUIRAUD, Pharm D
INSTITUT DE RECHERCHE PIERRE FABRE,
Centre de R&D Pierre Fabre – BP 13562
3 Avenue Hubert Curien
31035 TOULOUSE Cedex 1
Phone: +33 5 35 50 63 48
Fax: + 33 5 34 50 65 92
Email: marlene.guiraud@pierre-fabre.com

In case of non-inclusion the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose, and associated adverse event if any, are reported only on the Adverse Event page of the CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must be also transmitted to the sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug(s) should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is discontinued from the study.

The investigators must report to the sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The investigator must immediately notify the sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An electronic Case Report Forms (e-CRF) will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files and which will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants who will use this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRF (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. *Initiation Visit*

Before the start of the study at all investigation sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. *Follow-up Visits*

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. *Closing Visit*

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored

- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes,
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of measures of primary end point, the safety data and to recommend to the Sponsor whether to continue, modify, or to stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on a e-CRF.

The e-CRF used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate coding.

12.4. DATA STORAGE

The computer data files, as well as their modifications, will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e.: data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by Pierre Fabre Biométrie (PFB) or under the supervision of the statistician of PFB using SAS® software, according to the Statistical Analysis Plan (SAP) approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 evaluable patients per group is required to achieve, using a log-rang test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 2 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. *Clinical parameters evaluation*

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. *Biomarker analysis: red blood cell concentrations of DHA*

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patients will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAE
- With at least three TEAE
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.
- Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:
 - By system organ class
 - By system organ class and preferred term
 - By system organ class and preferred term, taking into consideration its most severe intensity
 - And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

"The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TE AE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patient).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

Serious adverse events will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all blood laboratory parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate. Each treatment group will be identified differently. The first bisecting line (45° line), the lines of lower

and upper normal range, the lines of PSC range and CNALV range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

Clinically noteworthy abnormal laboratory values (CNALV) (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. *Vital Sign Measurements Over Time*

For each parameter (systolic blood pressure, diastolic blood pressure and heart rate in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. *Body weight*

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. *Individual Patient Changes*

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) – number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days).

13.11. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study.

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Médicament, are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not

- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents
- Authorises direct access to source documents for monitoring, audits and inspections
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. Early Study Termination Decided by the Competent Authorities

The Competent Authorities may suspend or prohibit a study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both his representatives (Study Manager, CRA, ...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed to in writing with the Study Manager, the investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis, and clinical study report writing are under the Sponsor's responsibility.

Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results are drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version October 2012
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57;870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedaron for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedaron versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELINE D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY TO PIERRE FABRE PRODUCT SAFETY DEPARTMENT TO BE TRANSMITTED TO THE MONITOR BY FAX WITHIN 24H : M. GUIRAUD Fax n° +33 5 34 50 65 92	
Transmission date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	Country :
SAE N° <input type="text"/> <input type="text"/>	FIRST NOTIFICATION <input type="checkbox"/> FOLLOW-UP <input type="checkbox"/>

➤ **SUBJECT CHARACTERISTICS**

Surname <input type="text"/> <input type="text"/> <input type="text"/>	First name <input type="text"/> <input type="text"/>	Birth date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Gender <input type="text"/> 1=M, 2=F	Height <input type="text"/> <input type="text"/> <input type="text"/> cm	Weight <input type="text"/> <input type="text"/> <input type="text"/> kg

➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdose meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) : 	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐

➤ **CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE**
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

INN or trade name	Daily dose	Start date (ddmmyy)	Ongoing at occurrence of the event	Stop date (ddmmyy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ **MEASURES TAKEN FOLLOWING THE SAE**

• **Study treatment**

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• **The event led to :**

- ☐ Prescription of corrective or symptomatic treatments (specify names and dosages) :
- ☐ Discontinuation of concomitant treatments (specify names) :
- ☐ Others, specify :

➤ **OUTCOME**

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ **INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)**

- ☐ Not Suspected ☐ Suspected ☐ Insufficient data

comments :

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(a)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(a) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		• < 1 500/mm ³ whatever the baseline value
WBC (if missing value for neutrophils)		• < 3 000/mm ³ whatever the baseline value
PLATELETS		• < 100 000/mm ³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.2. Protocol and appendices
(version 2: 15 January 2013)***

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study
F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:
EudraCT Number:

F 373280 CA 2 01
2012 – 003487 - 48

Sponsor's Representative:

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Version 2– 15 JAN 2013

The information contained in this document is confidential and is the property of the Sponsor, Pierre Fabre Médicament. This information is given for the needs of the study and must not be disclosed without prior written consent of the Sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the study must be informed that it is confidential and must not be disclosed.

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 2 – 15 JAN 2013

Sponsor's Representative:**Head of Therapeutic Area:**

Alain DELARUE, MD

Date:

Signature:

18 January 2013

08 October 2013

I confirm that my original
signature was dated on 18 January 2013.

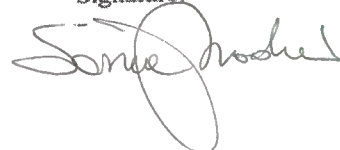
Study Coordinating Investigator:

Savina NODARI, MD

Date:

Signature:

29/01/2013



Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 2 – 15 JAN 2013

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
---------------	-------	------------

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 2 – 15 JAN 2013

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 15 January 2013 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament</i> represented by the <i>Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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.	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of Atrial Fibrillation (AF) induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PUFA (PolyUnsaturated Fatty Acid) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of Atrial Fibrillation recurrence in patients with persistent Atrial Fibrillation, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2014	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 (anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (Outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35± 2 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive), 2. Patients with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted. 3. History of first documented persistent AF less than 1 year 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule)) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area $\leq 40 \text{ cm}^2$) at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 12. Having signed his/her written informed consent, 13. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 1 year 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine $\geq 25 \text{ mg/L}$ or estimated glomerular filtration rate $< 30 \text{ mL/min}$) at selection 8. Bradycardia (HR $\leq 50 \text{ bpm}$) 9. Hyperkalemia or hypokalemia ($K > 5.5 \text{ mEq/L}$ or $K < 3.5 \text{ mEq/L}$) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration

	<p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Previous treatment with oral amiodarone within 12 months prior to inclusion 14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω3 or ω6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antithrombin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y₁₂ inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
Duration of Treatment:	Oral, one capsule each evening with dinner.
Reference Therapy	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Mode of Administration:	Placebo soft capsules
Evaluation Criteria:	<p>Placebo will be administered in the same conditions as the tested product.</p> <p>Oral, one capsule each evening with dinner</p> <p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of Atrial Fibrillation lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit) <p>Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24.</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).</p> <p>Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG traces will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p>

	<p>During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u></p> <p>During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All cause of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m², 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight), - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized). - Haematology: haematocrit, haemoglobin, RBC, WBC, differential count, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) - Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (PT)
Statistical Methods:	<p>Sample Size:</p> <p>Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis</p> <p>The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses</p> <p>All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses</p> <p>Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment)</p>

STUDY FLOW-CHART

F373280 CA 201	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 +/-2 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2) →				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS	X	X			X	X			
ECV (3)			X						
Drug administration		← →							
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4) →		← (5) →						
TTEM (6)					← →				

⁽¹⁾ Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

⁽²⁾ In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV.

⁽³⁾ In patients with AF

⁽⁴⁾ 24-hour Holter ECG

⁽⁵⁾ 7-day Holter ECG

⁽⁶⁾ TTEM everyday from week 6 to week 8. Then every 2 days from week 9 to week 24. In case of AF symptoms. In case of AF recurrence for at least 10 minutes and the patient does not stop the study treatment then TTEM every 4 weeks

LIST OF ABBREVIATIONS

aPTT	Activated partial thromboplastin time
AE	: Adverse event
AERP	Atrial effective refractory period
AF	: Atrial fibrillation
ALA	Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	Anti vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	Blood pressure
BSA	: Body Surface Area
CEP	Protocol evaluation committee
CHF	: Congestive heart failure
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	European heart rhythm association
EPA	Eicosapentaenoic acid
eCRF	Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate

HBs	:	Hepatitis B antigen
HCV	:	Hepatitis C virus
HDL		High density lipoprotein
HF		Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR		International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS		Interactive voice response system
LAA		Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL		Low density lipoprotein
LOQ	:	Limit of quantification
LVEF		Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR		Mineralocorticoid receptor
MR perfusion		Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA		New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
POC		Proof of concept
PUFA	:	PolyUnsaturated fatty acid
PK	:	Pharmacokinetics
p.o.	:	Per os
PP	:	Per protocol data set
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT		Thrombin clotting time
TEAEs		Treatment emergent adverse events
TTEM		TransTelephonic ECG monitoring
VTP	:	Ventricular tachypacing
WBC		White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of atrial fibrillation (AF) in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the PUFAs (Polyunsaturated Fatty Acids) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are ALA, EPA and DHA. First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or atrial fibrillation.

The potential anti-arrhythmic effects of a PUFA was previously developed in atrial fibrillation: nicotinyl ester of DHA (pro-drug based on DHA delivery) were assessed in a two-week

ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of atrial fibrillation (AF) induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll assessed n-3 Polyunsaturated Fatty Acids in the prevention of atrial fibrillation recurrences after electrical cardioversion. All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct electrical cardioversion (ECV) 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion [2]. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFA on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than placebo group at one month (3.3% vs 10%; $p=0.043$), at 3 months (10% vs 25%; $p=0.004$) and at 6 months (13.3% vs 40%; $p<0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effect of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with a chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 \pm 0.33 to 1.61 \pm 0.49 and increased from 1.83 \pm 0.38 to 2.14 \pm 0.65, respectively).

The hospitalization rates for HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($P = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: 24% \pm 7% vs 29% \pm 8%, $p = 0.005$) and 1 g/d treatment groups (24% \pm 8% vs 27% \pm 8%, $P = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent atrial fibrillation and heart failure in the maintenance of sinus rhythm after electrical cardioversion.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA (docosahexaenoic acid) is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of atrial fibrillation.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

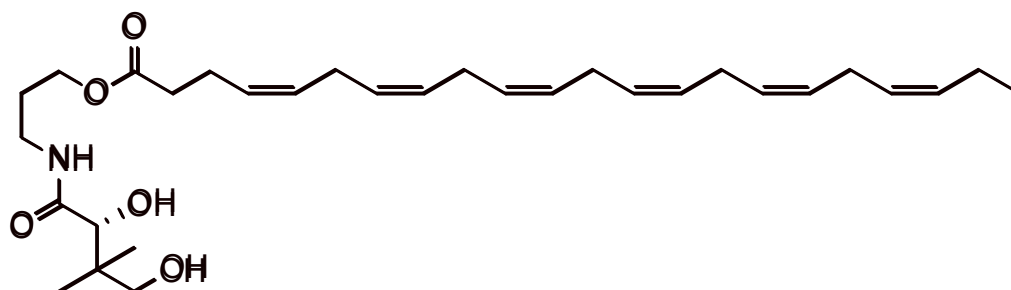
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: $C_{31}H_{49}NO_5$

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period (AERP) were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased AERP (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $P < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the ECG intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing (VTP)-induced congestive heart failure (CHF) provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses CHF-induced AF-promotion and fibrosis in the VTP canine model. Nicotinyl ester of DHA was tested in this model, at 1g/day and 5g/day, during 4 weeks, to prevent CHF-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in atrial fibrillation duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280

similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 gm/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies , no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

6 consecutive single ascending doses were tested (0.5g, 1g, 2g, 4g, 8g and 16g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 4 were observed in the placebo group (palpitation, dizziness in standing position, 2 symptomatic orthostatic hypotensions without loss of consciousness) and 4 in the group of F373280 at the dosage of 16g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events were reported in the groups of F373280 at the dosages of 0.5g, 1g, 2g, 4g and 8g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5g to 16 g in 36 young male healthy subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding PK parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple dose

Three consecutive repeated ascending doses (1, 2 and 4g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280 5/9 TEAE were classified according the SOC in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAE have already been reported with Poly Unsaturated Fatty Acids and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** Cmax and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of atrial fibrillation (AF) induced by burst pacing [1].

Moreover, the effectiveness of PUFA has been proven in the following conditions:

- Prevention of atrial fibrillation recurrence in patients with persistent atrial fibrillation in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor®, [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($> 1/100$, $< 1/10$); uncommon ($> 1/1000$ $< 1/100$); rare ($> 1/10000$, $< 1/1000$); very rare ($< 1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations

Uncommon: gastroenteritis

- Immune system disorders:

Uncommon: hypersensitivity

- Metabolism and nutrition disorders:

Rare: hyperglycaemia

- Nervous system disorders:

Uncommon: dizziness, dysgeusia

Rare: headache

- Vascular disorders:

Very rare: hypotension

- Respiratory thoracic and mediastinal disorders:

Very rare: nasal dryness

- Gastrointestinal disorders:

Common: dyspepsia, nausea

Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper

Rare: gastrointestinal pain

Very rare: lower gastrointestinal haemorrhage

- Hepatobiliary disorders:

Rare: hepatic disorders

- Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

- General disorders and administration site conditions:

Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1g and 4g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in Atrial Fibrillation studies [2, 8]. The range of PUFAs doses tested was between 2g to 3g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in heart failure patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1g to 5g (1g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct electrical cardioversion
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of atrial fibrillation and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (AVK), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication,
- Anticoagulation with anti-vitamin K for at least 3 weeks before ECV,
- ECV in patients with stabilized INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)

- Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent atrial fibrillation and chronic heart failure.

After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 2D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit

- Visit 9 (V9): W24 (D168 ± 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent atrial fibrillation and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent atrial fibrillation with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- early persistent atrial fibrillation history (less than one year) with a duration of the current episode between 7 days to 6 months
- a moderately abnormal moderately systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- A Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of electrical cardioversion, patients should have a stable medical treatment of heart failure and should not have myocardial infarction or unstable angina or

unstable ischemic coronaropathy (assessed by coronarography or cardiac stress test or effort test within 6 months before selection).

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on anti-arrhythmics on atrial fibrillation (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be developed as a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, anti-arrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent atrial fibrillation and requiring an electrical cardioversion will be included in order to assess the time to first documented recurrence of atrial fibrillation since cardioversion.

To confirm the persistent nature of atrial fibrillation, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before electrical cardioversion. According to guidelines for the management of atrial fibrillation [6], anti-vitamin K should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation, of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodary study [2], the duration of pre-treatment with PUFA before cardioversion appears to be a contributing factor in

success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of atrial fibrillation recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of atrial fibrillation recurrence occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using a more easy to carry and easy to use device, a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with atrial fibrillation [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of atrial fibrillation after cardioversion. Moreover, PUFAs at dosage of 1g and 2g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95mg/mL and 60 to 90mg/mL, respectively) (phase I study of F373280 and Salm and coll study) [16]. With regard to the rhythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a dose of 1 g daily of F373280 is considered to be appropriate to be tested in this POC study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive),
2. Patient with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted.
3. History of first documented persistent AF less than 1 year
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion

Ethical /legal considerations:

12. Having signed his/her written informed consent,
13. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation),

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 1 year,

2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (K $>$ 5.5 mEq/L or K $<$ 3.5 mEq/L) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Previous treatment with oral amiodarone within 12 months prior to inclusion
14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antithrombin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y₁₂ inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO,...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENTS IDENTIFICATION

The patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

The reasons for a patient's premature withdrawal from the study may be the following:

- The patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- The Investigator's decision in the patient's interest. Particularly, if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.

- An erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion / non inclusion criteria will immediately be withdrawn and an appropriate treatment will be instored by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with anti-vitamin K for at least 3 weeks before ECV,
- Patients who will not stabilize INR between 2 and 3 on at least 3 consecutive weekly tests
- Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 week for whom a trans-oesophageal echocardiography can not be performed before ECV or for whom a trans-oesophageal echocardiography shows a thrombus in the atria.
- Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV (i.e. unsuccessful ECV) will be considered to have finished follow-up.
- An occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and uncomfortable clinical symptoms.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit, a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator

and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number,
- c) packaging batch number,
- d) the treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”.

On the treatment unit, another label will be affixed with the mention of the investigator name and patient number (completed by the investigator).

In addition, on each case, will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person.

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the *IRPF*. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion Visit and another one at Visit 6.

For each patient, the treatment number given at Visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once the patient's eligibility is confirmed, at selection visit:

- The Investigator:
 - Calls the vocal server
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the vocal server.
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 5, the Investigator will contact again the IVRS/IWRS to obtain for visit 6 the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure will be 24 weeks, with F373280 or placebo.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator, in collaboration with the Sponsor representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF, according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (Selection Visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on e-CRF. All treatments should be evaluated by the investigator at selection and their prolongation during the study or their stop should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

Anti-vitamin K should be given for at least 3 weeks before ECV and continued for the whole study duration. The anti-vitamin K used will be left to the decision of the each investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Any Polyunsaturated Fatty Acid (PUFA)
- Any anticoagulant treatment other than antivitamin K: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the case report form. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION:

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first Atrial Fibrillation recurrence is defined by the first episode of Atrial Fibrillation (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of electrical cardioversion visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM)

- Trans Telephonic ECG Monitoring (TTEM):

Thus, the follow up will be documented using the TTEM: daily transmission from visit 4 to visit 6. Then, every two days from visit 6 to visit 9.

Moreover, during this TTEM period, if patient experiences AF symptoms, it should be documented using the TTEM.

In case of AF recurrence, and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at the investigator's judgement, he/she could be maintained in the study with the treatment, in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be faxed to the site. The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. *Definition*

Number of Atrial Fibrillation episodes will consist in the assessment of episodes of AF with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.1.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the study visit 4.

8.1.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. *Duration of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episodes.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. *Clinical parameters evaluation*

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition:*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month); intermediate (1/month to almost daily); and frequent at least daily.

8.1.2.3.1.2. Schedule

This evaluation will be performed in case of symptoms evocative of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

This evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of number of AF recurrence associated with a symptom (Palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG in atrial fibrillation.

8.1.2.3.3. *Number and duration of hospitalization*

- Number and duration of hospitalization for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalization for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shock distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL),

8.1.2.5.2. *. Schedule*

The measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

The measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. *Evaluation method*

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, for volume measurements, the recommended method is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. **BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA**

8.2.1. **Definition**

Because of the limited accessibility of human tissues for biopsy, red blood cell DHA contents is a marker for tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. *Collection schedule*

Blood samples will be collected for determination of red blood cells (RBC) concentrations of DHA.

Blood samples will be performed as follows:

- Visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the electronic Case Report Forms (e-CRFs).

8.2.2.2. *Technical handling*

Two blood samples will be collected containing EDTA. They will be gently shaken and centrifuged at 3000g for 15 min at room temperature, within 30 minutes after collection. Plasma and white blood cells will be discarded. Red blood cells will be stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C) within 3 weeks following collection. Analysis will be performed within 2 weeks following reception at the Analytical centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol, after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will

be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock), in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of adverse events (AEs) since the last visit will be based on the patient's spontaneous reporting, the investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only an haematology examination will be performed.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The volume of blood samples complete haematology, biochemistry should not exceed 30 mL.

8.3.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *Hematocrit, haemoglobin, Red blood cells (RBC) count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning, in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L,$

in women:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L] \times 0.85$

- with serum creatinine expressed as $\mu mol/l$:

$GFR (mL/min) = [(140-age) \times weight / serum\ creatinine\ in\ \mu mol/l] \times k,$ where $k = 1.23$ for men, 1.04 for women.

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patients' interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. *Schedule*

Vital signs will be measured at each visit.

8.3.4.2. *Technical Procedure and Parameters*

Systolic (SBP) and diastolic (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation, after at least 5 minutes in supine position and after 2 minutes in standing position by counting the beats for at least 30 seconds.

Bodyweight will be measured in patient in underwear and with the same balance at each visit.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. *Schedule*

An electrocardiogram will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram (ECG):

The global interpretation from manual reading (normality, clinical relevance) and heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent atrial fibrillation.

8.3.6. Coagulation parameters

The assessment of coagulation will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV,
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV,
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by anti-vitamin K should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.3.7. Concomitant Treatments

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial can be found in section 7.

8.4. COMPLIANCE

The patient will be reminded at each visit to bring back any remaining soft capsules, blister, case (used or unused) at the following visit.

At each visit, the Investigator will record the number of supplied and remaining Soft Capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If he/she accepts to participate in the study, he/she will sign the informed consent and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and Atrial Fibrillation characteristics
- Echocardiography using a two-dimensional echocardiography.
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory (CRL). The CRL will send his/her assessment regarding the confirmation of persistent atrial fibrillation within 2 working days to the Investigator.
- The patient will enter the selection period in which anticoagulant (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will contact the IVRS/IWRS system to confirm the patient selection and order the treatment delivery and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent atrial fibrillation by the CRL during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography.

- 12-lead ECG
- Urine pregnancy test for women of child bearing potential.

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS system.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6), in order to ensure that the INR is stable, between 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, Red Blood Cell concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be

induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 ± 2 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of Adverse Events
- Concomitant treatments (authorised, disallowed)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device (Trans Telephonic ECG Monitoring) for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using a TTEM device (Trans Telephonic ECG Monitoring). The device will be given to the patient who will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 5, the investigator will contact the IVRS/IWRS to obtain another treatment unit to be dispensed at visit 6 for the last 12-week period.
- at visit 6, an echocardiography will be performed, an haematology examination will be done and the red blood cell concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An adverse event is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

This includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values, which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as

those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity.

10.1.3. Reporting of Adverse Events

The records of adverse events in the electronic Case Report Form (e-CRF) describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A serious adverse event (SAE) includes, but is not necessarily restricted to any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect.

Other events such as cancer, and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough, or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure,
- preparation for routine health assessment/procedure (e.g. routine colonoscopy),
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All serious adverse events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, must be recorded by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") (see appendix 17.2) with all the available information about the event, to the Sponsor's representative:

Marlène GUIRAUD, Pharm D

INSTITUT DE RECHERCHE PIERRE FABRE,

Centre de R&D Pierre Fabre – BP 13562

3 Avenue Hubert Curien

31035 TOULOUSE Cedex 1

Phone: +33 5 35 50 63 48

Fax: + 33 5 34 50 65 92

Email: marlene.guiraud@pierre-fabre.com

In case of non-inclusion the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose, and associated adverse event if any, are reported only on the Adverse Event page of the CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must be also transmitted to the sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug(s) should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is discontinued from the study.

The investigators must report to the sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The investigator must immediately notify the sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An electronic Case Report Forms (e-CRF) will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files and which will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants who will use this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRF (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigation sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. *Follow-up Visits*

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. *Closing Visit*

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes,
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of measures of primary end point, the safety data and to recommend to the Sponsor whether to continue, modify, or to stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on a e-CRF.

The e-CRF used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate coding.

12.4. DATA STORAGE

The computer data files, as well as their modifications, will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e.: data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by Pierre Fabre Biométrie (PFB) or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan (SAP) approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 evaluable patients per group is required, using a log-rang test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 2 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patients will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAE

- With at least three TEAE
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.
- Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:
- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

"The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TE AE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patient).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

Serious adverse events will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time

of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be identified differently. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of PSC range and CNALV range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

Clinically noteworthy abnormal laboratory values (CNALV) (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and heart rate in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. *Individual Patient Changes*

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) – number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days).

13.11. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study.

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor *Pierre Fabre Médicament*, are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents
- Authorises direct access to source documents for monitoring, audits and inspections
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. *Early Study Termination Decided by the Sponsor*

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. *Early Study Termination Decided by the Competent Authorities*

The Competent Authorities may suspend or prohibit a study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both his representatives (Study Manager, CRA, ...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed to in writing with the Study Manager, the investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis, and clinical study report writing are under the Sponsor's responsibility.

Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results are drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version January 2013
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57:870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedaron for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedaron versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELIN D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY TO PIERRE FABRE PRODUCT SAFETY DEPARTMENT TO BE TRANSMITTED TO THE MONITOR BY FAX WITHIN 24H : M. GUIRAUD Fax n° +33 5 34 50 65 92	
Transmission date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	Country :
SAE N° <input type="text"/> <input type="text"/>	FIRST NOTIFICATION <input type="checkbox"/> FOLLOW-UP <input type="checkbox"/>

➤ **SUBJECT CHARACTERISTICS**

Surname <input type="text"/> <input type="text"/> <input type="text"/>	First name <input type="text"/> <input type="text"/>	Birth date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Gender <input type="text"/> 1=M, 2=F	Height <input type="text"/> <input type="text"/> <input type="text"/> cm	Weight <input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg

➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdose meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) : 	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐

➤ **CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE**
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

INN or trade name	Daily dose	Start date (ddmmyy)	Ongoing at occurrence of the event	Stop date (ddmmyy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ **MEASURES TAKEN FOLLOWING THE SAE**

• **Study treatment**

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• **The event led to :**

- ☐ Prescription of corrective or symptomatic treatments (specify names and dosages) :
- ☐ Discontinuation of concomitant treatments (specify names) :
- ☐ Others, specify :

➤ **OUTCOME**

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ **INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)**

- ☐ Not Suspected ☐ Suspected ☐ Insufficient data

comments :

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(a)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	µmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	µmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	µmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(a) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		<ul style="list-style-type: none"> • < 1 500/mm³ whatever the baseline value
WBC (if missing value for neutrophils)		<ul style="list-style-type: none"> • < 3 000/mm³ whatever the baseline value
PLATELETS		<ul style="list-style-type: none"> • < 100 000/mm³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

16.1.1.3. Protocol amendment n° PA01
Local (Italy) and substantial dated on 01 March 2013 linked to
Protocol and appendices (version3: 01 March 2013)

CLINICAL STUDY PROTOCOL AMENDMENT n° PA01 – Version 1
Local (Italy) - Substantial

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

CLINICAL STUDY PROTOCOL AMENDMENT n° PA01 – Version 1

Local (Italy) - Substantial

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code:	F373280 CA 2 01
EudraCT Number:	2012-003487-48
Sponsor's Representative:	Marlène GUIRAUD
Coordinating Investigator:	Pr Savina NODARI
Date of amendment PA01:	1 st March 2013

Confidential

Clinical Study Protocol Amendment n° PA01 – Version 1
Local (Italy) - Substantial
SIGNATURE FORM

Sponsor's representative:

• **Head of Therapeutic Area**

Alain DELARUE, MD

Date:

05-03-2013

Signature:



Study Coordinating Investigator:

Date:

Signature:

Pr Savina NODARI

Clinical Study Protocol Amendment n° PA 01 – Version 1

Local (Italy) - Substantial

COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

Country Coordinating Investigator:

Date:

Signature:

Pr Savina NODARI

Clinical Study Protocol Amendment n° PA 01 – Version 1

Local (Italy) - Substantial

INVESTIGATOR SIGNATURE FORM

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA 01, dated __ / __ / __ and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF PROTOCOL VERSIONS

PROTOCOL VERSIONS		MODIFICATIONS	COMMENTS
Version 1	09/11/2012	Initial version	Version 1 submitted in Italy (to Central Ethics Committee)
Version 2	15/01/2013	Following French CA request (ANSM) : - Add of a non inclusion criteria : "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6	Version 2 not submitted to CEC in Italy – The version 3 will be directly submitted

1. AMENDMENT RATIONALE

This substantial local amendment follows the submission of the study protocol and Informed Consent Form (ICF) to the Central Ethics Committee (CEC) and Competent Authority (CA) in Italy.

According to the CEC and CA requirements and, in order to harmonise the protocol and the ICF , the following changes have been done to the study protocol :

- adjustment of the selection criteria n°10 related to the contraception method
- addition of a letter that is given by the patient to his/her general practitioner (GP)
- precision that the sponsor can not collect a copy of the Informed Consent Form
- precision that the patient card is in Italian language only (without any English mention)

In addition, the modification performed in the protocol version 2, on French Medicinal Agency have been included :

- Addition of a non-inclusion criteria related to breast-feeding female patient
- Addition of haematology dosage at visit 3 and 6

2. CHANGES DESCRIPTION

PREVIOUS VERSION	MODIFIED VERSION
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<p>STUDY SYNOPSIS AND 5.1 INCLUSION CRITERIA</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>10. For female patient of child-bearing potential:</p> <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or - documented as 	<p>STUDY SYNOPSIS AND 5.1 INCLUSION CRITERIA</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>10. For female patient of child-bearing potential:</p> <ul style="list-style-type: none"> - absolute abstinence from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized <p>11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion</p> <p>12. For male with a childbearing potential partner:</p> <ul style="list-style-type: none"> - absolute abstinence from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study.
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<p>surgical ly sterilize d</p> <p>11. For female patient of child- bearing potential: negative urine pregnancy test at inclusion</p>	
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PREVIOUS VERSION	MODIFIED VERSION
<p>STUDY SYNOPSIS AND 5.2 NON INCLUSION CRITERIA</p> <p><i>Others criteria:</i></p> <p>20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,</p> <p>21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,</p> <p>22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,</p> <p>23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,</p> <p>24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,</p>	<p>STUDY SYNOPSIS AND 5.2 NON INCLUSION CRITERIA</p> <p><i>Others criteria:</i></p> <p>20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,</p> <p>21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,</p> <p>22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,</p> <p>23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,</p> <p>24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,</p> <p>25. Breastfeeding female patient.</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>5.9 STUDY CARD</p> <p>The patient will receive from the Investigating Centre at Visit 1 - Selection Visit, a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83.</p>	<p>5.9 STUDY CARD AND LETTER FOR GENERAL PRACTITIONERS (GP)</p> <p>The patient will receive from the Investigating Centre at Visit 1 - Selection Visit :</p> <ul style="list-style-type: none"> - a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. This card will be in Italian without any English mention. - a letter to be given to his/her general practitioner. This letter intends to inform the GP (and any other doctors who take care of the patient) that the patient participate to this clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

PREVIOUS VERSION	MODIFIED VERSION
<p>8.3 SAFETY ASSESSMENT</p> <p>8.3.2 Laboratory Investigations</p> <p>8.3.2.1 Schedule</p> <p>Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.</p> <p>Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.</p> <p>8.3.2.2. Technical Procedures and Parameters</p> <p>The following tests will be performed:</p> <p><u>Haematology:</u> <i>Hematocrit, haemoglobin, Red blood cells (RBC) count, white blood cells (WBC) count, WBC differential counts (% and absolute), platelets.</i></p>	<p>8.3 SAFETY ASSESSMENT</p> <p>8.3.2 Laboratory Investigations</p> <p>8.3.2.1 Schedule</p> <p>Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.</p> <p>At visit 3 and 6, only an haematology examination will be performed.</p> <p>Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.</p> <p>8.3.2.2. Technical Procedures and Parameters</p> <p>The following tests will be performed:</p> <p><u>Haematology:</u> <i>Hematocrit, haemoglobin, Red blood cells (RBC) count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.</i></p>

PREVIOUS VERSION	MODIFIED VERSION
<p style="text-align: center;">9. STUDY PROCEDURES</p> <p>Visit 3 (Week 4: D28 -2/+7 days) cardioversion</p> <p>Patient will be assessed for the following criteria:</p> <p>...</p> <ul style="list-style-type: none"> Laboratory examination: Red Blood Cell concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT) <p>....</p> <p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>Patient will be assessed for the following criteria:</p> <p>- ...</p> <p>- at visit 6, an echocardiography will be performed and the red blood cell concentration of DHA will be measured.</p> <p>...</p>	<p style="text-align: center;">9. STUDY PROCEDURES</p> <p>Visit 3 (Week 4: D28 -2/+7 days) cardioversion</p> <p>Patient will be assessed for the following criteria:</p> <p>...</p> <ul style="list-style-type: none"> Laboratory examination: Haematology, Red Blood Cell concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT) <p>....</p> <p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>Patient will be assessed for the following criteria:</p> <p>- ...</p> <p>- at visit 6, an echocardiography will be performed, an haematology examination will be done and the red blood cell concentration of DHA will be measured.</p> <p>....</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>11.2. STUDY MONITORING</p> <p><i>11.2.1.4. Closing Visit</i></p> <p>At the end of the study, a final visit will be carried out by the CRA to:</p> <ul style="list-style-type: none"> • Verify that the e-CRFs CD-ROM with pdf files are correctly stored • Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the <i>IRPF</i> for destruction • Obtain the last data clarifications and/or solutions if any • Collect the patient's consent forms in sealed envelopes, • Make an on-site review of all study documentation and complete it if necessary • And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration. 	<p>11.2. STUDY MONITORING</p> <p><i>11.2.1.4. Closing Visit</i></p> <p>At the end of the study, a final visit will be carried out by the CRA to:</p> <ul style="list-style-type: none"> • Verify that the e-CRFs CD-ROM with pdf files are correctly stored • Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the <i>IRPF</i> for destruction • Obtain the last data clarifications and/or solutions if any • Collect the patient's consent forms in sealed envelopes (except in case of specific country requirement), • Make an on-site review of all study documentation and complete it if necessary • And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

PREVIOUS VERSION	MODIFIED VERSION
<p data-bbox="236 443 633 481">13.8 SAFETY ANALYSIS</p> <p data-bbox="209 533 778 571">13.8.2 Clinical Laboratory Evaluation</p> <p data-bbox="209 604 837 965">For all blood laboratory parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.</p> <p data-bbox="209 1021 837 1279">Each treatment group will be identified differently. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of PSC range and CNALV range added on the plots (see Appendix 17.3).</p>	<p data-bbox="885 443 1283 481">13.8 SAFETY ANALYSIS</p> <p data-bbox="858 533 1428 571">13.8.2 Clinical Laboratory Evaluation</p> <p data-bbox="858 604 1492 965">For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.</p> <p data-bbox="858 1021 1492 1440">For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.</p> <p data-bbox="858 1496 1492 1753">Each treatment group will be identified differently. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of PSC range and CNALV range added on the plots (see Appendix 17.3).</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>14.3 PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM</p> <p>The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study.</p>	<p>14.3 PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM</p> <p>The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).</p>

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study
F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:
EudraCT Number:

F 373280 CA 2 01
2012 – 003487 - 48

Sponsor's Representative:

Marlène GUIRAUD, Pharm D
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Study Coordinating Investigator

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Version 3– 01 MAR 2013

The information contained in this document is confidential and is the property of the Sponsor, Pierre Fabre Médicament. This information is given for the needs of the study and must not be disclosed without prior written consent of the Sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the study must be informed that it is confidential and must not be disclosed.

SPONSOR PERSONNEL

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represented by
Institut de Recherche Pierre Fabre

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E-mail: richard.roche@pierre-fabre.com

CONTRACT RESEARCH ORGANISATIONS

For Feasibility, Monitoring and Regulatory issues:

Pharmaceutical Service Network (PSN)

Rufino Gonzalez

28 037 Madrid - SPAIN

Phone: +34 91 375 6930 - Fax: +34 91 375 6931

E-mail: www.psnglobal.org

For Centralised Randomisation and Electronic Case Report Form

S-Clinica

6, Chaussée de Boondael

B-1050 Brussels - BELGIUM

Phone: +32 2 645 0567 - Fax: +32 2 645 0569

E-mail: irena.seredina@s-clinica.com

For Centralised Reading of Holder ECG and TTEM and equipment supply:

Biomedical System

1945 Chaussée de Wavre

B-1160 Brussels - BELGIUM

Phone: +32 2 661 20 70 - Fax: +32 2 661 20 71

E-mail: sjacobs@biomedsys.com

For intra erythrocyte DHA dosage

Agrocampus Ouest

Laboratoire de Biochimie

65 rue de Saint Briec – CS 84215

35042 RENNES Cedex - FRANCE

Phone: +33 2 23 48 55 49 - Fax: +33 2 23 48 55 50

E-mail: daniel.catheline@agrocampus-ouest.fr

Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 3 – 01 MAR 2013

Sponsor's Representative:

Head of Therapeutic Area:
Alain DELARUE, MD

Date:

05-03-2013

Signature:



Study Coordinating Investigator:

Savina NODARI, MD

Date:

Signature:

Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 3 – 01 MAR 2013

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
---------------	-------	------------

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 3 – 01 MAR 2013

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 1st March 2013 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament</i> represented by the <i>Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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.	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of Atrial Fibrillation (AF) induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PUFA (PolyUnsaturated Fatty Acid) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of Atrial Fibrillation recurrence in patients with persistent Atrial Fibrillation, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2014	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 (anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (Outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35± 2 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive), 2. Patients with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted. 3. History of first documented persistent AF less than 1 year 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule)) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area $\leq 40 \text{ cm}^2$) at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential : <ul style="list-style-type: none"> ● in all the countries except Italy: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized ● in Italy only: <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion 12. For male with a child-bearing potential partner (In Italy only): <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study. <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 13. Having signed his/her written informed consent, 14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 1 year

	<ol style="list-style-type: none"> 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (K $>$ 5.5 mEq/L or K $<$ 3.5 mEq/L) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Previous treatment with oral amiodarone within 12 months prior to inclusion 14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω3 or ω6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
Duration of Treatment:	Oral, one capsule each evening with dinner.
Reference Therapy	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
	Placebo soft capsules
	Placebo will be administered in the same conditions as the tested product.

Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of Atrial Fibrillation lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit)) <p>Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24.</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).</p> <p>Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG traces will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p> <p>During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u></p> <p>During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All cause of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m², 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight), - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized). - Haematology: haematocrit, haemoglobin, RBC, WBC, differential count, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) - Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (PT)
Statistical Methods:	<p>Sample Size:</p> <p>Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p>

	<p>Primary Efficacy Analysis</p> <p>The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses</p> <p>All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses</p> <p>Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment)</p>

STUDY FLOW-CHART

F373280 CA 201	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 +/-2 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2) →				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS	X	X			X	X			
ECV (3)			X						
Drug administration		← →							
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4) →		← (5) →						
TTEM (6)					← →				

⁽¹⁾ Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

⁽²⁾ In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV.

⁽³⁾ In patients with AF

⁽⁴⁾ 24-hour Holter ECG

⁽⁵⁾ 7-day Holter ECG

⁽⁶⁾ TTEM everyday from week 6 to week 8. Then every 2 days from week 9 to week 24. In case of AF symptoms. In case of AF recurrence for at least 10 minutes and the patient does not stop the study treatment then TTEM every 4 weeks

LIST OF ABBREVIATIONS

aPTT	Activated partial thromboplastin time
AE	: Adverse event
AERP	Atrial effective refractory period
AF	: Atrial fibrillation
ALA	Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	Anti vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	Blood pressure
BSA	: Body Surface Area
CEP	Protocol evaluation committee
CHF	: Congestive heart failure
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosaehaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	European heart rhythm association
EPA	Eicosapentaenoic acid
eCRF	Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate

HBs	:	Hepatitis B antigen
HCV	:	Hepatitis C virus
HDL		High density lipoprotein
HF		Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR		International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS		Interactive voice response system
LAA		Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL		Low density lipoprotein
LOQ	:	Limit of quantification
LVEF		Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR		Mineralocorticoid receptor
MR perfusion		Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA		New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
POC		Proof of concept
PUFA	:	PolyUnsaturated fatty acid
PK	:	Pharmacokinetics
p.o.	:	Per os
PP	:	Per protocol data set
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT		Thrombin clotting time
TEAEs		Treatment emergent adverse events
TTEM		TransTelephonic ECG monitoring
VTP	:	Ventricular tachypacing
WBC		White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of atrial fibrillation (AF) in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the PUFAs (Polyunsaturated Fatty Acids) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are ALA, EPA and DHA. First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or atrial fibrillation.

The potential anti-arrhythmic effects of a PUFA was previously developed in atrial fibrillation: nicotinyl ester of DHA (pro-drug based on DHA delivery) were assessed in a two-week

ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of atrial fibrillation (AF) induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll assessed n-3 Polyunsaturated Fatty Acids in the prevention of atrial fibrillation recurrences after electrical cardioversion. All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct electrical cardioversion (ECV) 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion [2]. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFA on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than placebo group at one month (3.3% vs 10%; $p=0.043$), at 3 months (10% vs 25%; $p=0.004$) and at 6 months (13.3% vs 40%; $p<0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effect of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with a chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 \pm 0.33 to 1.61 \pm 0.49 and increased from 1.83 \pm 0.38 to 2.14 \pm 0.65, respectively).

The hospitalization rates for HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($P = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: 24% \pm 7% vs 29% \pm 8%, $p = 0.005$) and 1 g/d treatment groups (24% \pm 8% vs 27% \pm 8%, $P = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent atrial fibrillation and heart failure in the maintenance of sinus rhythm after electrical cardioversion.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA (docosahexaenoic acid) is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of atrial fibrillation.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

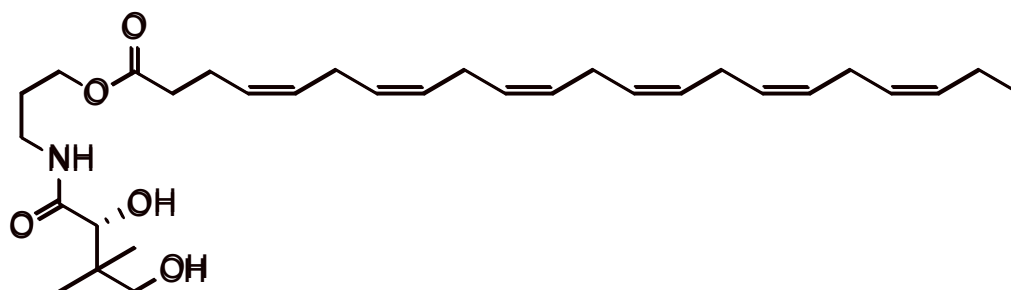
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period (AERP) were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased AERP (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $P < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the ECG intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing (VTP)-induced congestive heart failure (CHF) provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses CHF-induced AF-promotion and fibrosis in the VTP canine model. Nicotinyl ester of DHA was tested in this model, at 1g/day and 5g/day, during 4 weeks, to prevent CHF-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in atrial fibrillation duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280

similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 gm/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies , no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

6 consecutive single ascending doses were tested (0.5g, 1g, 2g, 4g, 8g and 16g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 4 were observed in the placebo group (palpitation, dizziness in standing position, 2 symptomatic orthostatic hypotensions without loss of consciousness) and 4 in the group of F373280 at the dosage of 16g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events were reported in the groups of F373280 at the dosages of 0.5g, 1g, 2g, 4g and 8g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5g to 16 g in 36 young male healthy subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding PK parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple dose

Three consecutive repeated ascending doses (1, 2 and 4g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280 5/9 TEAE were classified according the SOC in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAE have already been reported with Poly Unsaturated Fatty Acids and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** Cmax and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of atrial fibrillation (AF) induced by burst pacing [1].

Moreover, the effectiveness of PUFA has been proven in the following conditions:

- Prevention of atrial fibrillation recurrence in patients with persistent atrial fibrillation in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor®, [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($> 1/100$, $< 1/10$); uncommon ($> 1/1000$ $< 1/100$); rare ($> 1/10000$, $< 1/1000$); very rare ($< 1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations

Uncommon: gastroenteritis

- Immune system disorders:

Uncommon: hypersensitivity

- Metabolism and nutrition disorders:

Rare: hyperglycaemia

- Nervous system disorders:

Uncommon: dizziness, dysgeusia

Rare: headache

- Vascular disorders:

Very rare: hypotension

- Respiratory thoracic and mediastinal disorders:

Very rare: nasal dryness

- Gastrointestinal disorders:

Common: dyspepsia, nausea

Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper

Rare: gastrointestinal pain

Very rare: lower gastrointestinal haemorrhage

- Hepatobiliary disorders:

Rare: hepatic disorders

- Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

- General disorders and administration site conditions:

Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1g and 4g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in Atrial Fibrillation studies [2, 8]. The range of PUFAs doses tested was between 2g to 3g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in heart failure patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1g to 5g (1g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct electrical cardioversion
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of atrial fibrillation and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (AVK), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication,
- Anticoagulation with anti-vitamin K for at least 3 weeks before ECV,
- ECV in patients with stabilized INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)

- Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent atrial fibrillation and chronic heart failure.

After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 2D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit

- Visit 9 (V9): W24 (D168 ± 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent atrial fibrillation and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent atrial fibrillation with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- early persistent atrial fibrillation history (less than one year) with a duration of the current episode between 7 days to 6 months
- a moderately abnormal moderately systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- A Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of electrical cardioversion, patients should have a stable medical treatment of heart failure and should not have myocardial infarction or unstable angina or

unstable ischemic coronaropathy (assessed by coronarography or cardiac stress test or effort test within 6 months before selection).

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on anti-arrhythmics on atrial fibrillation (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be developed as a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, anti-arrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent atrial fibrillation and requiring an electrical cardioversion will be included in order to assess the time to first documented recurrence of atrial fibrillation since cardioversion.

To confirm the persistent nature of atrial fibrillation, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before electrical cardioversion. According to guidelines for the management of atrial fibrillation [6], anti-vitamin K should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation, of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodary study [2], the duration of pre-treatment with PUFA before cardioversion appears to be a contributing factor in

success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of atrial fibrillation recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of atrial fibrillation recurrence occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using a more easy to carry and easy to use device, a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with atrial fibrillation [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of atrial fibrillation after cardioversion. Moreover, PUFAs at dosage of 1g and 2g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95mg/mL and 60 to 90mg/mL, respectively) (phase I study of F373280 and Salm and coll study) [16]. With regard to the rhythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a dose of 1 g daily of F373280 is considered to be appropriate to be tested in this POC study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive),
2. Patient with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted.
3. History of first documented persistent AF less than 1 year
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - **in all the countries except Italy:**
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
 - **in Italy only:**
 - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or

- use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,
14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation),

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 1 year,
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be check in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (K $>$ 5.5 mEq/L or K $<$ 3.5 mEq/L) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Previous treatment with oral amiodarone within 12 months prior to inclusion
14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,

21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO,...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENTS IDENTIFICATION

The patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

The reasons for a patient's premature withdrawal from the study may be the following:

- The patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form

- obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- The Investigator's decision in the patient's interest. Particularly, if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.
 - An erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion / non inclusion criteria will immediately be withdrawn and an appropriate treatment will be instored by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
 - Patients who could not be treated with anti-vitamin K for at least 3 weeks before ECV,
 - Patients who will not stabilize INR between 2 and 3 on at least 3 consecutive weekly tests
 - Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 week for whom a trans-oesophagoal echocardiography can not be performed before ECV or for whom a trans-oesophagoal echocardiography shows a thrombus in the atria.
 - Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV (i.e. unsuccessful ECV) will be considered to have finished follow-up.
 - An occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and uncomfortable clinical symptoms.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit :

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.
- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number,
- c) packaging batch number,
- d) the treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units

- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”.

On the treatment unit, another label will be affixed with the mention of the investigator name and patient number (completed by the investigator).

In addition, on each case, will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person.

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion Visit and another one at Visit 6.

For each patient, the treatment number given at Visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once the patient's eligibility is confirmed, at selection visit:

- The Investigator:
 - Calls the vocal server
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the vocal server.
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator

- Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 5, the Investigator will contact again the IVRS/IWRS to obtain for visit 6 the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure will be 24 weeks, with F373280 or placebo.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made

available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator, in collaboration with the Sponsor representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF, according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (Selection Visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on e-CRF. All treatments should be evaluated by the investigator at selection and their prolongation during the study or their stop should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

Anti-vitamin K should be given for at least 3 weeks before ECV and continued for the whole study duration. The anti-vitamin K used will be left to the decision of the each investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Any Polyunsaturated Fatty Acid (PUFA)
- Any anticoagulant treatment other than antivitamin K: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the case report form. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION:

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first Atrial Fibrillation recurrence is defined by the first episode of Atrial Fibrillation (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of electrical cardioversion visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM)

- Trans Telephonic ECG Monitoring (TTEM):

Thus, the follow up will be documented using the TTEM: daily transmission from visit 4 to visit 6. Then, every two days from visit 6 to visit 9.

Moreover, during this TTEM period, if patient experiences AF symptoms, it should be documented using the TTEM.

In case of AF recurrence, and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at the investigator's judgement, he/she could be maintained in the study with the treatment, in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be faxed to the site. The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. *Definition*

Number of Atrial Fibrillation episodes will consist in the assessment of episodes of AF with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.1.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the study visit 4.

8.1.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. *Duration of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episodes.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. *Clinical parameters evaluation*

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition:*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month); intermediate (1/month to almost daily); and frequent at least daily.

8.1.2.3.1.2. Schedule

This evaluation will be performed in case of symptoms evocative of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

This evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of number of AF recurrence associated with a symptom (Palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG in atrial fibrillation.

8.1.2.3.3. *Number and duration of hospitalization*

- Number and duration of hospitalization for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalization for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shock distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL),

8.1.2.5.2. *. Schedule*

The measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

The measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. *Evaluation method*

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, for volume measurements, the recommended method is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. **BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA**

8.2.1. **Definition**

Because of the limited accessibility of human tissues for biopsy, red blood cell DHA contents is a marker for tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. *Collection schedule*

Blood samples will be collected for determination of red blood cells (RBC) concentrations of DHA.

Blood samples will be performed as follows:

- Visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the electronic Case Report Forms (e-CRFs).

8.2.2.2. *Technical handling*

Two blood samples will be collected containing EDTA. They will be gently shaken and centrifuged at 3000g for 15 min at room temperature, within 30 minutes after collection. Plasma and white blood cells will be discarded. Red blood cells will be stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C) within 3 weeks following collection. Analysis will be performed within 2 weeks following reception at the Analytical centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol, after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will

be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock), in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of adverse events (AEs) since the last visit will be based on the patient's spontaneous reporting, the investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only an haematology examination will be performed.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The volume of blood samples complete haematology, biochemistry should not exceed 30 mL.

8.3.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *Hematocrit, haemoglobin, Red blood cells (RBC) count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning, in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L,$

in women:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L] \times 0.85$

- with serum creatinine expressed as $\mu mol/l$:

$GFR (mL/min) = [(140-age) \times weight / serum\ creatinine\ in\ \mu mol/l] \times k,$ where $k = 1.23$ for men, 1.04 for women.

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patients' interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. *Schedule*

Vital signs will be measured at each visit.

8.3.4.2. *Technical Procedure and Parameters*

Systolic (SBP) and diastolic (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation, after at least 5 minutes in supine position and after 2 minutes in standing position by counting the beats for at least 30 seconds.

Bodyweight will be measured in patient in underwear and with the same balance at each visit.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. *Schedule*

An electrocardiogram will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram (ECG):

The global interpretation from manual reading (normality, clinical relevance) and heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent atrial fibrillation.

8.3.6. Coagulation parameters

The assessment of coagulation will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV,
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV,
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by anti-vitamin K should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.3.7. Concomitant Treatments

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial can be found in section 7.

8.4. COMPLIANCE

The patient will be reminded at each visit to bring back any remaining soft capsules, blister, case (used or unused) at the following visit.

At each visit, the Investigator will record the number of supplied and remaining Soft Capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If he/she accepts to participate in the study, he/she will sign the informed consent and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and Atrial Fibrillation characteristics
- Echocardiography using a two-dimensional echocardiography.
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory (CRL). The CRL will send his/her assessment regarding the confirmation of persistent atrial fibrillation within 2 working days to the Investigator.
- The patient will enter the selection period in which anticoagulant (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will contact the IVRS/IWRS system to confirm the patient selection and order the treatment delivery and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent atrial fibrillation by the CRL during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography.

- 12-lead ECG
- Urine pregnancy test for women of child bearing potential.

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS system.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6), in order to ensure that the INR is stable, between 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, Red Blood Cell concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be

induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 ± 2 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of Adverse Events
- Concomitant treatments (authorised, disallowed)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device (Trans Telephonic ECG Monitoring) for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using a TTEM device (Trans Telephonic ECG Monitoring). The device will be given to the patient who will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 5, the investigator will contact the IVRS/IWRS to obtain another treatment unit to be dispensed at visit 6 for the last 12-week period.
- at visit 6, an echocardiography will be performed, an haematology examination will be done and the red blood cell concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An adverse event is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

This includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values, which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as

those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity.

10.1.3. Reporting of Adverse Events

The records of adverse events in the electronic Case Report Form (e-CRF) describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A serious adverse event (SAE) includes, but is not necessarily restricted to any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect.

Other events such as cancer, and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough, or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure,
- preparation for routine health assessment/procedure (e.g. routine colonoscopy),
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All serious adverse events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, must be recorded by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") (see appendix 17.2) with all the available information about the event, to the Sponsor's representative:

Marlène GUIRAUD, Pharm D
INSTITUT DE RECHERCHE PIERRE FABRE,
Centre de R&D Pierre Fabre – BP 13562
3 Avenue Hubert Curien
31035 TOULOUSE Cedex 1
Phone: +33 5 35 50 63 48
Fax: + 33 5 34 50 65 92
Email: marlene.guiraud@pierre-fabre.com

In case of non-inclusion the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose, and associated adverse event if any, are reported only on the Adverse Event page of the CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must be also transmitted to the sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug(s) should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is discontinued from the study.

The investigators must report to the sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The investigator must immediately notify the sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An electronic Case Report Forms (e-CRF) will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files and which will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants who will use this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRF (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigation sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. *Follow-up Visits*

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. *Closing Visit*

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of measures of primary end point, the safety data and to recommend to the Sponsor whether to continue, modify, or to stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on a e-CRF.

The e-CRF used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate coding.

12.4. DATA STORAGE

The computer data files, as well as their modifications, will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e.: data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by Pierre Fabre Biométrie (PFB) or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan (SAP) approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 evaluable patients per group is required, using a log-rang test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 2 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patients will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAE

- With at least three TEAE
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.
- Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:
- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

"The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TE AE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patient).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

Serious adverse events will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time

of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be identified differently. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of PSC range and CNALV range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

Clinically noteworthy abnormal laboratory values (CNALV) (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and heart rate in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. *Individual Patient Changes*

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) – number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days).

13.11. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor *Pierre Fabre Médicament*, are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents
- Authorises direct access to source documents for monitoring, audits and inspections
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. *Early Study Termination Decided by the Sponsor*

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. *Early Study Termination Decided by the Competent Authorities*

The Competent Authorities may suspend or prohibit a study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both his representatives (Study Manager, CRA, ...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed to in writing with the Study Manager, the investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis, and clinical study report writing are under the Sponsor's responsibility.

Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results are drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version January 2013
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57:870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedarone for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELIN D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY TO PIERRE FABRE PRODUCT SAFETY DEPARTMENT TO BE TRANSMITTED TO THE MONITOR BY FAX WITHIN 24H : M. GUIRAUD Fax n° +33 5 34 50 65 92	
Transmission date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	Country :
SAE N° <input type="text"/> <input type="text"/>	FIRST NOTIFICATION <input type="checkbox"/> FOLLOW-UP <input type="checkbox"/>

➤ **SUBJECT CHARACTERISTICS**

Surname <input type="text"/> <input type="text"/> <input type="text"/>	First name <input type="text"/> <input type="text"/>	Birth date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Gender <input type="text"/> 1=M, 2=F	Height <input type="text"/> <input type="text"/> <input type="text"/> cm	Weight <input type="text"/> <input type="text"/> <input type="text"/> kg

➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) : 	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐

➤ **CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE**
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

INN or trade name	Daily dose	Start date (ddmmyy)	Ongoing at occurrence of the event	Stop date (ddmmyy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ **MEASURES TAKEN FOLLOWING THE SAE**

• **Study treatment**

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• **The event led to :**

- ☐ Prescription of corrective or symptomatic treatments (specify names and dosages) :
- ☐ Discontinuation of concomitant treatments (specify names) :
- ☐ Others, specify :

➤ **OUTCOME**

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ **INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)**

- ☐ Not Suspected ☐ Suspected ☐ Insufficient data

comments :

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(α)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(α) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		• < 1 500/mm ³ whatever the baseline value
WBC (if missing value for neutrophils)		• < 3 000/mm ³ whatever the baseline value
PLATELETS		• < 100 000/mm ³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.4. Protocol amendment n° PA02
General and non-substantial dated on 28 March 2013 linked
to Protocol and appendices (version 4: 28 March 2013)***

CLINICAL STUDY PROTOCOL AMENDMENT n° PA02 – Version 1
General – Non Substantial

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

CLINICAL STUDY PROTOCOL AMENDMENT n° PA02 – Version 1

General – Non Substantial

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code:	F373280 CA 2 01
EudraCT Number:	2012-003487-48
Sponsor's Representative:	Gaëlle ALCARAZ
Coordinating Investigator:	Pr Savina NODARI
Date of amendment PA02:	28 March 2013

Confidential

Clinical Study Protocol Amendment n° PA02 – Version 1
General – Non Substantial
SIGNATURE FORM

Sponsor's representative:

Medical Director

Richard ROCHE, MD

Date: 14/05/13 Signature:



Study Coordinating Investigator:

Pr Savina NODARI

Date:

20/05/13

Signature:



Clinical Study Protocol Amendment n° PA 02 – Version 1

General – Non substantial

COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

Country Coordinating Investigator:

Date:

Signature:

Clinical Study Protocol Amendment n° PA 02 – Version 1

General – Non Substantial

INVESTIGATOR SIGNATURE FORM

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA 02, dated 28 MAR 2013 and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF PROTOCOL VERSIONS

PROTOCOL VERSIONS	DATE	MODIFICATIONS	COMMENTS
Version 1	09/11/2012	Initial version	General
Version 2 (General)	15/01/2013	Following French CA request (ANSM) : - Add of a non inclusion criteria : "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6	General
Version 3 (Local Italy)	01/03/2013	Following to the Italian Central Ethics Committee and Competent Authority requirements and, in order to harmonise the protocol and the Informed Consent Form, the following changes have been done to the study protocol : - adjustment of the selection criteria n°10 related to the contraception method - addition of a letter that is given by the patient to his/her general practitioner (GP) - precision that the sponsor can not collect a copy of the Informed Consent Form - precision that the patient card is in Italian language only (without any English mention)	Local Italy

N°	DATES	TYPE	APPLICATION AREA	MODIFICATIONS	PROTOCOL VERSIONS	
NA	_____	NA	General	_____	Version 1	09/11/2012
NA	_____	NA	General	Following French CA request (ANSM) : - Add of a non inclusion criteria : “Breast-feeding female patient” - Add of haematology examination at visit 3 and 6	Version 2	15/01/2013
PA01	01.03.2013	Substantial	Local (Italy)	Following to the Italian Central Ethics Committee and Competent Authority requirements and, in order to harmonise the protocol and the Informed Consent Form, the following changes have been done to the study protocol : - Integration of the modification included in the protocol version 2 - Harmonisation of the protocol and the Informed Consent Form : * adjustment of the selection criteria n°10 related to the contraception method * addition of a letter that is given by the patient to his/her general practitioner (GP) * precision that the sponsor can not collect a copy of the Informed Consent Form * precision that the patient card is in Italian language only (without any English mention)	Version 3	01/03/2013

1. AMENDMENT RATIONALE

The clinical study protocol is updated with the following changes :

- change of Sponsor's Representative (Clinical Study Manager),
- modification of the technical handling of the blood samples for determination of red blood cells concentration of DHA : the centrifugation is no more needed,
- precision on the function and address of the International Study Coordinator Pr Nodari,
- add of address and contacts details of two CRO newly involved in the study : Theradis (in charge of transportation of blood samples to the Analytical centre and material supply) and "Clinact" (in charge of refund of patients expenses linked to the study),
- adjustment of the wording, in agreement with the commitment to the French Ethics Committee. In the paragraphe 8.3.2.1, the wording "hematology examination" is replaced by "standard hematologic dosage",
- precision of the full title in the study synopsis (in agreement with the commitment to the Spanish Ethics Committee),
- correction of a mistake in section 8.1.1.3 (related to TTEM transmission) and sections 3, 9 and study synopsis (related to the definition of INR not stabilized).
- addition of the changes included in the local italian substantial protocol amendment (i.e : contraception method, letter to General Practitioner, patient card in Italian and no collection of the consent form by the sponsor in Italy).

2. CHANGES DESCRIPTION

PREVIOUS VERSION	MODIFIED VERSION
<p>Sponsor's Representative: Marlène GUIRAUD, Pharm D</p> <p>INSTITUT DE RECHERCHE PIERRE FABRE - Centre de R&D Pierre Fabre - BP 13562 3 avenue Hubert Curien 31035 TOULOUSE Cédex 1 Phone: +33 5 34 50 63 48</p> <p>Fax: +33 5 34 50 65 92 E-mail: marlene.guiraud@pierre-fabre.com</p> <p>Study Coordinating Investigator: Pr Savina NODARI Section of Cardiology Department of Experimental and Applied Sciences University of Brescia BRESCIA, ITALY Phone: +39 030 3996 587 - Fax: +39 030 3700 359 E-mail: savinanodari@gmail.com</p>	<p>Sponsor's Representative: Gaëlle ALCARAZ</p> <p>INSTITUT DE RECHERCHE PIERRE FABRE - Centre de R&D Pierre Fabre - BP 13562 3 avenue Hubert Curien 31035 TOULOUSE Cédex 1 Phone: +33 5 34 50 62 16 Fax: +33 5 34 50 XX XX (TBC) E-mail: gaelle.alcaraz@pierre-fabre.com</p> <p>Study Coordinating Investigator: Pr Savina NODARI – Associate Professor of Cardiology Department of Clinical and Surgical Specialities, Radiological Science and Public Health Section of Cardiovascular Diseases University Medical School and Spedali Civili Hospital of Brescia c/o Spedali Civili di Brescia Piazzale Spedali Civili, 1 25123 - BRESCIA, ITALY Phone: +39 030 3996 587 – +39 030 393849</p> <p>Fax: +39 030 3700359 E-mail: savinanodari@gmail.com ; nodari@med.unibs.it</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>CONTRACT RESEARCH ORGANISATIONS</p> <p>....</p> <p><u>For intra erythrocyte DHA dosage:</u> Agrocampus Ouest Laboratoire de Biochimie 65 rue de Saint Briec – CS 84215 35042 RENNES Cedex - FRANCE Phone: +33 2 23 48 55 49 - Fax: +33 2 23 48 55 50 E-mail: daniel.catheline@agrocampus-ouest.fr</p>	<p>CONTRACT RESEARCH ORGANISATIONS</p> <p>....</p> <p><u>For intra erythrocyte DHA dosage:</u> Agrocampus Ouest Laboratoire de Biochimie 65 rue de Saint Briec – CS 84215 35042 RENNES Cedex - FRANCE Phone: +33 2 23 48 55 49 - Fax: +33 2 23 48 55 50 E-mail: daniel.catheline@agrocampus-ouest.fr</p> <p><u>For transportation of blood sample to the Analytical centre (Agrocampus) and material supply :</u> Theradis Pharma 41, chemin des Presses 06800 CAGNES-SUR-MER – France Phone : +33 (0)4 97 02 07 07 Fax : +33 (0)4 97 10 08 78 E-mail: chantal.raffy@theradis.pharma.com</p> <p><u>For refund of patients expenses linked to the patients expenses linked to the study:</u> <u>CLINACT</u> <u>6-10 rue TROYON</u> <u>92310 SEVRES – FRANCE</u> <u>Phone : +33 1 46 90 27 27</u> <u>Fax : +33 1 46 23 01 56</u> <u>Email : sebastien.beaumont@clinact.com</u></p>

PREVIOUS VERSION	MODIFIED VERSION
<p>STUDY SYNOPSIS AND 5.1 INCLUSION CRITERIA</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>10. For female patient of child-bearing potential:</p> <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or - documented as surgically 	<p>STUDY SYNOPSIS AND 5.1 INCLUSION CRITERIA</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>10. For female patient of child-bearing potential:</p> <ul style="list-style-type: none"> • in all the countries except Italy: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or - documented as surgically sterilized • in Italy only: <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized <p>11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion</p> <p>12. For male with a childbearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study.

sterilized	
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion	

PREVIOUS VERSION	MODIFIED VERSION
<p>STUDY SYNOPSIS, SECTION 3. Ethical CONSIDERATIONS RELATING TO THE STUDY and section 9. Study procedures :</p> <p>Patients not stabilized for INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>5.9 Study CARD</p> <p>The patient will receive from the Investigating Centre at Visit 1 - Selection Visit, a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83.</p>	<p>STUDY SYNOPSIS, SECTION 3. Ethical CONSIDERATIONS RELATING TO THE STUDY and section 9. Study procedures :</p> <p>Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>5.9 Study CARD and LETTER FOR GENERAL PRACTITIONERS (GP)</p> <p>The patient will receive from the Investigating Centre at Visit 1 - Selection Visit :</p> <ul style="list-style-type: none"> - a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian without any English mention. - a letter to be given to his/her general practitioner. This letter intends to inform the GP (and any other doctors who take care of the patient) that the patient participates to this clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

PREVIOUS VERSION	MODIFIED VERSION
<p>8.1. PRIMARY EFFICACY CRITERION:</p> <p><i>8.1.1.3. Evaluation Methods</i></p> <ul style="list-style-type: none"> • Trans Telephonic ECG Monitoring (TTEM): <p>Thus, the follow up will be documented using the TTEM: daily transmission from visit 4 to visit 6. Then, every two days from visit 6 to visit 9.</p> <p>8.2 BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA</p> <p><i>8.2.2.2 Technical handling</i></p> <p>Two blood samples will be collected containing EDTA. They will be gently shaken and centrifuged at 3000g for 15 min at room temperature, within 30 minutes after collection. Plasma and white blood cells will be discarded. Red blood cells will be stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C) within 3 weeks following collection. Analysis will be performed within 2 weeks following reception at the Analytical centre.</p>	<p>8.1. PRIMARY EFFICACY CRITERION:</p> <p><i>8.1.1.3. Evaluation Methods</i></p> <ul style="list-style-type: none"> • Trans Telephonic ECG Monitoring (TTEM): <p>Thus, the follow up will be documented using the TTEM: daily transmission from visit 4 (week 6) to visit 5 (week 8). Then, every two days from visit 5 (week 8) to visit 9 (week 24 – End of study).</p> <p>8.2 BIOMARKER ASSESSMENT: RED BLOOD CELLCONCENTRATIONS OF DHA</p> <p><i>8.2.2.2 Technical handling</i></p> <p>Two blood samples will be collected containing EDTA. They will be gently shaken, stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical centre.</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>8.3 SAFETY ASSESSMENT</p> <p>8.3.2 Laboratory Investigations</p> <p>Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.</p> <p>At visit 3 and 6, only an haematology examination will be performed.</p> <p>10.2 Reporting of SAE</p> <p>Marlène GUIRAUD, Pharm D</p> <p>INSTITUT DE RECHERCHE PIERRE FABRE, Centre de R&D Pierre Fabre – BP 13562 3 Avenue Hubert Curien 31035 TOULOUSE Cedex 1 Phone: +33 5 35 50 63 48 Fax: + 33 5 34 50 65 92 Email: marlene.guiraud@pierre-fabre.com</p>	<p>8.3 SAFETY ASSESSMENT</p> <p>8.3.2 Laboratory Investigations</p> <p>Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.</p> <p>At visit 3 and 6, only a standard haematologic dosage will be performed.</p> <p>10.2 Reporting of SAE</p> <p>Gaëlle ALCARAZ</p> <p>INSTITUT DE RECHERCHE PIERRE FABRE, Centre de R&D Pierre Fabre – BP 13562 3 Avenue Hubert Curien 31035 TOULOUSE Cedex 1 Phone: +33 5 35 50 62 16 Fax: + 33 5 34 50 65 92 Email: gaelle.alcaraz@pierre-fabre.com</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>11.2. STUDY MONITORING</p> <p><i>11.2.1.4. Closing Visit</i></p> <p>At the end of the study, a final visit will be carried out by the CRA to:</p> <ul style="list-style-type: none"> • Verify that the e-CRFs CD-ROM with pdf files are correctly stored • Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the <i>IRPF</i> for destruction • Obtain the last data clarifications and/or solutions if any • Collect the patient's consent forms in sealed envelopes, • Make an on-site review of all study documentation and complete it if necessary • And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration. 	<p>11.2. STUDY MONITORING</p> <p><i>11.2.1.4. Closing Visit</i></p> <p>At the end of the study, a final visit will be carried out by the CRA to:</p> <ul style="list-style-type: none"> • Verify that the e-CRFs CD-ROM with pdf files are correctly stored • Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the <i>IRPF</i> for destruction • Obtain the last data clarifications and/or solutions if any • Collect the patient's consent forms in sealed envelopes (except in case of specific country requirement), • Make an on-site review of all study documentation and complete it if necessary • And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

PREVIOUS VERSION	MODIFIED VERSION
<p>14.3 PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM</p> <p>The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study.</p>	<p>14.3 PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM</p> <p>The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).</p>

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

Sponsor's Representative:

Gaëlle ALCARAZ

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Version 4– 28 MAR 2013

The information contained in this document is confidential and is the property of the Sponsor, Pierre Fabre Médicament. This information is given for the needs of the study and must not be disclosed without prior written consent of the Sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the study must be informed that it is confidential and must not be disclosed.

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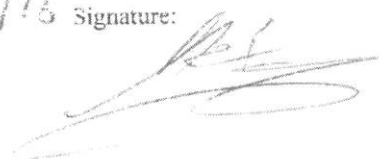
Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 4 – 28 MAR 2013

Sponsor's Representative:

Medical Director:

Richard ROCHE, MD

Date: 16/08/13 Signature:



Study Coordinating Investigator:

Savina NODARI, MD

Date: 20/05/13 Signature:

20/05/13 Savina Nodari

Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 4 – 28 MAR 2013

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
---------------	-------	------------

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 4 – 28 MAR 2013

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 28 March 2013 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of Atrial Fibrillation (AF) induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PUFA (PolyUnsaturated Fatty Acid) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of Atrial Fibrillation recurrence in patients with persistent Atrial Fibrillation, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2014	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 (anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (Outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35± 2 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive), 2. Patients with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted. 3. History of first documented persistent AF less than 1 year 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule)) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area $\leq 40 \text{ cm}^2$) at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> ● in all the countries except Italy: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized ● in Italy only: <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion 12. For male with a child-bearing potential partner (In Italy only): <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study. <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 13. Having signed his/her written informed consent, 14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 1 year

	<ol style="list-style-type: none"> 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (K $>$ 5.5 mEq/L or K $<$ 3.5 mEq/L) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Previous treatment with oral amiodarone within 12 months prior to inclusion 14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω3 or ω6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
Duration of Treatment:	Oral, one capsule each evening with dinner.
Reference Therapy	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
	Placebo soft capsules
	Placebo will be administered in the same conditions as the tested product.

Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of Atrial Fibrillation lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit)) <p>Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24.</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).</p> <p>Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG traces will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p> <p>During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u></p> <p>During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All cause of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m², 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight), - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized). - Haematology: haematocrit, haemoglobin, RBC, WBC, differential count, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) - Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (PT)
Statistical Methods:	<p>Sample Size:</p> <p>Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p>

	<p>Primary Efficacy Analysis</p> <p>The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses</p> <p>All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses</p> <p>Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment)</p>

STUDY FLOW-CHART

F373280 CA 201	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 +/-2 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	←→ (2)				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS	X	X			X	X			
ECV (3)			X						
Drug administration		←→							
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	←→ (4)		←→ (5)						
TTEM (6)					←→				

⁽¹⁾ Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

⁽²⁾ In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV.

⁽³⁾ In patients with AF

⁽⁴⁾ 24-hour Holter ECG

⁽⁵⁾ 7-day Holter ECG

⁽⁶⁾ TTEM everyday from week 6 to week 8. Then every 2 days from week 9 to week 24. In case of AF symptoms. In case of AF recurrence for at least 10 minutes and the patient does not stop the study treatment then TTEM every 4 weeks

LIST OF ABBREVIATIONS

aPTT	Activated partial thromboplastin time
AE	: Adverse event
AERP	Atrial effective refractory period
AF	: Atrial fibrillation
ALA	Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	Anti vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	Blood pressure
BSA	: Body Surface Area
CEP	Protocol evaluation committee
CHF	: Congestive heart failure
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosaehaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	European heart rhythm association
EPA	Eicosapentaenoic acid
eCRF	Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate

HBs	:	Hepatitis B antigen
HCV	:	Hepatitis C virus
HDL		High density lipoprotein
HF		Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR		International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS		Interactive voice response system
LAA		Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL		Low density lipoprotein
LOQ	:	Limit of quantification
LVEF		Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR		Mineralocorticoid receptor
MR perfusion		Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA		New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
POC		Proof of concept
PUFA	:	PolyUnsaturated fatty acid
PK	:	Pharmacokinetics
p.o.	:	Per os
PP	:	Per protocol data set
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT		Thrombin clotting time
TEAEs		Treatment emergent adverse events
TTEM		TransTelephonic ECG monitoring
VTP	:	Ventricular tachypacing
WBC		White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of atrial fibrillation (AF) in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the PUFAs (Polyunsaturated Fatty Acids) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are ALA, EPA and DHA. First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or atrial fibrillation.

The potential anti-arrhythmic effects of a PUFA was previously developed in atrial fibrillation: nicotinyl ester of DHA (pro-drug based on DHA delivery) were assessed in a two-week

ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of atrial fibrillation (AF) induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll assessed n-3 Polyunsaturated Fatty Acids in the prevention of atrial fibrillation recurrences after electrical cardioversion. All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct electrical cardioversion (ECV) 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion [2]. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFA on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than placebo group at one month (3.3% vs 10%; $p=0.043$), at 3 months (10% vs 25%; $p=0.004$) and at 6 months (13.3% vs 40%; $p<0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effect of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with a chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 \pm 0.33 to 1.61 \pm 0.49 and increased from 1.83 \pm 0.38 to 2.14 \pm 0.65, respectively).

The hospitalization rates for HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($P = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: 24% \pm 7% vs 29% \pm 8%, $p = 0.005$) and 1 g/d treatment groups (24% \pm 8% vs 27% \pm 8%, $P = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent atrial fibrillation and heart failure in the maintenance of sinus rhythm after electrical cardioversion.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA (docosahexaenoic acid) is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of atrial fibrillation.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

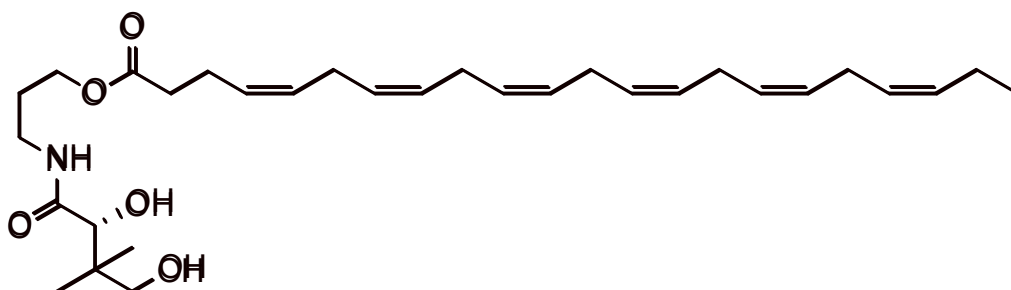
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period (AERP) were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased AERP (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $P < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the ECG intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing (VTP)-induced congestive heart failure (CHF) provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses CHF-induced AF-promotion and fibrosis in the VTP canine model. Nicotinyl ester of DHA was tested in this model, at 1g/day and 5g/day, during 4 weeks, to prevent CHF-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in atrial fibrillation duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280

similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 gm/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies , no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

6 consecutive single ascending doses were tested (0.5g, 1g, 2g, 4g, 8g and 16g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 4 were observed in the placebo group (palpitation, dizziness in standing position, 2 symptomatic orthostatic hypotensions without loss of consciousness) and 4 in the group of F373280 at the dosage of 16g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events were reported in the groups of F373280 at the dosages of 0.5g, 1g, 2g, 4g and 8g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5g to 16 g in 36 young male healthy subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding PK parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple dose

Three consecutive repeated ascending doses (1, 2 and 4g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280 5/9 TEAE were classified according the SOC in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAE have already been reported with Poly Unsaturated Fatty Acids and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** Cmax and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of atrial fibrillation (AF) induced by burst pacing [1].

Moreover, the effectiveness of PUFA has been proven in the following conditions:

- Prevention of atrial fibrillation recurrence in patients with persistent atrial fibrillation in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor®, [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($> 1/100$, $< 1/10$); uncommon ($> 1/1000$ $< 1/100$); rare ($> 1/10000$, $< 1/1000$); very rare ($< 1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:
Very rare: nasal dryness
- Gastrointestinal disorders:
Common: dyspepsia, nausea
Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper
Rare: gastrointestinal pain
Very rare: lower gastrointestinal haemorrhage
- Hepatobiliary disorders:
Rare: hepatic disorders
- Skin and subcutaneous tissue disorders:
Rare: acne, rash pruritic
Very rare: urticaria
- General disorders and administration site conditions:
Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1g and 4g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in Atrial Fibrillation studies [2, 8]. The range of PUFAs doses tested was between 2g to 3g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in heart failure patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1g to 5g (1g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct electrical cardioversion
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of atrial fibrillation and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (AVK), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication,
- Anticoagulation with anti-vitamin K for at least 3 weeks before ECV,
- ECV in patients with stabilized INR (i.e. values between 2 and 3) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)

- Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent atrial fibrillation and chronic heart failure.

After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 2D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit

- Visit 9 (V9): W24 (D168 ± 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent atrial fibrillation and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent atrial fibrillation with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- early persistent atrial fibrillation history (less than one year) with a duration of the current episode between 7 days to 6 months
- a moderately abnormal moderately systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- A Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent atrial fibrillation associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of electrical cardioversion, patients should have a stable medical treatment of heart failure and should not have myocardial infarction or unstable angina or

unstable ischemic coronaropathy (assessed by coronarography or cardiac stress test or effort test within 6 months before selection).

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on anti-arrhythmics on atrial fibrillation (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be developed as a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, anti-arrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent atrial fibrillation and requiring an electrical cardioversion will be included in order to assess the time to first documented recurrence of atrial fibrillation since cardioversion.

To confirm the persistent nature of atrial fibrillation, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before electrical cardioversion. According to guidelines for the management of atrial fibrillation [6], anti-vitamin K should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation, of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodary study [2], the duration of pre-treatment with PUFA before cardioversion appears to be a contributing factor in

success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of atrial fibrillation recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of atrial fibrillation recurrence occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using a more easy to carry and easy to use device, a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with atrial fibrillation [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of atrial fibrillation after cardioversion. Moreover, PUFAs at dosage of 1g and 2g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95mg/mL and 60 to 90mg/mL, respectively) (phase I study of F373280 and Salm and coll study) [16]. With regard to the rhythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a dose of 1 g daily of F373280 is considered to be appropriate to be tested in this POC study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive),
2. Patient with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted.
3. History of first documented persistent AF less than 1 year
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - **in all the countries except Italy:**
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
 - **in Italy only:**
 - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner **(In Italy only):**

- absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or

Ethical /legal considerations:

13. Having signed his/her written informed consent,
14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation),

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 1 year,
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be check in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (K $>$ 5.5 mEq/L or K $<$ 3.5 mEq/L) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Previous treatment with oral amiodarone within 12 months prior to inclusion
14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,

21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO,...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENTS IDENTIFICATION

The patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

The reasons for a patient's premature withdrawal from the study may be the following:

- The patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form

- obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- The Investigator's decision in the patient's interest. Particularly, if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.
 - An erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion / non inclusion criteria will immediately be withdrawn and an appropriate treatment will be instored by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
 - Patients who could not be treated with anti-vitamin K for at least 3 weeks before ECV,
 - Patients who will not stabilize INR between 2 and 3 on at least 3 consecutive weekly tests
 - Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 week for whom a trans-oesophagoal echocardiography can not be performed before ECV or for whom a trans-oesophagoal echocardiography shows a thrombus in the atria.
 - Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV (i.e. unsuccessful ECV) will be considered to have finished follow-up.
 - An occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and uncomfortable clinical symptoms.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit,

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.

- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number,
- c) packaging batch number,
- d) the treatment number
- e) storage conditions

- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”.

On the treatment unit, another label will be affixed with the mention of the investigator name and patient number (completed by the investigator).

In addition, on each case, will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected

- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person.

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion Visit and another one at Visit 6.

For each patient, the treatment number given at Visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once the patient's eligibility is confirmed, at selection visit:

- The Investigator:
 - Calls the vocal server
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the vocal server.

- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 5, the Investigator will contact again the IVRS/IWRS to obtain for visit 6 the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure will be 24 weeks, with F373280 or placebo.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator, in collaboration with the Sponsor representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF, according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (Selection Visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted

on e-CRF. All treatments should be evaluated by the investigator at selection and their prolongation during the study or their stop should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

Anti-vitamin K should be given for at least 3 weeks before ECV and continued for the whole study duration. The anti-vitamin K used will be left to the decision of the each investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Any Polyunsaturated Fatty Acid (PUFA)
- Any anticoagulant treatment other than antivitamin K: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the case report form. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION:

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first Atrial Fibrillation recurrence is defined by the first episode of Atrial Fibrillation (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of electrical cardioversion visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM)

- Trans Telephonic ECG Monitoring (TTEM):

Thus, the follow up will be documented using the TTEM: daily transmission from visit 4 (week 6) to visit 5 (week 8). Then, every two days from visit 5 (week 8) to visit 9 (week 24 – End of study).

Moreover, during this TTEM period, if patient experiences AF symptoms, it should be documented using the TTEM.

In case of AF recurrence, and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at the investigator's judgement, he/she could be maintained in the study with the treatment, in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be faxed to the site. The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. *Definition*

Number of Atrial Fibrillation episodes will consist in the assessment of episodes of AF with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.1.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the study visit 4.

8.1.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. ***Duration of Atrial Fibrillation episodes in the first week following visit 3 (ECV visit)***

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episodes.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful electrical cardioversion visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. ***Clinical parameters evaluation***

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition:*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected

- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month); intermediate (1/month to almost daily); and frequent at least daily.

8.1.2.3.1.2. Schedule

This evaluation will be performed in case of symptoms evocative of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

This evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of number of AF recurrence associated with a symptom (Palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG in atrial fibrillation.

8.1.2.3.3. *Number and duration of hospitalization*

- Number and duration of hospitalization for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalization for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shock distribution (1, 2 or 3 shocks)

- Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL),

8.1.2.5.2. *. Schedule*

The measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

The measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. *Evaluation method*

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, for volume measurements, the recommended method is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.2.1. Definition

Because of the limited accessibility of human tissues for biopsy, red blood cell DHA contents is a marker for tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. *Collection schedule*

Blood samples will be collected for determination of red blood cells (RBC) concentrations of DHA.

Blood samples will be performed as follows:

- Visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the electronic Case Report Forms (e-CRFs).

8.2.2.2. *Technical handling*

Two blood samples (4ml) will be collected in tubes containing EDTA. They will be gently shaken, stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol, after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells

(expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock), in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of adverse events (AEs) since the last visit will be based on the patient's spontaneous reporting, the investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. *Schedule*

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The volume of blood samples complete haematology, biochemistry should not exceed 30 mL.

8.3.2.2. *Technical Procedures and Parameters*

The following tests will be performed:

Haematology: *Hematocrit, haemoglobin, Red blood cells (RBC) count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning, in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L,$

in women:

$GFR (mL/min) = [(140-age)] \times weight / 7.2 \times serum\ creatinine\ in\ mg/L] \times 0.85$

- with serum creatinine expressed as $\mu mol/l$:

$GFR (mL/min) = [(140-age) \times weight / serum\ creatinine\ in\ \mu mol/l] \times k,$ where $k = 1.23$ for men, 1.04 for women.

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patients' interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. *Schedule*

Vital signs will be measured at each visit.

8.3.4.2. *Technical Procedure and Parameters*

Systolic (SBP) and diastolic (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation, after at least 5 minutes in supine position and after 2 minutes in standing position by counting the beats for at least 30 seconds.

Bodyweight will be measured in patient in underwear and with the same balance at each visit.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. *Schedule*

An electrocardiogram will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram (ECG):

The global interpretation from manual reading (normality, clinical relevance) and heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent atrial fibrillation.

8.3.6. Coagulation parameters

The assessment of coagulation will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV,
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV,
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by anti-vitamin K should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.3.7. Concomitant Treatments

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial can be found in section 7.

8.4. COMPLIANCE

The patient will be reminded at each visit to bring back any remaining soft capsules, blister, case (used or unused) at the following visit.

At each visit, the Investigator will record the number of supplied and remaining Soft Capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If he/she accepts to participate in the study, he/she will sign the informed consent and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and Atrial Fibrillation characteristics
- Echocardiography using a two-dimensional echocardiography.
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory (CRL). The CRL will send his/her assessment regarding the confirmation of persistent atrial fibrillation within 2 working days to the Investigator.
- The patient will enter the selection period in which anticoagulant (anti-vitamin K) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will contact the IVRS/IWRS system to confirm the patient selection and order the treatment delivery and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent atrial fibrillation by the CRL during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography.

- 12-lead ECG
- Urine pregnancy test for women of child bearing potential.

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS system.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6), in order to ensure that the INR is stable, between 2 to 3 before electrical cardioversion.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, Red Blood Cell concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be

induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 ± 2 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of Adverse Events
- Concomitant treatments (authorised, disallowed)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device (Trans Telephonic ECG Monitoring) for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using a TTEM device (Trans Telephonic ECG Monitoring). The device will be given to the patient who will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms additional transmission may be performed.

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 5, the investigator will contact the IVRS/IWRS to obtain another treatment unit to be dispensed at visit 6 for the last 12-week period.
- at visit 6, an echocardiography will be performed, an haematology examination will be done and the red blood cell concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all the cases, blisters and any unused soft capsules and count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An adverse event is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

This includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values, which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as

those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity.

10.1.3. Reporting of Adverse Events

The records of adverse events in the electronic Case Report Form (e-CRF) describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A serious adverse event (SAE) includes, but is not necessarily restricted to any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect.

Other events such as cancer, and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough, or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure,
- preparation for routine health assessment/procedure (e.g. routine colonoscopy),
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All serious adverse events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, must be recorded by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") (see appendix 17.2) with all the available information about the event, to the Sponsor's representative:

Gaëlle ALCARAZ

INSTITUT DE RECHERCHE PIERRE FABRE,
Centre de R&D Pierre Fabre – BP 13562
3 Avenue Hubert Curien
31035 TOULOUSE Cedex 1
Phone: +33 5 35 50 62 16
Fax: + 33 5 34 50 65 92
Email: gaelle.alcaraz@pierre-fabre.com

In case of non-inclusion the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose, and associated adverse event if any, are reported only on the Adverse Event page of the CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must be also transmitted to the sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug(s) should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is discontinued from the study.

The investigators must report to the sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The investigator must immediately notify the sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An electronic Case Report Forms (e-CRF) will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files and which will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants who will use this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRF (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigation sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. *Follow-up Visits*

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. *Closing Visit*

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of measures of primary end point, the safety data and to recommend to the Sponsor whether to continue, modify, or to stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on a e-CRF.

The e-CRF used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate coding.

12.4. DATA STORAGE

The computer data files, as well as their modifications, will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e.: data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by Pierre Fabre Biométrie (PFB) or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan (SAP) approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 evaluable patients per group is required, using a log-rang test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 2 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patients will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAE

- With at least three TEAE
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.
- Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:
- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

"The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TE AE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patient).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

Serious adverse events will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time

of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be identified differently. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of PSC range and CNALV range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

Clinically noteworthy abnormal laboratory values (CNALV) (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and heart rate in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. *Individual Patient Changes*

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) – number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days).

13.11. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor *Pierre Fabre Médicament*, are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents
- Authorises direct access to source documents for monitoring, audits and inspections
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. *Early Study Termination Decided by the Sponsor*

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. *Early Study Termination Decided by the Competent Authorities*

The Competent Authorities may suspend or prohibit a study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both his representatives (Study Manager, CRA, ...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed to in writing with the Study Manager, the investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis, and clinical study report writing are under the Sponsor's responsibility.

Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results are drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version January 2013
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57:870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedarone for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELIN D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY TO PIERRE FABRE PRODUCT SAFETY DEPARTMENT TO BE TRANSMITTED TO THE MONITOR BY FAX WITHIN 24H : G. ALCARAZ Fax n° +33 5 34 50 65 92	
Transmission date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	Country :
SAE N° <input type="text"/> <input type="text"/>	FIRST NOTIFICATION <input type="checkbox"/> FOLLOW-UP <input type="checkbox"/>

➤ **SUBJECT CHARACTERISTICS**

Surname <input type="text"/> <input type="text"/> <input type="text"/>	First name <input type="text"/> <input type="text"/>	Birth date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Gender <input type="text"/> 1=M, 2=F	Height <input type="text"/> <input type="text"/> <input type="text"/> cm	Weight <input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg

➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) : 	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐

➤ **CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE**
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

INN or trade name	Daily dose	Start date (ddmmyy)	Ongoing at occurrence of the event	Stop date (ddmmyy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ **MEASURES TAKEN FOLLOWING THE SAE**

• **Study treatment**

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• **The event led to :**

- ☐ Prescription of corrective or symptomatic treatments (specify names and dosages) :
- ☐ Discontinuation of concomitant treatments (specify names) :
- ☐ Others, specify :

➤ **OUTCOME**

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ **INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)**

- ☐ Not Suspected ☐ Suspected ☐ Insufficient data

comments :

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(α)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(α) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		• < 1 500/mm ³ whatever the baseline value
WBC (if missing value for neutrophils)		• < 3 000/mm ³ whatever the baseline value
PLATELETS		• < 100 000/mm ³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.5. Protocol amendment n° PA03
General and substantial dated on 23 October
2013 linked to Protocol and appendices
(version 5: 23 October 2013)***

CLINICAL STUDY PROTOCOL AMENDMENT n° PA03 Version 1
(General – Substantial)

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

CLINICAL STUDY PROTOCOL AMENDMENT n° PA03 Version 1

(General – Substantial)

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code: F373280 CA 2 01

EudraCT Number or equivalent : 2012-003487-48

Sponsor's Representative: **Gaëlle ALCARAZ**
INSTITUT DE RECHERCHE PIERRE FABRE - Centre de R&D Pierre
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Study Coordinating Investigator: **Pr 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
c/o Spedali Civili di Brescia
Piazzale Spedali Civili, 1
25123 - BRESCIA, ITALY

Date of amendment PA03: 23 October 2013

Confidential

APPROVAL FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA03 Version 1

(General – Substantial)

Dated: 23/10/2013

Sponsor's representative(s)

• Medical Director

Dr Richard ROCHE

Date: 29 Oct 2013 Signature: 

• Clinical Study Manager :

Gaëlle ALCARAZ

Date:

23 Oct 2013

Signature: 

Study Coordinating Investigator:

Pr Savina NODARI

Date:

30 Oct 2013

Signature: 

Confidential

COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA03 Version 1


(General – Substantial)

Dated: 23/10/2013

Country Coordinating Investigator: SAVINA NODARI

Date: 13/01/2014

Signature:



INVESTIGATOR SIGNATURE FORM

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.

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(General – Substantial)

Dated: 23/10/2013

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA03 and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF AMENDMENTS

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
NA	NA	General	NA	Following French CA request (ANSM) and leading to protocol version 2: - Add of a non inclusion criteria: "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6
PA01	Substantial	Local (Italy)	01.03.2013	Corresponding to Protocol Version 3: - Integration of the modification included in the protocol version 2 - Harmonisation of the protocol and the Informed Consent Form: * adjustment of the selection criteria n°10 related to the contraception method * addition of a letter that is given by the patient to his/her general practitioner (GP) * precision that the sponsor can not collect a copy of the Informed Consent Form * precision that the patient card is in Italian language only (without any English mention)
PA02	Non Substantial	General	28.03.2013	Corresponding to Protocol Version 4 : - change of Sponsor's Representative (Clinical Study Manager), - modification of the technical handling of the blood samples for determination of red blood cells concentration of DHA: the centrifugation is no more needed, - precision on the function and address of the International Study Coordinator Pr Nodari, - add of address and contacts details of two CRO newly involved in the study: Theradis (in charge of transportation of blood samples to the Analytical centre and material supply) and "Clinact" (in charge of refund of patients expenses linked to the study), - adjustment of the wording, in agreement with the commitment to the French Ethics Committee. In the paragraphe 8.3.2.1, the wording "hematology examination" is replaced by "standard hematologic dosage", - precision of the full title in the study synopsis (in agreement with the commitment to the Spanish Ethics Committee), - correction of a mistake in section 8.1.1.3 (related to TTEM transmission) and sections 3, 9 and study synopsis (related to the definition of INR not stabilized). - addition of the changes included in the local italian substantial protocol amendment (i.e: contraception method, letter to General Practionner, patient card in Italian and no collection of the consent form by the sponsor in Italy).

1. AMENDMENT RATIONALE

This amendment relates to an adjustment of some criteria in order to improve the feasibility of the study and to minor changes as typographical errors or style. Finally a change affects the recipient of the SAEs reports.

The clinical study protocol is updated with the following changes:

- Due to a recruitment rate significantly lower than expected the planned end of study is postponed to January 2015.
 - The authorized history of the first documented persistent atrial fibrillation passes from less than 1 year to less than 3 years. This modification will expand our target population without changing the characteristics of the selected patients by enabling the management of patients who experienced a longer period without relapse.
 - At selection a hyperkalemia or a hypokalemia will be better defined by the standards of the local laboratories.
 - Regarding previous treatments by amiodarone the non inclusion criteria of the protocol are adapted as follow:
 - Previous treatment with oral amiodarone within 4 months prior to inclusion
 - Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion
 - Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion
- Despite the long half life of amiodarone, these time limits relating to its non-use before inclusion allow to ensure the absence of amiodarone at sufficient levels to interfere with the assessment of the product.
- For male with a child-bearing potential partner (in Italy only):
Taking into account the duration of spermatogenesis the absolute abstention from sexual intercourse or the use of double barrier contraception method are extended to 3 months after the end of the study.
 - Ranolazine is an antiangina treatment with antiarrhythmic properties. This treatment is added to the prohibited treatments in order to exclude a potential association between the study product and a treatment having an antiarrhythmic effect.
 - Updated Serious Adverse Events (SAEs) form. Main change is the SAE sending: SAEs have to be reported to the Corporate Vigilance Department, and not anymore to the clinical study manager. Also SAEs can be sent by e-mail and by fax.
 - Addition of Alpha BioResearch as CRO involved for Feasibility, Monitoring and Regulatory issues in Spain.
 - Some minor typographic errors are corrected in the protocol.

2. CHANGES DESCRIPTION

PREVIOUS VERSION	MODIFIED VERSION
<p>Sponsor's Representative:</p> <p>Gaëlle ALCARAZ INSTITUT DE RECHERCHE PIERRE FABRE - Centre de R&D Pierre Fabre - BP 13562 3 avenue Hubert Curien 31035 TOULOUSE Cédex 1 Phone: +33 5 34 50 62 16 Fax: +33 5 34 50 65 92 E-mail: gaelle.alcaraz@pierre-fabre.com</p> <p>Medical Director :</p> <p>Richard ROCHE, MD Institut de Recherche Pierre Fabre Centre de R&D Pierre Fabre BP 13 562 3, Avenue Hubert Curien 31035 TOULOUSE Cedex 1 Phone: +33 5 34 50 61 94 Fax: +33 5 34 50 65 92 E-mail: richard.roche@pierre-fabre.com</p>	<p>Sponsor's Representative:</p> <p>Gaëlle ALCARAZ INSTITUT DE RECHERCHE PIERRE FABRE - Centre de R&D Pierre Fabre - BP 13562 3 avenue Hubert Curien 31035 TOULOUSE Cédex 1 Phone: +33 5 34 50 62 16 Fax: +33 5 34 50 69 69 E-mail: gaelle.alcaraz@pierre-fabre.com</p> <p>Medical Director :</p> <p>Richard ROCHE, MD Institut de Recherche Pierre Fabre Centre de R&D Pierre Fabre BP 13 562 3, Avenue Hubert Curien 31035 TOULOUSE Cedex 1 Phone: +33 5 34 50 61 94 Fax: +33 5 34 50 69 69 E-mail: richard.roche@pierre-fabre.com</p>
<p>CONTRACT RESEARCH ORGANISATIONS</p> <p><u>For Feasibility, Monitoring and Regulatory issues:</u> Pharmaceutical Service Network (PSN) Rufino Gonzalez 28 037 Madrid - SPAIN Phone: +34 91 375 6930 - Fax: +34 91 375 6931 E-mail: www.psnglobal.org</p>	<p>CONTRACT RESEARCH ORGANISATIONS</p> <p><u>For Feasibility, Monitoring and Regulatory issues:</u> Pharmaceutical Service Network (PSN) Rufino Gonzalez 28 037 Madrid - SPAIN Phone: +34 91 375 6930 - Fax: +34 91 375 6931 E-mail: www.psnglobal.org</p> <p><u>For Feasibility, Monitoring and Regulatory issues (in Spain):</u> Alpha Bioresearch Paseo de la Castellana, 163 - 2º Izquierda 28 046 Madrid - SPAIN Phone: +34 91 745 2520 - Fax: +34 91 745 0653 E-mail: teresa.bricio@alphabioresearch.com</p>
<p>SYNOPSIS</p> <p>Planned Study Period: January 2013 – April 2014</p> <p>Diagnosis and Criteria for Inclusion:</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> Patients with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is 	<p>SYNOPSIS</p> <p>Planned Study Period: January 2013 – January 2015</p> <p>Diagnosis and Criteria for Inclusion:</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical

<p>warranted.</p> <p>3. History of first documented persistent AF less than 1 year.</p> <p>12. For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 1 year <p>[...]</p> <ol style="list-style-type: none"> 9. Hyperkalemia or hypokalemia ($K > 5.5$ mEq/L or $K < 3.5$ mEq/L) at selection <p><i>Criteria related to treatments:</i></p> <p>[...]</p> <ol style="list-style-type: none"> 12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Previous treatment with oral amiodarone within 12 months prior to inclusion 14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion <p>Evaluation Criteria:</p> <p>Efficacy evaluation variables:</p> <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL) Left ventricular end systolic diameter (mm), Left ventricular end systolic volume (mL)) <p>Safety criteria:</p> <ul style="list-style-type: none"> - Haematology: haematocrit, haemoglobin, RBC, WBC, differential count, platelets 	<p>cardioversion is warranted</p> <p>3. History of first documented persistent AF less than 3 years</p> <p>12. For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 3 years <p>[...]</p> <ol style="list-style-type: none"> 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection <p><i>Criteria related to treatments:</i></p> <p>[...]</p> <ol style="list-style-type: none"> 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Oral amiodarone: <ol style="list-style-type: none"> 13a Previous treatment with oral amiodarone within 4 months prior to inclusion 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion 14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion <p>Evaluation Criteria:</p> <p>Efficacy evaluation variables:</p> <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (mL/ m²), Left ventricular end systolic volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL) Left ventricular end systolic diameter (mm), Left ventricular end systolic volume (mL)) <p>Safety criteria:</p> <ul style="list-style-type: none"> - Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, differential count, reticulocytes, platelets
<p>STUDY FLOW-CHART</p> <p>Please see flow-chart of previous version in appendix 1.</p>	<p>STUDY FLOW-CHART</p> <p>Please see flow-chart of modified version in appendix 2.</p>

<p>1. INTRODUCTION AND STUDY RATIONALE</p> <p>1.2. Information on the test product</p> <p>1.2.3. Clinical data</p> <p>Part A: Single dose</p> <p>Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 4 were observed in the placebo group (palpitation, dizziness in standing position, 2 symptomatic orthostatic hypotensions without loss of consciousness) and 4 in the group of F373280 at the dosage of 16g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position).</p>	<p>1. INTRODUCTION AND STUDY RATIONALE</p> <p>1.2. Information on the test product</p> <p>1.2.3. Clinical data</p> <p>Part A: Single dose</p> <p>Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 3 TEAs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotensions without loss of consciousness) and 4 in the group of F373280 at the dosage of 16g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position).</p>
<p>3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY</p> <p>During the study, in case of AF recurrence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure</p>	<p>3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY</p> <p>During the study, in case of AF recurrence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure</p>
<p>4. STUDY DESIGN</p> <p>4.1. Overall description</p> <ul style="list-style-type: none"> - Visit 4 (V4): W5 (D35 ± 2D): follow-up visit (removing of Holter ECG device and installation of the TTEM) <p>4.2. Discussion of the study design</p> <p>4.2.1. Choice of the study population</p> <p>The study aim is to investigate the product effect in patients with: Persistent AF history (less than one year) with a duration of the current episode from 7 days to 6 months</p> <p>[...]</p> <p>For the successful rate of electrical cardioversion, patients should have a stable medical treatment of heart failure and should not have myocardial infarction or unstable angina or unstable ischemic coronaropathy (assessed by coronarography or cardiac stress test or effort test within 6 months before selection).</p>	<p>4. STUDY DESIGN</p> <p>4.1. Overall description</p> <ul style="list-style-type: none"> - Visit 4 (V4): W5 (D35 -2/+7D): follow-up visit (removing of Holter ECG device and installation of the TTEM) <p>4.2. Discussion of the study design</p> <p>4.2.1. Choice of the study population</p> <p>The study aim is to investigate the product effect in patients with: Persistent AF history (less than three years) with a duration of the current episode from 7 days to 6 months</p> <p>[...]</p> <p>For the successful rate of electrical cardioversion, patients should have a stable medical treatment of heart failure and should not have myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.</p>
<p>5. STUDY POPULATION</p> <p>5.1. Inclusion criteria</p>	<p>5. STUDY POPULATION</p> <p>5.1. Inclusion criteria</p>

<p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. [...] 2. Patient with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. History of first documented persistent AF less than 1 year <p>[...]</p> <p>12 For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to a month after the end of the study <p>5.2. Non Inclusion criteria</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 1 year, [...] 9. Hyperkalemia or hypokalemia ($K > 5.5$ mEq/L or $K < 3.5$ mEq/L) at selection <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 12. Concomitant treatment with any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Previous treatment with oral amiodarone within 12 months prior to inclusion 14. Previous treatment with intravenous amiodarone within 6 months prior to inclusion <p>5.6. Withdrawal criteria</p> <ul style="list-style-type: none"> • Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV (i.e. unsuccessful ECV) will be considered to have finished follow-up. • An occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and uncomfortable clinical symptoms. 	<p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. [...] 2. Patient with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. History of first documented persistent AF less than 3 years <p>[...]</p> <p>12. For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study <p>5.2. Non Inclusion criteria</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 3 years, [...] 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Oral amiodarone: <ol style="list-style-type: none"> 13a Previous treatment with oral amiodarone within 4 months prior to inclusion 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion 14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion <p>5.6. Withdrawal criteria</p> <ul style="list-style-type: none"> • Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early relapse within the observation period after ECV will be considered to have finished follow-up. • Occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.
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<p>6. STUDY TREATMENT</p> <p>6.3. Distribution to centre and storage</p> <p>As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's file.</p> <p>6.4. Allocation of treatments and dispensation to patient</p> <p>Practically, once the patient's eligibility is confirmed, at selection visit:</p> <ul style="list-style-type: none"> • The Investigator: <ul style="list-style-type: none"> – Calls the vocal server – Answers the questions relating to the patient – In return, the treatment number to be allocated for the first 12-week period to the patient is given by the vocal server. <p>[...]</p> <p>At visit 5, the Investigator will contact again the IVRS/IWRS to obtain for visit 6 the treatment number for the last 12-week period of treatment according to the same process as described above.</p>	<p>6. STUDY TREATMENT</p> <p>6.3. Distribution to centre and storage</p> <p>As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file.</p> <p>6.4. Allocation of treatments and dispensation to patient</p> <p>Practically, once the patient's eligibility is confirmed, at selection visit:</p> <ul style="list-style-type: none"> • The Investigator: <ul style="list-style-type: none"> – Contacts the IVRS/IWRS – Answers the questions relating to the patient – In return, the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS. <p>[...]</p> <p>At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment according to the same process as described above.</p>
<p>7. CONCOMITANT TREATMENTS</p> <p>7.2. Prohibited treatments</p> <p>[...]</p>	<p>7. CONCOMITANT TREATMENTS</p> <p>7.2. Prohibited treatments</p> <p>[...]</p> <p>- Ranolazine</p>
<p>8. EVALUATION CRITERIA</p> <p>8.1.2.5. Evolution of echocardiographic parameters</p> <p><i>8.1.2.5.1. Definition</i></p> <p>The following echocardiographic parameters will be assessed: Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular volume (mL), Left ventricular volume/BSA (mL/m², Left ventricular end diastolic diameter (mm) Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL),</p>	<p>8. EVALUATION CRITERIA</p> <p>8.1.2.5. Evolution of echocardiographic parameters</p> <p><i>8.1.2.5.1. Definition</i></p> <p>The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), LVEF (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA (mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL).</p>
<p>9. STUDY PROCEDURES</p> <p>Visit 1 - Selection Visit (Week -4 to Week -1)</p> <ul style="list-style-type: none"> • The patient will enter the selection period in which anticoagulant (anti-vitamin K) will be adjusted to achieve an 	<p>9. STUDY PROCEDURES</p> <p>Visit 1 - Selection Visit (Week -4 to Week -1)</p> <ul style="list-style-type: none"> • The patient will enter the selection period in which anticoagulant (AVK) will be adjusted to achieve an

<p>International Normalized Ratio (INR) of 2 to 3 before electrical cardioversion.</p> <p>Visit 4 (Week 5: D35 ± 2 days)</p>	<p>International Normalized Ratio of 2 to 3 before ECV.</p> <p>Visit 4 (Week 5: D35 -2/+7 days)</p> <ul style="list-style-type: none"> • Body weight (body weight measured at V3 to be used)
<p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>In addition:</p> <ul style="list-style-type: none"> - at visit 5, the investigator will contact the IVRS/IWRS to obtain another treatment unit to be dispensed at visit 6 for the last 12-week period. - at visit 6, an echocardiography will be performed, an haematology examination will be done and the red blood cell concentration of DHA will be measured. 	<p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>In addition:</p> <ul style="list-style-type: none"> - at visit 6: <ul style="list-style-type: none"> • the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period. • an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.
<p>10.2.2. Reporting of SAE</p> <p>All serious adverse events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, must be reported by the Investigator as soon as he/she is informed of the event.</p> <p>The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") (see appendix 17.2) with all the available information about the event, to the Sponsor's representative:</p> <p>Gaëlle ALCARAZ INSTITUT DE RECHERCHE PIERRE FABRE, Centre de R&D Pierre Fabre – BP 13562 3 Avenue Hubert Curien 31035 TOULOUSE Cedex 1 Phone: +33 5 35 50 62 16 Fax: + 33 5 34 50 65 92 Email: gaelle.alcaraz@pierre-fabre.com</p> <p>In case of non-inclusion the reporting period ends when the non-inclusion is documented.</p>	<p>10.2.2. Reporting of SAE</p> <p>All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.</p> <p>The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:</p> <p><u>HQ.pharmacovigilance@pierre-fabre.com</u></p> <p>In case it is not possible to send the report by e-mail it can be sent by FAX at the following number: + 33 1 49 10 80 90</p> <p>In case of non-inclusion, the reporting period ends when the non-inclusion is documented.</p>
<p>13. STATISTICAL ANALYSIS</p> <p>13.4. Data sets analysed</p> <p>The following 2 data sets will be analysed (as defined by the Validation Committee): [...]</p> <ul style="list-style-type: none"> • The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy 	<p>13. STATISTICAL ANALYSIS</p> <p>13.4. Data sets analysed</p> <p>The following 3 data sets will be analysed (as defined by the Validation Committee): [...]</p> <ul style="list-style-type: none"> • The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy

<p>criteria available and without any major protocol deviation or other source of bias for primary criteria analyses.</p> <p>16. REFERENCES</p> <p>[1] F373280 INVESTIGATOR'S BROCHURE, version January 2013</p>	<p>criteria available and without any major protocol deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.</p> <p>16. REFERENCES</p> <p>[1] F373280 INVESTIGATOR'S BROCHURE, version October 2013</p>
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APPENDIX 1

STUDY FLOW-CHART FROM PROTOCOL VERSION 4

F373280 CA 201	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 +/-2 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2) →				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS	X	X			X	X			
ECV (3)			X						
Drug administration		← →							
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4) →		← (5) →						
TTEM (6)					← →				

⁽¹⁾ Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

⁽²⁾ In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV.

⁽³⁾ In patients with AF

⁽⁴⁾ 24-hour Holter ECG

⁽⁵⁾ 7-day Holter ECG

⁽⁶⁾ TTEM everyday from week 6 to week 8. Then every 2 days from week 9 to week 24. In case of AF symptoms. In case of AF recurrence for at least 10 minutes and the patient does not stop the study treatment then TTEM every 4 weeks

APPENDIX 2

STUDY FLOW-CHART FROM PROTOCOL VERSION 5 (modified version)

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	←	→	(2)		X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		←	→						→
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	↔ (4)		←	→ (5)					
TTEM (6)				←	→	←	→	→	→

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV.

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: everyday from week 6 to week 8; then every 2 days from week 9 to week 24; at any time in case of AF symptoms.

In case of AF recurrence for at least 10 minutes and if the patient does not stop the study treatment then TTEM once a week

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

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Version 5 –23OCT2013

The information contained in this document is confidential and is the property of the Sponsor, Pierre Fabre Médicament. This information is given for the needs of the study and must not be disclosed without prior written consent of the Sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the study must be informed that it is confidential and must not be disclosed.

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 5 – 23 OCT 2013

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Medical Director:
Richard ROCHE, MD

Date: 29/10/2013

Signature:



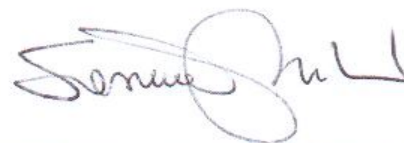
Study Coordinating Investigator:

Savina NODARI, MD

Date:

Signature:

30/10/2013



Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 5 – 23 OCT 2013

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
---------------	-------	------------

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 5 – 23 OCT 2013

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 23 October 2013 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament</i> represented by the <i>Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PolyUnsaturated Fatty Acid (PUFA) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of AF recurrence in patients with persistent AF, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – January 2015	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35± 2 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive) 2. Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. History of first documented persistent AF less than 3 years. 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area ≤ 40 cm² at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> ● in all the countries except Italy: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized ● in Italy only: <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion 12. For male with a child-bearing potential partner (In Italy only): <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study. <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 13. Having signed his/her written informed consent, 14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 3 years 2. More than two successful cardioversions (electrical or pharmacological) in the last 6

	<p>months</p> <ol style="list-style-type: none"> 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Oral amiodarone: <ol style="list-style-type: none"> 13a Previous treatment with oral amiodarone within 4 months prior to inclusion 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion 14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω 3 or ω 6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antithrombin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y₁₂ inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
	Oral, one capsule each evening with dinner.

Duration of Treatment:	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Reference Therapy	Placebo soft capsules Placebo will be administered in the same conditions as the tested product.
Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of AF lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit). Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24. For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5). Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM. All ECG traces will be evaluated by a Central Reading Laboratory. <p><u>Secondary evaluation variables:</u> During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u> During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All causes of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA(mL/m²), 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight) - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized) - Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>)

	<p>- Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (<i>PT</i>)</p>
Statistical Methods:	<p>Sample Size: Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment).</p>

STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2)				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		←	←	←	←	←	←	←	←
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4)		← (5)	←	←	←	←	←	←
TTEM (6)				←	←	←	←	←	←

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: everyday from week 6 to week 8; then every 2 days from week 9 to week 24; at any time in case of AF symptoms.

In case of AF recurrence for at least 10 minutes and if the patient does not stop the study treatment, then TTEM once a week

LIST OF ABBREVIATIONS

aPTT	: Activated partial thromboplastin time
AE	: Adverse event
AF	: Atrial fibrillation
ALA	: Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	: Anti-vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body Surface Area
CEP	: Protocol evaluation committee
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	: Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	: Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	: Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	: Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	: European heart rhythm association
EPA	: Eicosapentaenoic acid
e-CRF	: Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate
HBs	: Hepatitis B antigen
HCV	: Hepatitis C virus

HDL	:	High density lipoprotein
HF	:	Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR	:	International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS	:	Interactive voice response system
LAA	:	Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL	:	Low density lipoprotein
LOQ	:	Limit of quantification
LVEF	:	Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR	:	Mineralocorticoid receptor
MR perfusion	:	Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA	:	New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
PSC	:	Potentially Clinically Significant Change
PSCV	:	Potentially Clinically Significant Value
PUFA	:	PolyUnsaturated fatty acid
p.o.	:	Per os
PP	:	Per protocol data set
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT	:	Thrombin clotting time
TEAEs	:	Treatment emergent adverse events
TTEM	:	TransTelephonic ECG monitoring
WBC	:	White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of AF in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the Polyunsaturated Fatty Acids (PUFAs) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or AF.

The potential anti-arrhythmic effects of a PUFA were previously developed in AF: nicotinyl ester of DHA (pro-drug based on DHA delivery) was assessed in a two-week ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotinyl ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of AF induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll [2] assessed n-3 PUFAs in the prevention of AF recurrences after electrical cardioversion (ECV). All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct ECV 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFAs on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than in the placebo group at 1 month (3.3% vs 10%; $p = 0.043$), at 3 months (10% vs 25%; $p = 0.004$) and at 6 months (13.3% vs 40%; $p < 0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effects of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of

functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 ± 0.33 to 1.61 ± 0.49 and increased from 1.83 ± 0.38 to 2.14 ± 0.65 , respectively).

The hospitalization rates for patients with HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($p = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: $24\% \pm 7\%$ vs $29\% \pm 8\%$, $p = 0.005$) and 1 g/d treatment groups ($24\% \pm 8\%$ vs $27\% \pm 8\%$, $p = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent AF and heart failure in the maintenance of sinus rhythm after ECV.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of AF.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

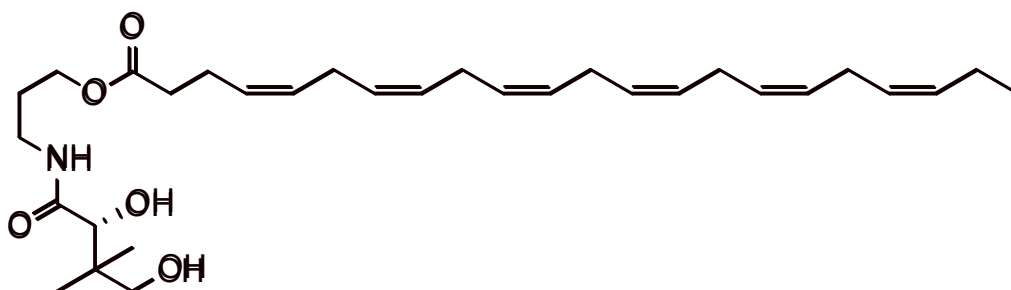
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased atrial effective refractory period (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $p < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the electrocardiogram (ECG) intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing-induced congestive heart failure provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses congestive heart failure-induced AF-promotion and fibrosis in the ventricular tachypacing canine model. Nicotinyl ester of DHA was tested in this model, at 1 g/day and 5 g/day, during 4 weeks, to prevent congestive heart failure-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in AF duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1 g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5 g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of

DHA in the left atrial tissue. Because F373280 similarly to Nicotiny ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 mg/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies, no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

Six consecutive single ascending doses were tested (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events (SAE) occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 3 TEAEs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotension without loss of consciousness) and 4 in the group of F373280 at the dosage of 16 g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events (AE) were reported in the groups of F373280 at the dosages of 0.5 g, 1 g, 2 g, 4 g and 8 g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5 g to 16 g in 36 young healthy male subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16 g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1 g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding Pharmacokinetics parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16 g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple doses

Three consecutive repeated ascending doses (1, 2 and 4 g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280, 5/9 TEAEs were classified according the System Organ Class in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAEs have already been reported with PUFAs and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** C_{max} and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after ECV in persistent AF patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing [1].

Moreover, the effectiveness of PUFAs has been proven in the following conditions:

- Prevention of AF recurrence in patients with persistent AF in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent AF and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after ECV in patients with persistent AF and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1 g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor® [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations:
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:
Very rare: nasal dryness
- Gastrointestinal disorders:
Common: dyspepsia, nausea
Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper
Rare: gastrointestinal pain
Very rare: lower gastrointestinal haemorrhage
- Hepatobiliary disorders:
Rare: hepatic disorders
- Skin and subcutaneous tissue disorders:
Rare: acne, rash pruritic
Very rare: urticaria
- General disorders and administration site conditions:
Rare: malaise sensation
- Investigations:
Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépantène® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1 g and 4 g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in AF studies [2, 8]. The range of PUFAs doses tested was between 2 g to 3 g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in HF patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1 g to 5 g (1 g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent form.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on AF and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the

included patients will remain under the standard treatment of AF and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (anti-vitamin K), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication
- Anticoagulation with anti-vitamin K (AVK) for at least 3 weeks before ECV
- ECV in patients with stabilized INR (i.e. values between 2 and 3;sp to) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent AF and chronic heart failure.

After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1 g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 7D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit
- Visit 9 (V9): W24 (D168 \pm 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent AF and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent AF with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- Persistent AF history (less than three years) with a duration of the current episode from 7 days to 6 months.
- a moderately abnormal systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- a Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of ECV, patients should have a stable medical treatment of heart failure and should not have any myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on antiarrhythmics in AF (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, antiarrhythmic class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF since cardioversion.

To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before ECV. According to guidelines for the management of AF [6], AVK should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodari's study [2], the duration of pre-treatment with PUFAs before cardioversion appears to be a contributing factor in success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of AF recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of AF recurrences occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using an easier device to carry and to use, i.e. a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with AF [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of AF after cardioversion. Moreover, PUFAs at dosage of 1 g and 2 g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1 g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95 mg/mL and 60 to 90 mg/mL, respectively) (phase I study of F373280 and [16]). With regard to the rhythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports an once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a 1 g daily dose of F373280 is considered to be appropriate for this proof of concept study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive)
2. Patient with current episode of persistent AF between 7 days and 6 months duration for whomelectrical cardioversion is warranted

3. History of first documented persistent AF less than 3 years
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - **in all the countries except Italy:**
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
 - **in Italy only:**
 - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or
 - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,
14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation)

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 3 years,
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),

4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Oral amiodarone:
 - 13a Previous treatment with oral amiodarone within 4 months prior to inclusion
 - 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion
14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
 - Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENT IDENTIFICATION

Patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

Reasons for a patient's premature withdrawal from the study may be the following:

- Patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- Investigator's decision in the patient's interest, particularly if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.

- Erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion/non inclusion criteria will immediately be withdrawn and an appropriate treatment will be given by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with AVK for at least 3 weeks before ECV.
- Patients who will not have a stabilized INR between 2 and 3 on at least 3 consecutive weekly tests.
- Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 weeks for whom a trans-oesophagoal echocardiography can not be performed before ECV or for whom a trans-oesophagoal echocardiography shows a thrombus in the atria.
- Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early relapse within the observation period after ECV will be considered to have finished follow-up.
- Occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit:

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the

Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.

- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1 g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number
- c) packaging batch number
- d) treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”

On the treatment unit, another label will be affixed with the mention of the Investigator’s name and patient’s code (completed by the Investigator).

In addition, on each case will be mentioned the case number, and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date

- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion visit (V2) and another one at visit 6.

For each patient, the treatment number given at visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once patient's eligibility is confirmed at selection visit (V1):

- The Investigator:
 - Contacts the IVRS/IWRS
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure to F373280 or placebo will be 24 weeks.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator in collaboration with the Sponsor's representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (at selection visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the electronic Case Report Forms (e-CRF). All treatments should be evaluated by the Investigator at patient's selection, and treatment prolongation or stop during the study should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

AVK should be given for at least 3 weeks before ECV and continued for the whole study duration. The AVK used will be left to the decision of the each Investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Ranolazine
- Any PUFA
- Any anticoagulant treatment other than AVK: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the e-CRF. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first AF recurrence is defined by the first episode of AF (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring, the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM).

- Trans Telephonic ECG Monitoring:

The ECG follow up will be documented using the TTEM: daily transmission from visit 4 (week 5) to visit 5 (week 8). Then every two days from visit 5 (week 8) to visit 9 (week 24 – End of study).

Moreover, if patient experiences AF symptoms during this TTEM period, it should be documented using the TTEM.

In case of AF recurrence and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be faxed to the site. The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of AF episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. *Definition*

Number of AF episodes will consist in the assessment of AF episodes with duration at least 10 minutes ($N_{\text{Sup}10}$) and of less than 10 minutes ($N_{\text{Inf}10}$), respectively.

8.1.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the study visit 4.

8.1.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. *Duration of AF episodes in the first week following visit 3 (ECV visit)*

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episode.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. *Clinical parameters evaluation*

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily.

8.1.2.3.1.2. Schedule

EHRA evaluation will be performed in case of evocative symptoms of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

EHRA evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.

8.1.2.3.3. *Number and duration of hospitalizations*

- Number and duration of hospitalizations for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalizations for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shock distribution (1, 2 or 3 shocks)
 - Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), LVEF (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA (mL/m²), Left

ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL).

8.1.2.5.2. Schedule

Measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

Measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. Evaluation method

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, the recommended method for volume measurements is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.2.1. Definition

Because of the limited human tissue accessibility for biopsy, red blood cell DHA contents is a marker of tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. Collection schedule

Blood samples will be collected to determine the red blood cells (RBC) concentrations of DHA.

Blood samples will be performed at visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the e-CRFs.

8.2.2.2. *Technical handling*

Two blood samples (4 ml) will be collected in EDTA tubes. They will be gently shaken, stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock) in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of AEs since the last visit will be based on the patient's spontaneous reporting, the

Investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The total volume of blood samples taken for haematology and biochemistry analysis should not exceed 30 mL.

8.3.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *hematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula:

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$$\text{GFR (mL/min)} = [(140 - \text{age})] \times \text{weight} / 7.2 \times \text{serum creatinine in mg/L}]$$

in women:

$GFR (mL/min) = [(140 - \text{age})] \times \text{weight} / 7.2 \times \text{serum creatinine in mg/L}] \times 0.85$

- with serum creatinine expressed as $\mu\text{mol/L}$:

$GFR (mL/min) = [(140 - \text{age}) \times \text{weight} / \text{serum creatinine in } \mu\text{mol/L}] \times k$, where $k = 1.23$ for men, 1.04 for women.

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. Schedule

Vital signs will be measured at each visit.

8.3.4.2. Technical Procedure and Parameters

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation by counting the beats for at least 30 seconds, after at least 5 minutes in supine position and after 2 minutes in standing position.

Bodyweight will be measured with patient in underwear and with the same balance at each visit.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. *Schedule*

An ECG will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent AF.

8.3.6. Coagulation parameters

Coagulation assessment will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by AVK should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.3.7. Concomitant Treatments

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial, can be found in section 7.

8.4. COMPLIANCE

The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.

At each visit, the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If the patient accepts to participate in the study, he/she will sign the informed consent form and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history

- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and AF characteristics
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory. The Central Reading Laboratory will send his/her assessment regarding the confirmation of persistent AF within 2 working days to the Investigator.
- The patient will enter the selection period in which anticoagulant (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before ECV.

At the end of the visit, the Investigator will contact the IVRS/IWRS to confirm the patient selection (which will automatically order the treatment delivery) and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent AF by the Central Reading Laboratory during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6) in order to ensure that the INR is stable (between 2 to 3 before electrical cardioversion).

At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, RBC concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE performed in the same day (and before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 -2/+7 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of AE
- Concomitant treatments (authorised, disallowed)
- Body weight (body weight measured at V3 to be used)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms, additional transmissions may be performed.

Visit 5 (Week 8: D56 \pm 7 days) – Visit 6 (Week 12: D84 \pm 7 days) - Visit 7 (Week 16: D112 \pm 7 days) - Visit 8 (Week 20: D140 \pm 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of

discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.

- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using a TTEM device. The device will be given to the patient who will be requested to perform daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms, additional transmissions may be performed.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 6:

- the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period.
- an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)

- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT), Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An AE is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

AE includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

10.1.3. Reporting of Adverse Events

The records of AE in the e-CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A SAE includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect

Other events such as cancer and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure
- preparation for routine health assessment/procedure (e.g. routine colonoscopy)
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required)
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by FAX at the following number:

+ 33 1 49 10 80 90

In case of non-inclusion, the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial, an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose and associated adverse event if any, are reported only on the Adverse Event page of the e-CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must also be transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the Sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and must be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is withdrawn from the study.

The Investigator must report to the Sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The Investigator must immediately notify the Sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the Investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the Sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An e-CRF will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files that will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and should include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants using this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRFs (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. *Site Preselection Visit*

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. *Initiation Visit*

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. *Follow-up Visits*

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of primary end point measures, the safety data. The IDMC will thereafter recommend to the Sponsor whether to continue, modify, or stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on the e-CRFs.

The e-CRFs used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate the coding.

12.4. DATA STORAGE

Computer data files as well as their modifications will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e. data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by PFB or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 3 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety.

- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAEs
- With at least three TEAEs
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.

Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:

- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TEAE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patients).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

SAE will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration

assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

CNALV (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)

- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and HR in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. Individual Patient Changes

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) minus number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days \pm 7days)

13.11. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi

Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Médicament are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not.
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents.
- Authorises direct access to source documents for monitoring, audits and inspections.
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety

- Stopping of the development ...

15.3.2.2. *Early Study Termination Decided by the Competent Authorities*

The Competent Authorities may suspend or prohibit a study if they consider that either the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both its representatives (Study Manager, CRA...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed in writing with the Study Manager, the Investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the Sponsor's responsibility.

Upon data analysis completion, a final report including a review of the objectives and methods, a presentation and a discussion of the results is drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the Investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow the use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The Investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) Investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all Investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version October 2013
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57;870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedaron for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedaron versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELIN D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY
TO PIERRE FABRE CORPORATE VIGILANCES DIVISION

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION BY E-MAIL WITHIN 24H TO
HQ.pharmacovigilance@pierre-fabre.com OR BY FAX WITHIN 24H – Fax N°: 33 (0) 1.49.10.80.90

Transmission date (ddmm/yyyy) Country :
SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ SUBJECT CHARACTERISTICS

Gender	<input type="checkbox"/> 1=M, 2=F	Height	<input type="text"/> <input type="text"/> <input type="text"/> cm	Birth date	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Weight	<input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg
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➤ DESCRIPTION OF THE EVENT

The serious adverse event resulted in :

- ☐ Death (whatever may be the cause)
☐ Hospitalisation (*) or extension thereof
☐ Life threatening
☐ Invalidity or disability

- ☐ Congenital abnormality or abnormal pregnancy outcome
☐ Cancer
☐ Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts)

Other fact to be notified :

- ☐ Pregnancy exposure

Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :

.....
.....
.....

AE onset date (ddmm/yyyy)

Seriousness onset date (ddmm/yyyy)

Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) :

(*) Except hospitalisations with durations and goals planned in the protocol

➤ THE SAE IN RELATION TO THE TRIAL

	TREATMENT NUMBER	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
• Time of occurrence of SAE		
<input type="checkbox"/> During the selection or run-in period		
<input type="checkbox"/> During the administration phase of the study treatment		
<input type="checkbox"/> After the administration phase of the study treatment		
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	(ddmm/yyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	(ddmm/yyyy)
• Was the blind broken ?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable	
If yes, or if this is an open study, drug(s) administered :		
.....		
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :		
.....		

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ **CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE**
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ **MEASURES TAKEN FOLLOWING THE SAE**

• **Study treatment**

☐ No change

☐ Dosage modification, specify : Modification Date : __/__/__

☐ Temporarily discontinued Readministration date : __/__/__

☐ Withdrawn End date : __/__/__

☐ Not applicable

• **The event led to :**

☐ Prescription of corrective or symptomatic treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

☐ Discontinuation of concomitant treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

☐ Others, specify :

➤ **OUTCOME**

☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown

In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ **INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)**

Study drug:

Related to study protocol:

☐ Not Suspected

☐ Suspected

☐ Not Suspected

☐ Suspected

Comments:

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(a)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	µmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	µmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	µmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(a) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		<ul style="list-style-type: none"> • < 1 500/mm³ whatever the baseline value
WBC (if missing value for neutrophils)		<ul style="list-style-type: none"> • < 3 000/mm³ whatever the baseline value
PLATELETS		<ul style="list-style-type: none"> • < 100 000/mm³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.6. Protocol and appendices
(version 06: 02 December 2013)***

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

Sponsor's Representative:

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Version 6 –02DEC2013

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 6 – 02 DEC 2013

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Date: 02/12/2013 Signature:




Study Coordinating Investigator:
Savina NODARI, MD

Date:

Signature:

02/12/2013



Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 6 – 02 DEC 2013

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
---------------	-------	------------

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 6 – 02 DEC 2013

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 02 December 2013 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament</i> represented by the <i>Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PolyUnsaturated Fatty Acid (PUFA) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of AF recurrence in patients with persistent AF, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – January 2015	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56 ± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive) 2. Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. History of first documented persistent AF less than 3 years. 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area ≤ 40 cm² at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> ● in all the countries except Italy: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized ● in Italy only: <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion 12. For male with a child-bearing potential partner (In Italy only): <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study. <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 13. Having signed his/her written informed consent, 14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 3 years 2. More than two successful cardioversions (electrical or pharmacological) in the last 6

	<p>months</p> <ol style="list-style-type: none"> 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Oral amiodarone: <ol style="list-style-type: none"> 13a Previous treatment with oral amiodarone within 4 months prior to inclusion 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion 14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω 3 or ω 6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antithrombin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y₁₂ inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
	Oral, one capsule each evening with dinner.

Duration of Treatment:	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Reference Therapy	Placebo soft capsules Placebo will be administered in the same conditions as the tested product.
Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of AF lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit). Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24. For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5). Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM. All ECG traces will be evaluated by a Central Reading Laboratory. <p><u>Secondary evaluation variables:</u> During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u> During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All causes of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA(mL/m²), 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight) - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized) - Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>)

	<p>- Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (<i>PT</i>)</p>
Statistical Methods:	<p>Sample Size: Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment).</p>

STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2)				X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		←							→
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4)		← (5)						
TTEM (6)				←	←				→

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: everyday from week 6 to week 8; then every 2 days from week 9 to week 24; at any time in case of AF symptoms.

In case of AF recurrence for at least 10 minutes and if the patient does not stop the study treatment, then TTEM once a week

LIST OF ABBREVIATIONS

aPTT	: Activated partial thromboplastin time
AE	: Adverse event
AF	: Atrial fibrillation
ALA	: Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	: Anti-vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body Surface Area
CEP	: Protocol evaluation committee
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	: Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	: Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	: Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	: Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	: European heart rhythm association
EPA	: Eicosapentaenoic acid
e-CRF	: Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate
HBs	: Hepatitis B antigen
HCV	: Hepatitis C virus

HDL	:	High density lipoprotein
HF	:	Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR	:	International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS	:	Interactive voice response system
LAA	:	Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL	:	Low density lipoprotein
LOQ	:	Limit of quantification
LVEF	:	Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR	:	Mineralocorticoid receptor
MR perfusion	:	Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA	:	New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
PSC	:	Potentially Clinically Significant Change
PSCV	:	Potentially Clinically Significant Value
PUFA	:	PolyUnsaturated fatty acid
p.o.	:	Per os
PP	:	Per protocol data set
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT	:	Thrombin clotting time
TEAEs	:	Treatment emergent adverse events
TTEM	:	TransTelephonic ECG monitoring
WBC	:	White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of AF in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the Polyunsaturated Fatty Acids (PUFAs) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or AF.

The potential anti-arrhythmic effects of a PUFA were previously developed in AF: nicotinyl ester of DHA (pro-drug based on DHA delivery) was assessed in a two-week ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotinyl ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of AF induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll [2] assessed n-3 PUFAs in the prevention of AF recurrences after electrical cardioversion (ECV). All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct ECV 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFAs on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than in the placebo group at 1 month (3.3% vs 10%; $p = 0.043$), at 3 months (10% vs 25%; $p = 0.004$) and at 6 months (13.3% vs 40%; $p < 0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effects of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of

functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 ± 0.33 to 1.61 ± 0.49 and increased from 1.83 ± 0.38 to 2.14 ± 0.65 , respectively).

The hospitalization rates for patients with HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($p = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: $24\% \pm 7\%$ vs $29\% \pm 8\%$, $p = 0.005$) and 1 g/d treatment groups ($24\% \pm 8\%$ vs $27\% \pm 8\%$, $p = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent AF and heart failure in the maintenance of sinus rhythm after ECV.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of AF.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

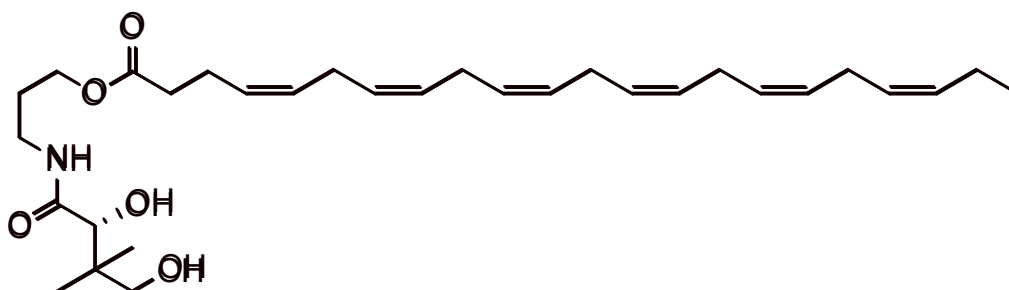
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased atrial effective refractory period (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $p < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the electrocardiogram (ECG) intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing-induced congestive heart failure provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses congestive heart failure-induced AF-promotion and fibrosis in the ventricular tachypacing canine model. Nicotinyl ester of DHA was tested in this model, at 1 g/day and 5 g/day, during 4 weeks, to prevent congestive heart failure-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in AF duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1 g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5 g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of

DHA in the left atrial tissue. Because F373280 similarly to Nicotinyln ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 mg/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies, no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

Six consecutive single ascending doses were tested (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events (SAE) occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 3 TEAEs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotension without loss of consciousness) and 4 in the group of F373280 at the dosage of 16 g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events (AE) were reported in the groups of F373280 at the dosages of 0.5 g, 1 g, 2 g, 4 g and 8 g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5 g to 16 g in 36 young healthy male subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16 g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1 g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding Pharmacokinetics parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16 g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple doses

Three consecutive repeated ascending doses (1, 2 and 4 g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280, 5/9 TEAEs were classified according the System Organ Class in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAEs have already been reported with PUFAs and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** C_{max} and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after ECV in persistent AF patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing [1].

Moreover, the effectiveness of PUFAs has been proven in the following conditions:

- Prevention of AF recurrence in patients with persistent AF in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent AF and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after ECV in patients with persistent AF and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1 g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor® [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations:
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:
Very rare: nasal dryness
- Gastrointestinal disorders:
Common: dyspepsia, nausea
Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper
Rare: gastrointestinal pain
Very rare: lower gastrointestinal haemorrhage
- Hepatobiliary disorders:
Rare: hepatic disorders
- Skin and subcutaneous tissue disorders:
Rare: acne, rash pruritic
Very rare: urticaria
- General disorders and administration site conditions:
Rare: malaise sensation
- Investigations:
Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1 g and 4 g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in AF studies [2, 8]. The range of PUFAs doses tested was between 2 g to 3 g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in HF patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1 g to 5 g (1 g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent form.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on AF and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the

included patients will remain under the standard treatment of AF and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (anti-vitamin K), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication
- Anticoagulation with anti-vitamin K (AVK) for at least 3 weeks before ECV
- ECV in patients with stabilized INR (i.e. values between 2 and 3;sp to) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent AF and chronic heart failure.

After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1 g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 7D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit
- Visit 9 (V9): W24 (D168 \pm 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent AF and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent AF with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- Persistent AF history (less than three years) with a duration of the current episode from 7 days to 6 months.
- a moderately abnormal systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- a Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of ECV, patients should have a stable medical treatment of heart failure and should not have any myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on antiarrhythmics in AF (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, antiarrhythmic class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF since cardioversion.

To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before ECV. According to guidelines for the management of AF [6], AVK should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodari's study [2], the duration of pre-treatment with PUFAs before cardioversion appears to be a contributing factor in success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of AF recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of AF recurrences occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using an easier device to carry and to use, i.e. a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with AF [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of AF after cardioversion. Moreover, PUFAs at dosage of 1 g and 2 g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1 g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95 mg/mL and 60 to 90 mg/mL, respectively) (phase I study of F373280 and [16]). With regard to the rhythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports an once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a 1 g daily dose of F373280 is considered to be appropriate for this proof of concept study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive)
2. Patient with current episode of persistent AF between 7 days and 6 months duration for whomelectrical cardioversion is warranted

3. History of first documented persistent AF less than 3 years
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - **in all the countries except Italy:**
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
 - **in Italy only:**
 - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or
 - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,
14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation)

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 3 years,
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),

4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Oral amiodarone:
 - 13a Previous treatment with oral amiodarone within 4 months prior to inclusion
 - 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion
14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
 - Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENT IDENTIFICATION

Patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

Reasons for a patient's premature withdrawal from the study may be the following:

- Patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- Investigator's decision in the patient's interest, particularly if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.

- Erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion/non inclusion criteria will immediately be withdrawn and an appropriate treatment will be given by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with AVK for at least 3 weeks before ECV.
- Patients who will not have a stabilized INR between 2 and 3 on at least 3 consecutive weekly tests.
- Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 weeks for whom a trans-oesophagoal echocardiography can not be performed before ECV or for whom a trans-oesophagoal echocardiography shows a thrombus in the atria.
- Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early relapse within the observation period after ECV will be considered to have finished follow-up.
- Occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit:

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the

Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.

- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1 g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number
- c) packaging batch number
- d) treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”

On the treatment unit, another label will be affixed with the mention of the Investigator’s name and patient’s code (completed by the Investigator).

In addition, on each case will be mentioned the case number, and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date

- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion visit (V2) and another one at visit 6.

For each patient, the treatment number given at visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once patient's eligibility is confirmed at selection visit (V1):

- The Investigator:
 - Contacts the IVRS/IWRS
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure to F373280 or placebo will be 24 weeks.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator in collaboration with the Sponsor's representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (at selection visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the electronic Case Report Forms (e-CRF). All treatments should be evaluated by the Investigator at patient's selection, and treatment prolongation or stop during the study should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

AVK should be given for at least 3 weeks before ECV and continued for the whole study duration. The AVK used will be left to the decision of the each Investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Ranolazine
- Any PUFA
- Any anticoagulant treatment other than AVK: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the e-CRF. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first AF recurrence is defined by the first episode of AF (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring, the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM).

- Trans Telephonic ECG Monitoring:

The ECG follow up will be documented using the TTEM: daily transmission from visit 4 (week 5) to visit 5 (week 8). Then every two days from visit 5 (week 8) to visit 9 (week 24 – End of study).

Moreover, if patient experiences AF symptoms during this TTEM period, it should be documented using the TTEM.

In case of AF recurrence and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be faxed to the site. The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of AF episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. *Definition*

Number of AF episodes will consist in the assessment of AF episodes with duration at least 10 minutes ($N_{\text{Sup}10}$) and of less than 10 minutes ($N_{\text{Inf}10}$), respectively.

8.1.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the study visit 4.

8.1.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. *Duration of AF episodes in the first week following visit 3 (ECV visit)*

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episode.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. *Clinical parameters evaluation*

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily.

8.1.2.3.1.2. Schedule

EHRA evaluation will be performed in case of evocative symptoms of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

EHRA evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.

8.1.2.3.3. *Number and duration of hospitalizations*

- Number and duration of hospitalizations for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalizations for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shock distribution (1, 2 or 3 shocks)
 - Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), LVEF (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA (mL/m²), Left

ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL).

8.1.2.5.2. Schedule

Measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

Measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. Evaluation method

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, the recommended method for volume measurements is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.2.1. Definition

Because of the limited human tissue accessibility for biopsy, red blood cell DHA contents is a marker of tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. Collection schedule

Blood samples will be collected to determine the red blood cells (RBC) concentrations of DHA.

Blood samples will be performed at visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the e-CRFs.

8.2.2.2. *Technical handling*

Two blood samples (4 ml) will be collected in EDTA tubes. They will be gently shaken, stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock) in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of AEs since the last visit will be based on the patient's spontaneous reporting, the

Investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The total volume of blood samples taken for haematology and biochemistry analysis should not exceed 30 mL.

8.3.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *hematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula:

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$$\text{GFR (mL/min)} = [(140 - \text{age})] \times \text{weight} / 7.2 \times \text{serum creatinine in mg/L}]$$

in women:

$GFR (mL/min) = [(140 - \text{age})] \times \text{weight} / 7.2 \times \text{serum creatinine in mg/L}] \times 0.85$

- with serum creatinine expressed as $\mu\text{mol/L}$:

$GFR (mL/min) = [(140 - \text{age}) \times \text{weight} / \text{serum creatinine in } \mu\text{mol/L}] \times k$, where $k = 1.23$ for men, 1.04 for women.

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. Schedule

Vital signs will be measured at each visit.

8.3.4.2. Technical Procedure and Parameters

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation by counting the beats for at least 30 seconds, after at least 5 minutes in supine position and after 2 minutes in standing position.

Bodyweight will be measured with patient in underwear and with the same balance at each visit.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. *Schedule*

An ECG will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent AF.

8.3.6. Coagulation parameters

Coagulation assessment will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by AVK should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.3.7. Concomitant Treatments

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial, can be found in section 7.

8.4. COMPLIANCE

The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.

At each visit, the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If the patient accepts to participate in the study, he/she will sign the informed consent form and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history

- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and AF characteristics
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory. The Central Reading Laboratory will send his/her assessment regarding the confirmation of persistent AF within 2 working days to the Investigator.
- The patient will enter the selection period in which anticoagulant (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before ECV.

At the end of the visit, the Investigator will contact the IVRS/IWRS to confirm the patient selection (which will automatically order the treatment delivery) and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent AF by the Central Reading Laboratory during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6) in order to ensure that the INR is stable (between 2 to 3 before electrical cardioversion).

At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, RBC concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE performed in the same day (and before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 -2/+7 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of AE
- Concomitant treatments (authorised, disallowed)
- Body weight (body weight measured at V3 to be used)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms, additional transmissions may be performed.

Visit 5 (Week 8: D56 \pm 7 days) – Visit 6 (Week 12: D84 \pm 7 days) - Visit 7 (Week 16: D112 \pm 7 days) - Visit 8 (Week 20: D140 \pm 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of

discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.

- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using a TTEM device. The device will be given to the patient who will be requested to perform daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24. Moreover, in case of AF symptoms, additional transmissions may be performed.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 6:

- the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period.
- an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)

- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT), Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An AE is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

AE includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

10.1.3. Reporting of Adverse Events

The records of AE in the e-CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A SAE includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect

Other events such as cancer and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure
- preparation for routine health assessment/procedure (e.g. routine colonoscopy)
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required)
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by FAX at the following number:

+ 33 1 49 10 80 90

In case of non-inclusion, the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial, an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose and associated adverse event if any, are reported only on the Adverse Event page of the e-CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must also be transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the Sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and must be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is withdrawn from the study.

The Investigator must report to the Sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The Investigator must immediately notify the Sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the Investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the Sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An e-CRF will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files that will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and should include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants using this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRFs (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. *Site Preselection Visit*

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. *Initiation Visit*

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. *Follow-up Visits*

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of primary end point measures, the safety data. The IDMC will thereafter recommend to the Sponsor whether to continue, modify, or stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on the e-CRFs.

The e-CRFs used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate the coding.

12.4. DATA STORAGE

Computer data files as well as their modifications will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e. data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by PFB or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 3 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety.

- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAEs
- With at least three TEAEs
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.

Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:

- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TEAE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patients).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

SAE will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration

assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

CNALV (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)

- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and HR in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. Individual Patient Changes

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) minus number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days \pm 7days)

13.11. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi

Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Médicament are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not.
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents.
- Authorises direct access to source documents for monitoring, audits and inspections.
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety

- Stopping of the development ...

15.3.2.2. *Early Study Termination Decided by the Competent Authorities*

The Competent Authorities may suspend or prohibit a study if they consider that either the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both its representatives (Study Manager, CRA...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed in writing with the Study Manager, the Investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the Sponsor's responsibility.

Upon data analysis completion, a final report including a review of the objectives and methods, a presentation and a discussion of the results is drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the Investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow the use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The Investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) Investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all Investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version October 2013
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57;870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedaron for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedaron versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELINE D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY
TO PIERRE FABRE CORPORATE VIGILANCES DIVISION

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION BY E-MAIL WITHIN 24H TO HQ.pharmacovigilance@pierre-fabre.com OR BY FAX WITHIN 24H – Fax N°: 33 (0) 1.49.10.80.90

Transmission date (ddmmyyyy) Country :
SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ **SUBJECT CHARACTERISTICS**

Gender	<input type="checkbox"/> 1=M, 2=F	Height	<input type="text"/> <input type="text"/> <input type="text"/> cm	Birth date	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Weight	<input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg
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➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) : 	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ **CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE**
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ **MEASURES TAKEN FOLLOWING THE SAE**

• **Study treatment**

☐ No change

☐ Dosage modification, specify : Modification Date : __/__/__

☐ Temporarily discontinued Readministration date : __/__/__

☐ Withdrawn End date : __/__/__

☐ Not applicable

• **The event led to :**

☐ Prescription of corrective or symptomatic treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

☐ Discontinuation of concomitant treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

☐ Others, specify :

➤ **OUTCOME**

☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown

In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ **INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)**

Study drug:

Related to study protocol:

☐ Not Suspected

☐ Suspected

☐ Not Suspected

☐ Suspected

Comments:

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(α)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(α) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		• < 1 500/mm ³ whatever the baseline value
WBC (if missing value for neutrophils)		• < 3 000/mm ³ whatever the baseline value
PLATELETS		• < 100 000/mm ³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.7. Protocol amendment n° PA04
General and non-substantial dated on 03 June
2014 linked to Protocol and appendices
(version 7: 03 June 2014)***

CLINICAL STUDY PROTOCOL AMENDMENT n° PA04 Version 1
(General – Non Substantial)

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

CLINICAL STUDY PROTOCOL AMENDMENT n° PA04 Version 1

(General – Non Substantial)

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code: F373280 CA 2 01

EudraCT Number or equivalent : 2012-003487-48

Sponsor's Representative: **Gaëlle ALCARAZ**
INSTITUT DE RECHERCHE PIERRE FABRE
Centre de R&D Pierre Fabre - BP 13562
3 avenue Hubert Curien
31035 TOULOUSE Cedex 1

Study Coordinating Investigator: **Pr 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
c/o Spedali Civili di Brescia
Piazzale Spedali Civili, 1
25123 - BRESCIA, ITALY

Date of amendment PA04: 03 Jun 2014

APPROVAL FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA04 Version 1

(General – Non Substantial)

Dated: 03JUN2014

Sponsor's representative(s)

• Medical Director

Date: 06/06/2014 Signature:

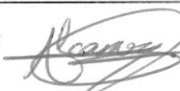
Dr Richard ROCHE



• Clinical Study Manager :

Date: 06 JUN 2014 Signature:

Gaëlle ALCARAZ



Study Coordinating Investigator:

Date:

Signature:

Pr Savina NODARI

APPROVAL FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA04 Version 1

(General – Non Substantial)

Dated: 03JUN2014

Sponsor's representative(s)

• Medical Director

Date:

Signature:

Dr Richard ROCHE

• Clinical Study Manager :

Date:

Signature:

Gaëlle ALCARAZ

Study Coordinating Investigator:

Date:

Signature:

Pr Savina NODARI

11/06/2014 

COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA04 Version 1

(General – Non Substantial)

Dated: 03JUN2014

Country Coordinating Investigator:

Date:

Signature:

INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA04 Version 1

(General – Non Substantial)

Dated: 03JUN2014

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA04 and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF AMENDMENTS

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
NA	NA	General	NA	Following French CA request (ANSM) and leading to protocol version 2: - Add of a non inclusion criteria: "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6
PA01	Substantial	Local (Italy)	01MAR2013	Corresponding to Protocol Version 3: - Integration of the modification included in the protocol version 2 - Harmonisation of the protocol and the Informed Consent Form: * adjustment of the selection criteria n°10 related to the contraception method * addition of a letter that is given by the patient to his/her general practitioner (GP) * precision that the sponsor can not collect a copy of the Informed Consent Form * precision that the patient card is in Italian language only (without any English mention)
PA02	Non Substantial	General	28MAR2013	Corresponding to Protocol Version 4 : - change of Sponsor's Representative (Clinical Study Manager), - modification of the technical handling of the blood samples for determination of red blood cells concentration of DHA: the centrifugation is no more needed, - precision on the function and address of the International Study Coordinator Pr Nodari, - add of address and contacts details of two CRO newly involved in the study: Theradis (in charge of transportation of blood samples to the Analytical centre and material supply) and "Clinact" (in charge of refund of patients expenses linked to the study), - adjustment of the wording, in agreement with the commitment to the French Ethics Committee. In the paragraphe 8.3.2.1, the wording "hematology examination" is replaced by "standard hematologic dosage", - precision of the full title in the study synopsis (in agreement with the commitment to the Spanish Ethics Committee), - correction of a mistake in section 8.1.1.3 (related to TTEM transmission) and sections 3, 9 and study synopsis (related to the definition of INR not stabilized). - addition of the changes included in the local italian substantial protocol amendment (i.e: contraception method, letter to General Practionner, patient card in Italian and no collection of the consent form by the sponsor in Italy).

PA03	Substantial	General	23OCT2013	<p>Corresponding to Protocol Version 5:</p> <ul style="list-style-type: none"> - Fax modification of the sponsor's representatives - Planned end of study postponed to January 2015. - The authorized history of the first documented persistent atrial fibrillation is less than 3 years. - At selection a hyperkalemia or a hypokalemia is better defined by the standards of the local laboratories. - Regarding previous treatments by amiodarone the non inclusion criteria of the protocol are adapted as follow: <ul style="list-style-type: none"> • Previous treatment with oral amiodarone within 4 months prior to inclusion • Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion • Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion. - For male with a child-bearing potential partner (in Italy only): taking into account the duration of spermatogenesis the absolute abstention from sexual intercourse or the use of double barrier contraception method are extended to 3 months after the end of the study. - Ranolazine is an antiarrhythmic treatment added to the prohibited treatments. - Update of Serious Adverse Events (SAEs) form: Main change is the SAE sending: SAEs have to be reported to the Corporate Vigilance Department, and not anymore to the clinical study manager. Also SAEs can be sent by e-mail and by fax. - Addition of Alpha Bioresarch as CRO involved for Feasibility, Monitoring and Regulatory issues in Spain. - Correction of some minor typographic errors
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1. AMENDMENT RATIONALE

The purpose of this non-substantial amendment is to clarify or specify some points of the protocol. Theses changes do not affect the balance of the risk and benefits in the study nor change the specific aims or design of the study.

2. CHANGES DESCRIPTION

PREVIOUS VERSION	MODIFIED VERSION
<p>SYNOPSIS</p> <p>Study Schedule:</p> <p>[...]</p> <ul style="list-style-type: none"> - V2/ D1: Inclusion visit (start of treatment) <p>Evaluation Criteria:</p> <p>Efficacy evaluation variables:</p> <p>[...]</p> <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Number of patients needing an other cardioversion after the initial ECV <p>[...]</p> <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (from V4 to V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA(mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL) Left ventricular end systolic diameter (mm), Left ventricular end systolic volume (mL)) <p>[...]</p> <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight) - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns (ECG not centralized) 	<p>SYNOPSIS</p> <p>Study Schedule:</p> <p>[...]</p> <ul style="list-style-type: none"> - V2/ D1: Inclusion visit (start of study treatment) <p>Evaluation Criteria:</p> <p>Efficacy evaluation variables:</p> <p>[...]</p> <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Shocks distribution (1, 2 or 3 shocks) • Number of patients needing an other cardioversion after the initial ECV <p>[...]</p> <p><u>Other:</u></p> <p>Evolution of echocardiographic parameters (at V4, V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA(mL/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL) Left ventricular end systolic diameter (mm), Left ventricular end systolic volume (mL))</p> <p>[...]</p> <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight, body surface area) - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns (ECG not centralized) <p>Concomitant treatments</p> <p>Compliance</p>

<p>4. STUDY DESIGN</p> <p>4.1 OVERALL DESCRIPTION</p> <p>[...]</p> <p>After a 1 to 4-week of run-in period without treatment, patients will be randomised into one of the following treatment groups: F373280 1 g or placebo for 24 weeks.</p> <p>Nine visits are planned for the study:</p> <ul style="list-style-type: none"> - Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit) - Visit 2 (V2): D1: Inclusion visit (start of treatment) 	<p>4. STUDY DESIGN</p> <p>OVERALL DESCRIPTION</p> <p>[...]</p> <p>After a 1 to 4-week of run-in period without study treatment, patients will be randomised into one of the following treatment groups: F373280 1 g or placebo for 24 weeks.</p> <p>Nine visits are planned for the study:</p> <ul style="list-style-type: none"> - Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit) - Visit 2 (V2): D1: Inclusion visit (start of study treatment)
<p>8. EVALUATION CRITERIA</p> <p>PRIMARY EFFICACY CRITERION</p> <p>Time to the first Atrial Fibrillation Recurrence</p> <p>8.1.1.3. Evaluation Methods</p> <p>[...]</p> <ul style="list-style-type: none"> • Trans Telephonic ECG Monitoring: <p>The ECG follow up will be documented using the TTEM: daily transmission from visit 4 (week 5) to visit 5 (week 8). Then every two days from visit 5 (week 8) to visit 9 (week 24 – End of study).</p> <p>[...]</p> <p>The cardiologist interpretation will be faxed to the site.</p> <p>8.1.2.4. Cardioversion assessment</p> <p>[...]</p> <ul style="list-style-type: none"> • Shock distribution (1, 2 or 3 shocks) 	<p>8. EVALUATION CRITERIA</p> <p>8.1 PRIMARY EFFICACY CRITERION</p> <p>8.1.1 Time to the first Atrial Fibrillation Recurrence</p> <p>8.1.1.3 Evaluation Methods</p> <p>[...]</p> <ul style="list-style-type: none"> • Trans Telephonic ECG Monitoring: <p>The ECG follow up will be documented using the TTEM: daily transmission from the day after visit 4 (week 6) to visit 5 (week 8). Then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study).</p> <p>[...]</p> <p>The cardiologist interpretation will be emailed to the site (or per fax on request of the site).</p> <p>8.1.2.4. Cardioversion assessment</p> <p>[...]</p> <ul style="list-style-type: none"> • Shocks distribution (1, 2 or 3 shocks)

8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.2.2 Blood samples

8.2.2.2 Technical handling

Two blood samples (4 ml) will be collected in EDTA tubes. They will be gently shaken, stored at +4°C (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.3. SAFETY ASSESSMENT

8.3.3 Global physical examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The physical examination will be globally evaluated as “normal/abnormal”. Further target inspection will be undertaken for any abnormal finding.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. Schedule

An ECG will be recorded at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. Technical Procedure and Parameters

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), repolarisation patterns will be reported in the e-CRF.

8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.2.2 Blood samples

8.2.2.2 Technical handling

Two blood samples (4 ml) will be collected in EDTA tubes. They will be gently shaken, stored **between +2°C/+8°C in a fridge** (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.3. SAFETY ASSESSMENT

8.3.3 Global physical examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The Body surface area (BSA) will be calculated at the same visits using Mostellers’ formula:

$$\text{BSA} = [(\text{Weight} \times \text{Height})/3600]^{1/2}$$

(Weight in kg, height in cm)

The physical examination will be globally evaluated as “normal/abnormal”. Further target inspection will be undertaken for any abnormal finding.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. Schedule

An ECG will be recorded **after at least 10 minutes of rest** at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. Technical Procedure and Parameters

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), **QTcB (ms), QTcF (ms)**, repolarisation patterns will be reported in the e-CRF.

<p>8.3.7. Concomitant Treatments</p> <p>8.4. COMPLIANCE</p> <p>The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.</p> <p>At each visit, the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.</p>	<p>8.4. CONCOMITANT TREATMENTS</p> <p>8.5. COMPLIANCE</p> <p>The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.</p> <p>At each visit (except at visit 4), the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.</p>
<p>9. STUDY PROCEDURES</p> <p>Visit 4 (Week 5: D35 -2/+7 days)</p> <p>[...]</p> <p>The patient will be requested to performed daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24.</p>	<p>9. STUDY PROCEDURES</p> <p>Visit 4 (Week 5: D35 -2/+7 days)</p> <p>[...]</p> <p>The patient will be requested to perform daily transmission from the day after visit 4 (week 6) to visit 5 (week 8), then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study).</p>
<p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>[...]</p> <p>The cardiac monitoring will be continued using a TTEM device. The device will be given to the patient who will be requested to perform daily transmission from week 6 to week 8, then every 2 days from week 9 to week 24.</p>	<p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>[...]</p> <p>The cardiac monitoring will be continued using a TTEM device. The device will be given to the patient who will be requested to perform daily transmission from the day after visit 4 (week 6) to visit 5 (week 8), then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study).</p>

<p>13. STATISTICAL ANALYSIS</p> <p>13.11. INTERIM ANALYSIS AND DATA MONITORING</p> <p>No interim analysis is planned.</p>	<p>13. STATISTICAL ANALYSIS</p> <p>13.11. INTERIM ANALYSIS AND DATA MONITORING</p> <p>No analyses of efficacy data are planned for IDMC that ensures that the overall probability of type I error is controlled. No Type I error and sample size adjustments are necessary. Any recommendations of the IDMC to alter study conduct will be based on safety, so IDMC monitoring of the study will not affect the statistical operating characteristics of the final analysis. The IDMC will review, three times during the study period (after the first 30 subjects will have been randomized, when the first 80 subjects will have terminated their study participation and when 130 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.</p>
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F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

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Version 7 – 03JUN2014

The information contained in this document is confidential and is the property of the Sponsor, Pierre Fabre Médicament. This information is given for the needs of the study and must not be disclosed without prior written consent of the Sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the study must be informed that it is confidential and must not be disclosed.

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 7 – 03 JUN2014

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Date: 06/06/2014 Signature:



Study Coordinating Investigator:

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 7 – 03 JUN2014

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Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 7 – 03 JUN 2014

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
---------------	-------	------------

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 7 – 03 JUN 2014

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 03 June 2014 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament</i> represented by the <i>Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PolyUnsaturated Fatty Acid (PUFA) has been proven in the following conditions:</p> <ul style="list-style-type: none"> – prevention of AF recurrence in patients with persistent AF, in co-administration with amiodarone (add on therapy) [2] – Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – January 2015	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: <ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms - Treatment duration: 24 weeks 	
Study Schedule:	<p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of study treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to 	

	<p>clinical practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56 ± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive) 2. Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. History of first documented persistent AF less than 3 years. 4. History of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area ≤ 40 cm² at selection and at inclusion 9. Patients treated or having to be treated by anti-vitamin K 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> ● in all the countries except Italy: <ul style="list-style-type: none"> - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - documented as surgically sterilized ● in Italy only: <ul style="list-style-type: none"> - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or - documented as surgically sterilized 11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion 12. For male with a child-bearing potential partner (In Italy only): <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study. <p><i>Ethical /legal considerations:</i></p> <ol style="list-style-type: none"> 13. Having signed his/her written informed consent, 14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation) <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. History of first documented episode of persistent AF more than 3 years 2. More than two successful cardioversions (electrical or pharmacological) in the last 6

	<p>months</p> <ol style="list-style-type: none"> 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers 13. Oral amiodarone: <ol style="list-style-type: none"> 13a Previous treatment with oral amiodarone within 4 months prior to inclusion 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion 14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω 3 or ω 6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with other anticoagulant treatment than antithrombin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y₁₂ inhibitors such as Clopidogrel or Prasugrel <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p> <p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280
Dose:	Soft Capsules
Mode of Administration:	Arm with 1g of F373280
	Oral, one capsule each evening with dinner.

Duration of Treatment:	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Reference Therapy	Placebo soft capsules Placebo will be administered in the same conditions as the tested product.
Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of AF lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 (ECV visit). Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24. For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5). Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM. All ECG traces will be evaluated by a Central Reading Laboratory. <p><u>Secondary evaluation variables:</u> During the 7-day continuous ECG monitoring,</p> <ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u> During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All causes of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Shocks distribution (1, 2 or 3 shocks) • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (at V4, V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA(mL/m²), 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> - Adverse events (observed and / or spontaneously reported) - Vital signs (Blood pressure (supine and standing), heart rate) - Physical examination (body weight, body surface area) - Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), QTcB. (ms), QTcF. (ms), repolarisation patterns (ECG not centralized) - Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets - Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol

	<p>(HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>)</p> <p>- Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (<i>PT</i>)</p> <p>Concomitant treatments</p> <p>Compliance</p>
Statistical Methods:	<p>Sample Size: Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment).</p>

STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	←		→ (2)		X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		←							→
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	↔ (4)		←	→ (5)					
TTEM (6)				←	→				→

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: everyday from week 6 to week 8; then every 2 days from week 9 to week 24; at any time in case of AF symptoms.

In case of AF recurrence for at least 10 minutes and if the patient does not stop the study treatment, then TTEM once a week

LIST OF ABBREVIATIONS

aPTT	: Activated partial thromboplastin time
AE	: Adverse event
AF	: Atrial fibrillation
ALA	: Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
AVK	: Anti-vitamin K
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body Surface Area
CEP	: Protocol evaluation committee
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	: Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	: Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	: Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	: Trans-esophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	: European heart rhythm association
EPA	: Eicosapentaenoic acid
e-CRF	: Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate
HBs	: Hepatitis B antigen
HCV	: Hepatitis C virus

HDL	:	High density lipoprotein
HF	:	Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR	:	International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS	:	Interactive voice response system
LAA	:	Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL	:	Low density lipoprotein
LOQ	:	Limit of quantification
LVEF	:	Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR	:	Mineralocorticoid receptor
MR perfusion	:	Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA	:	New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
PSC	:	Potentially Clinically Significant Change
PSCV	:	Potentially Clinically Significant Value
PUFA	:	PolyUnsaturated fatty acid
p.o.	:	Per os
PP	:	Per protocol data set
QTcB	:	QT interval using Bazett’s correction formula
QTcF	:	QT interval using Fridericia’s correction formula
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT	:	Thrombin clotting time
TEAEs	:	Treatment emergent adverse events
TTEM	:	TransTelephonic ECG monitoring
WBC	:	White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of AF in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the Polyunsaturated Fatty Acids (PUFAs) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or AF.

The potential anti-arrhythmic effects of a PUFA were previously developed in AF: nicotinyl ester of DHA (pro-drug based on DHA delivery) was assessed in a two-week ventricular tachypaced canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotinyl ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of AF induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll [2] assessed n-3 PUFAs in the prevention of AF recurrences after electrical cardioversion (ECV). All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct ECV 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFAs on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than in the placebo group at 1 month (3.3% vs 10%; $p = 0.043$), at 3 months (10% vs 25%; $p = 0.004$) and at 6 months (13.3% vs 40%; $p < 0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effects of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of

functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 \pm 0.33 to 1.61 \pm 0.49 and increased from 1.83 \pm 0.38 to 2.14 \pm 0.65, respectively).

The hospitalization rates for patients with HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and LVEF < 35%). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA (n = 14), 4 g/d n3-PUFA (n = 13), or placebo (n = 16)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($p = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: 24% \pm 7% vs 29% \pm 8%, $p = 0.005$) and 1 g/d treatment groups (24% \pm 8% vs 27% \pm 8%, $p = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent AF and heart failure in the maintenance of sinus rhythm after ECV.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of AF.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

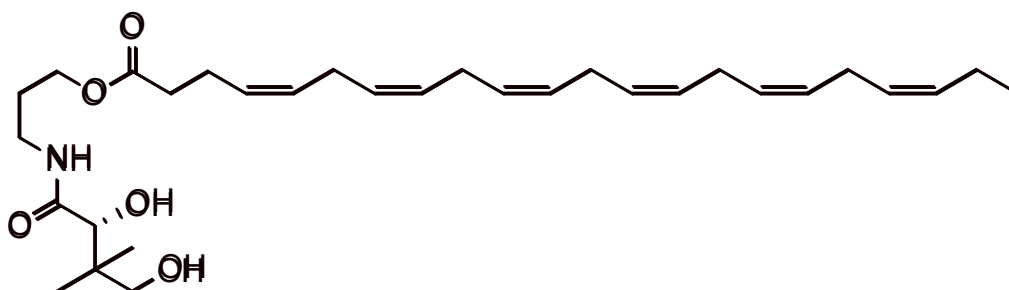
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. *Pharmacological profile*

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased atrial effective refractory period (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $p < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the electrocardiogram (ECG) intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing-induced congestive heart failure provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses congestive heart failure-induced AF-promotion and fibrosis in the ventricular tachypacing canine model. Nicotinyl ester of DHA was tested in this model, at 1 g/day and 5 g/day, during 4 weeks, to prevent congestive heart failure-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in AF duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1 g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5 g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of

DHA in the left atrial tissue. Because F373280 similarly to Nicotiny ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 mg/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies, no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: single dose

Six consecutive single ascending doses were tested (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events (SAE) occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of an alternative explanation, 3 TEAEs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotension without loss of consciousness) and 4 in the group of F373280 at the dosage of 16 g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events (AE) were reported in the groups of F373280 at the dosages of 0.5 g, 1 g, 2 g, 4 g and 8 g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5 g to 16 g in 36 young healthy male subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16 g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1 g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding Pharmacokinetics parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16 g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple doses

Three consecutive repeated ascending doses (1, 2 and 4 g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280, 5/9 TEAEs were classified according the System Organ Class in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAEs have already been reported with PUFAs and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** C_{max} and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after ECV in persistent AF patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing [1].

Moreover, the effectiveness of PUFAs has been proven in the following conditions:

- Prevention of AF recurrence in patients with persistent AF in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent AF and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after ECV in patients with persistent AF and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1 g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor® [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations:
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:
Very rare: nasal dryness
- Gastrointestinal disorders:
Common: dyspepsia, nausea
Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper
Rare: gastrointestinal pain
Very rare: lower gastrointestinal haemorrhage
- Hepatobiliary disorders:
Rare: hepatic disorders
- Skin and subcutaneous tissue disorders:
Rare: acne, rash pruritic
Very rare: urticaria
- General disorders and administration site conditions:
Rare: malaise sensation
- Investigations:
Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépantène® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1 g and 4 g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in AF studies [2, 8]. The range of PUFAs doses tested was between 2 g to 3 g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in HF patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1 g to 5 g (1 g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent form.

A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on AF and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the

included patients will remain under the standard treatment of AF and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (anti-vitamin K), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication
- Anticoagulation with anti-vitamin K (AVK) for at least 3 weeks before ECV
- ECV in patients with stabilized INR (i.e. values between 2 and 3;sp to) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent AF and chronic heart failure.

After a 1 to 4-week of run-in period without study treatment, patients will be randomised into one of the following treatment groups: F373280 1 g or placebo for 24 weeks.

Nine visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of study treatment)
- Visit 3 (V3): W4 (D28 \pm 7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)
- Visit 4 (V4): W5 (D35 \pm 7D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 5 (V5): W8 (D56 \pm 7D): follow-up visit
- Visit 6 (V6): W12 (D84 \pm 7D): follow-up visit
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 8 (V8): W20 (D140 \pm 7D): follow-up visit
- Visit 9 (V9): W24 (D168 \pm 7D): final study visit

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent AF and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent AF with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- Persistent AF history (less than three years) with a duration of the current episode from 7 days to 6 months.
- a moderately abnormal systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.
- a Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of ECV, patients should have a stable medical treatment of heart failure and should not have any myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on antiarrhythmics in AF (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, antiarrhythmic class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF since cardioversion.

To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before ECV. According to guidelines for the management of AF [6], AVK should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodari's study [2], the duration of pre-treatment with PUFAs before cardioversion appears to be a contributing factor in success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of AF recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of AF recurrences occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using an easier device to carry and to use, i.e. a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with AF [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of AF after cardioversion. Moreover, PUFAs at dosage of 1 g and 2 g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1 g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95 mg/mL and 60 to 90 mg/mL, respectively) (phase I study of F373280 and [16]). With regard to the rhythm of administration, mean peak/trough fluctuation (baseline corrected) was around 0.3. This value supports an once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a 1 g daily dose of F373280 is considered to be appropriate for this proof of concept study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive)
2. Patient with current episode of persistent AF between 7 days and 6 months duration for whomelectrical cardioversion is warranted

3. History of first documented persistent AF less than 3 years
4. History of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers
8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by anti-vitamin K
10. For female patient of child-bearing potential:
 - **in all the countries except Italy:**
 - use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - documented as surgically sterilized
 - **in Italy only:**
 - absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or
 - use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,
14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation)

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. History of first documented episode of persistent AF more than 3 years,
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),

4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 mL/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, beta-blockers, calcium-blockers.
13. Oral amiodarone:
 - 13a Previous treatment with oral amiodarone within 4 months prior to inclusion
 - 13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion
14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months
16. Treatment with any Polyunsaturated Fatted Acid within the last 3 months
 - Dietary supplement with ω 3 or ω 6 according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENT IDENTIFICATION

Patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

Reasons for a patient's premature withdrawal from the study may be the following:

- Patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- Investigator's decision in the patient's interest, particularly if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.

- Erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion/non inclusion criteria will immediately be withdrawn and an appropriate treatment will be given by the investigator under his/her responsibility. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with AVK for at least 3 weeks before ECV.
- Patients who will not have a stabilized INR between 2 and 3 on at least 3 consecutive weekly tests.
- Patients with only 2 consecutives INR tests between 2 and 3 in the last 3 weeks for whom a trans-oesophagoal echocardiography can not be performed before ECV or for whom a trans-oesophagoal echocardiography shows a thrombus in the atria.
- Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early relapse within the observation period after ECV will be considered to have finished follow-up.
- Occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate to another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit:

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the

Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.

- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the *Institut de Recherche Pierre Fabre (IRPF)* will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- F373280

Formulation of F373280, 1 g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- Placebo

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the *IRPF* according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

The Investigator will provide the patient with the treatment according to the following schedule:

At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.

At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:

- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number
- c) packaging batch number
- d) treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:
 - “for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”

On the treatment unit, another label will be affixed with the mention of the Investigator’s name and patient’s code (completed by the Investigator).

In addition, on each case will be mentioned the case number, and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date

- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the *IRPF* will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient's selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion visit (V2) and another one at visit 6.

For each patient, the treatment number given at visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

Practically, once patient's eligibility is confirmed at selection visit (V1):

- The Investigator:
 - Contacts the IVRS/IWRS
 - Answers the questions relating to the patient
 - In return, the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.

At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment according to the same process as described above.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure to F373280 or placebo will be 24 weeks.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator in collaboration with the Sponsor's representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (at selection visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the electronic Case Report Forms (e-CRF). All treatments should be evaluated by the Investigator at patient's selection, and treatment prolongation or stop during the study should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. ANTI-VITAMIN K TREATMENT

AVK should be given for at least 3 weeks before ECV and continued for the whole study duration. The AVK used will be left to the decision of the each Investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:
 - Class I
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
 - Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.
- Ranolazine
- Any PUFA
- Any anticoagulant treatment other than AVK: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel
- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the e-CRF. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION

8.1.1. Time to the first Atrial Fibrillation Recurrence

8.1.1.1. *Definition*

Time to first AF recurrence is defined by the first episode of AF (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring, the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM).

- Trans Telephonic ECG Monitoring:

The ECG follow up will be documented using the TTEM: daily transmission from the day after visit 4 (week 6) to visit 5 (week 8). Then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study).

Moreover, if patient experiences AF symptoms during this TTEM period, it should be documented using the TTEM.

In case of AF recurrence and provided that the patient does not required a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be emailed to the site (or per fax on request of the site). The investigator will be asked to review and sign this document.

The TTEM process will be fully described in a separate document.

8.1.2. Secondary Efficacy Criteria

8.1.2.1. *Numbers of AF episodes in the first week following visit 3 (ECV visit)*

8.1.2.1.1. Definition

Number of AF episodes will consist in the assessment of AF episodes with duration at least 10 minutes ($N_{\text{Sup}10}$) and of less than 10 minutes ($N_{\text{Inf}10}$), respectively.

8.1.2.1.2. Schedule

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the study visit 4.

8.1.2.1.3. Evaluation Methods

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.1.2.2. *Duration of AF episodes in the first week following visit 3 (ECV visit)*

8.1.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episode.

8.1.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the follow up study visit (visit 4).

8.1.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.1.2.3. *Clinical parameters evaluation*

8.1.2.3.1. *EHRA score assessment*

8.1.2.3.1.1. *Definition*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily.

8.1.2.3.1.2. Schedule

EHRA evaluation will be performed in case of evocative symptoms of arrhythmia.

8.1.2.3.1.3. Evaluation Methods

EHRA evaluation will be collected by Central Reading Laboratory during all the study period.

8.1.2.3.2. *Number of recurrence of symptomatic AF*

It consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.

8.1.2.3.3. *Number and duration of hospitalizations*

- Number and duration of hospitalizations for cardiovascular events
 - Hospitalization for AF treatment
 - Hospitalization for worsening of heart failure
 - Hospitalization for myocardial infarction
 - All cause of hospitalization
- Number and duration of hospitalizations for thromboembolic stroke

8.1.2.4. *Cardioversion assessment*

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shocks distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.1.2.5. *Evolution of echocardiographic parameters*

8.1.2.5.1. *Definition*

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (mL), Left atrial volume/BSA (mL/m²), LVEF (%), Left ventricular end diastolic volume/BSA (mL/m²), Left ventricular end systolic volume/BSA (mL/m²), Left

ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (mL).

8.1.2.5.2. Schedule

Measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

Measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.1.2.5.3. Evaluation method

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European Association of Echocardiography [23]. So, the recommended method for volume measurements is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.2.1. Definition

Because of the limited human tissue accessibility for biopsy, red blood cell DHA contents is a marker of tissue DHA concentration [13], [14].

8.2.2. Blood samples

8.2.2.1. Collection schedule

Blood samples will be collected to determine the red blood cells (RBC) concentrations of DHA.

Blood samples will be performed at visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the e-CRFs.

8.2.2.2. *Technical handling*

Two blood samples (4 ml) will be collected in EDTA tubes. They will be gently shaken, stored between +2°C/+8°C in a fridge (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.2.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent) and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock) in a separate file.

8.3. SAFETY ASSESSMENT

8.3.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of AEs since the last visit will be based on the patient's spontaneous reporting, the

Investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.3.2. Laboratory Investigations

8.3.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kaliemia will be checked before electrical cardioversion at visit 3.

The total volume of blood samples taken for haematology and biochemistry analysis should not exceed 30 mL.

8.3.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *hematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.*

Chemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula:

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$$\text{GFR (mL/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})]$$

in women:

$$\text{GFR (mL/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})] \times 0.85$$

- with serum creatinine expressed as $\mu\text{mol/L}$:

$$\text{GFR (mL/min)} = [(140 - \text{age}) \times \text{weight} / \text{serum creatinine in } \mu\text{mol/L}] \times k, \text{ where } k = 1.23 \text{ for men, } 1.04 \text{ for women.}$$

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.

8.3.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

The Body surface area (BSA) will be calculated at the same visits using Mostellers' formula:

$$\text{BSA} = [(\text{Weight} \times \text{Height})/3600]^{1/2}$$

(Weight in kg, height in cm)

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.3.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.3.4.1. *Schedule*

Vital signs will be measured at each visit.

8.3.4.2. *Technical Procedure and Parameters*

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation by counting the beats for at least 30 seconds, after at least 5 minutes in supine position and after 2 minutes in standing position.

Bodyweight will be measured with patient in underwear and with the same balance at each visit.

8.3.5. Electrocardiogram (ECG)

8.3.5.1. *Schedule*

An ECG will be recorded after at least 10 minutes of rest at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.

8.3.5.2. *Technical Procedure and Parameters*

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns will be reported in the e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent AF.

8.3.6. Coagulation parameters

Coagulation assessment will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:

- INR 2-3 times a week for the first week of treatment
- INR weekly up to ECV
- INR every 4 weeks after ECV

For patients already treated with AVK, INR monitoring will be as follow:

- INR weekly up to ECV
- INR every 4 weeks after ECV

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.

Anti-coagulation by AVK should be given at least 3 weeks before ECV and continued for the whole study duration.

The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.

8.4. CONCOMITANT TREATMENTS

Concomitant treatments will be evaluated at each study visit.

Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial, can be found in section 7.

8.5. COMPLIANCE

The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.

At each visit (except at visit 4), the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week -4 to Week -1)

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If the patient accepts to participate in the study, he/she will sign the informed consent form and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and AF characteristics
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory. The Central

Reading Laboratory will send his/her assessment regarding the confirmation of persistent AF within 2 working days to the Investigator.

- The patient will enter the selection period in which anticoagulant (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before ECV.

At the end of the visit, the Investigator will contact the IVRS/IWRS to confirm the patient selection (which will automatically order the treatment delivery) and organise the appointment for the next visit.

The patient will receive from the investigational centre the study card to be kept for the duration of the study.

Visit 2 - Inclusion Visit (Day 1)

If the patient's behaviour during the selection period and/or the result of complementary examinations particularly the confirmation of the presence of persistent AF by the Central Reading Laboratory during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6) in order to ensure that the INR is stable (between 2 to 3 before electrical cardioversion).

At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period.

Visit 3 (Week 4: D28 -2/+7 days) cardioversion

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, RBC concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target international normalized ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE performed in the same day (and before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of

sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge. Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.

Visit 4 (Week 5: D35 -2/+7 days)

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of AE
- Concomitant treatments (authorised, disallowed)
- Body weight (body weight measured at V3 to be used)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to perform daily transmission from the day after visit 4 (week 6) to visit 5 (week 8), then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study). Moreover, in case of AF symptoms, additional transmissions may be performed.

Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using a TTEM device. The device will be given to the patient who will be requested to perform daily transmission from the day after visit 4 (week 6) to visit 5 (week 8), then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study). Moreover, in case of AF symptoms, additional transmissions may be performed.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.

In addition:

- at visit 6:

- the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period.

- an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.

End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days)

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT), Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An AE is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

AE includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

10.1.3. Reporting of Adverse Events

The records of AE in the e-CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A SAE includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *

- Is a congenital anomaly or birth defect

Other events such as cancer and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure
- preparation for routine health assessment/procedure (e.g. routine colonoscopy)
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required)
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by FAX at the following number:

+ 33 1 49 10 80 90

In case of non-inclusion, the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial, an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose and associated adverse event if any, are reported only on the Adverse Event page of the e-CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must also be transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the Sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and must be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is withdrawn from the study.

The Investigator must report to the Sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The Investigator must immediately notify the Sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the Investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the Sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An e-CRF will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files that will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and should include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF.

Training sessions will be held by the subcontractor for all participants using this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRFs (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. Follow-up Visits

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of primary end point measures, the safety data. The IDMC will thereafter recommend to the Sponsor whether to continue, modify, or stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on the e-CRFs.

The e-CRFs used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate the coding.

12.4. DATA STORAGE

Computer data files as well as their modifications will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e. data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by PFB or under the supervision of the statistician of PFB using SAS® software, according to the Statistical Analysis Plan approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 3 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety.
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAEs

- With at least three TEAEs
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.

Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:

- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TEAE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patients).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

SAE will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study

treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

CNALV (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and HR in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. *Individual Patient Changes*

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) minus number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days)

13.11. INTERIM ANALYSIS AND DATA MONITORING

No analyses of efficacy data are planned for IDMC that ensures that the overall probability of type I error is controlled. No Type I error and sample size adjustments are necessary. Any recommendations of the IDMC to alter study conduct will be based on safety, so IDMC monitoring of the study will not affect the statistical operating characteristics of the final analysis. The IDMC will review, three times during the study period (after the first 30 subjects will have been randomized, when the first 80 subjects will have terminated their study participation and when 130 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor *Pierre Fabre Médicament*, has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the Sponsor *Pierre Fabre Médicament* are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not.
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents.
- Authorises direct access to source documents for monitoring, audits and inspections.
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. *Early Study Termination Decided by the Sponsor*

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. *Early Study Termination Decided by the Competent Authorities*

The Competent Authorities may suspend or prohibit a study if they consider that either the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both its representatives (Study Manager, CRA...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at *Pierre Fabre Médicament* and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed in writing with the Study Manager, the Investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the Sponsor's responsibility.

Upon data analysis completion, a final report including a review of the objectives and methods, a presentation and a discussion of the results is drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the Investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow the use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The Investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) Investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all Investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1] **F373280 INVESTIGATOR'S BROCHURE**, version October 2013
- [2] NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3] NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57:870-879
- [4] MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5] GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6] CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7] KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8] BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9] **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10] **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11] TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedarone for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12] LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13] **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14] **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15] **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16] SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.

- [17] **LEGRAND P., SCHMITT B., MOUROT J., CATHELIN D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.**
The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human
Lipids, 2010, 45, 11-19.
- [18] **HARRIS WS, VON SCHACKY C.**
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19] **ABSTRACT: P5161 .**
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M., DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20] **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21] **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22] **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23] **ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.**
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY
TO PIERRE FABRE CORPORATE VIGILANCES DIVISION

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION BY E-MAIL WITHIN 24H TO
HQ.pharmacovigilance@pierre-fabre.com OR BY FAX WITHIN 24H – Fax N°: 33 (0) 1.49.10.80.90

Transmission date (ddmmyyyy) Country :
SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ SUBJECT CHARACTERISTICS

Gender	<input type="checkbox"/> 1=M, 2=F	Height	<input type="text"/> <input type="text"/> <input type="text"/> cm	Birth date	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Weight	<input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg
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➤ DESCRIPTION OF THE EVENT

The serious adverse event resulted in :

- ☐ Death (whatever may be the cause)
☐ Hospitalisation (*) or extension thereof
☐ Life threatening
☐ Invalidity or disability

- ☐ Congenital abnormality or abnormal pregnancy outcome
☐ Cancer
☐ Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts)

Other fact to be notified :

- ☐ Pregnancy exposure

Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :

.....
.....
.....

AE onset date (ddmmyyyy)

Seriousness onset date (ddmmyyyy)

Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) :

(*) Except hospitalisations with durations and goals planned in the protocol

➤ THE SAE IN RELATION TO THE TRIAL

	TREATMENT NUMBER	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
• Time of occurrence of SAE		
<input type="checkbox"/> During the selection or run-in period		
<input type="checkbox"/> During the administration phase of the study treatment		
<input type="checkbox"/> After the administration phase of the study treatment		
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	(ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	(ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable		
If yes, or if this is an open study, drug(s) administered :		
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :		
.....		

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ MEASURES TAKEN FOLLOWING THE SAE

• Study treatment

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readadministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• The event led to :

- ☐ Prescription of corrective or symptomatic treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Discontinuation of concomitant treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Others, specify :

➤ OUTCOME

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)

Study drug: Related to study protocol:

☐ Not Suspected ☐ Suspected ☐ Not Suspected ☐ Suspected

Comments:

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(α)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(α) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		• < 1 500/mm ³ whatever the baseline value
WBC (if missing value for neutrophils)		• < 3 000/mm ³ whatever the baseline value
PLATELETS		• < 100 000/mm ³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.8. Protocol amendment n° PA05 - General and
substantial dated on 22 October 2014 linked to
Protocol and appendices
(version 8: 22 October 2014)***

CLINICAL STUDY PROTOCOL AMENDMENT n° PA05
(General – Substantial)

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

CLINICAL STUDY PROTOCOL AMENDMENT n° PA05

(General – Substantial)

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code: F373280 CA 2 01

EudraCT Number or equivalent: 2012-003487-48

Sponsor's Representative: **Gaëlle ALCARAZ**
INSTITUT DE RECHERCHE PIERRE FABRE
Centre de R&D Pierre Fabre - BP 13562
3 avenue Hubert Curien
31035 TOULOUSE Cedex 1

Study Coordinating Investigator: **Pr 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
c/o Spedali Civili di Brescia
Piazzale Spedali Civili, 1
25123 - BRESCIA, ITALY

Date of amendment PA05: 22OCT2014

APPROVAL FORM

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.

International, multicentric, randomised, double-blind, placebo-controlled study

Clinical Study Protocol Amendment n° PA05

(General – Substantial)

Dated: 22OCT2014

Sponsor's representative(s)


• Medical Director

Date:

Signature:

Dr. Richard ROCHE

07/11/2014



• Clinical Study Manager :

Date:

Signature:

Gaëlle ALCARAZ

07/11/2014



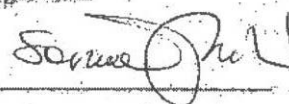
Study Coordinating Investigator:

Date:

Signature:

Pr Savina NODARI

07/11/2014



COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA05

(General – Substantial)

Dated: 22OCT2014

Country Coordinating Investigator:

Date:

Signature:

INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA05

(General – Substantial)

Dated: 22OCT2014

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA05 and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF AMENDMENTS

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
NA	NA	General	NA	<p><u>Corresponding to Protocol Version 2:</u></p> <p>Following French CA request (ANSM) and leading to protocol version 2:</p> <ul style="list-style-type: none"> - Add of a non inclusion criteria: "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6
PA01	Substantial	Local (Italy)	01MAR2013	<p><u>Corresponding to Protocol Version 3:</u></p> <ul style="list-style-type: none"> - Integration of the modification included in the protocol version 2 - Harmonisation of the protocol and the Informed Consent Form: <ul style="list-style-type: none"> • adjustment of the selection criteria n°10 related to the contraception method • addition of a letter that is given by the patient to his/her general practitioner (GP) • precision that the sponsor can not collect a copy of the Informed Consent Form • precision that the patient card is in Italian language only (without any English mention)
PA02	Non Substantial	General	28MAR2013	<p><u>Corresponding to Protocol Version 4 :</u></p> <ul style="list-style-type: none"> - change of Sponsor's Representative (Clinical Study Manager), - modification of the technical handling of the blood samples for determination of red blood cells concentration of DHA: the centrifugation is no more needed, - precision on the function and address of the International Study Coordinator Pr Nodari, - add of address and contacts details of two CRO newly involved in the study: Theradis (in charge of transportation of blood samples to the Analytical centre and material supply) and "Clinact" (in charge of refund of patients expenses linked to the study), - adjustment of the wording, in agreement with the commitment to the French Ethics Committee. In the paragraphe 8.3.2.1, the wording "hematology examination" is replaced by "standard hematologic dosage", - precision of the full title in the study synopsis (in agreement with the commitment to the Spanish Ethics Committee), - correction of a mistake in section 8.1.1.3 (related to TTEM transmission) and sections 3, 9 and study synopsis (related to the definition of INR not stabilized). - addition of the changes included in the local italian substantial protocol amendment (i.e: contraception method, letter to General Practionner, patient card

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
				in Italian and no collection of the consent form by the sponsor in Italy).
PA03	Substantial	General	23OCT2013	<p><u>Corresponding to Protocol Version 5:</u></p> <ul style="list-style-type: none"> - Fax modification of the sponsor's representatives - Planned end of study postponed to January 2015. - The authorized history of the first documented persistent atrial fibrillation is less than 3 years. - At selection a hyperkalemia or a hypokalemia is better defined by the standards of the local laboratories. - Regarding previous treatments by amiodarone the non inclusion criteria of the protocol are adapted as follow: <ul style="list-style-type: none"> • Previous treatment with oral amiodarone within 4 months prior to inclusion • Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion • Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion. - For male with a child-bearing potential partner (in Italy only): taking into account the duration of spermatogenesis the absolute abstention from sexual intercourse or the use of double barrier contraception method are extended to 3 months after the end of the study. - Ranolazine is an antiarrhythmic treatment added to the prohibited treatments. - Update of Serious Adverse Events (SAEs) form: Main change is the SAE sending: SAEs have to be reported to the Corporate Vigilance Department, and not anymore to the clinical study manager. Also SAEs can be sent by e-mail and by fax. - Addition of Alpha Bioresearch as CRO involved for Feasibility, Monitoring and Regulatory issues in Spain. - Correction of some minor typographic errors
PA04	Non Substantial	General	03JUN2014	<p><u>Corresponding to protocol V7:</u></p> <ul style="list-style-type: none"> - Precision on the temperature storage of DHA samples - Precision on the BSA formula - Addition of QTcB and QTcF - Precision on TTEM recording timelines - Clarification of the section Interim analysis and data monitoring (13.11) - Clarifications and specifications on some minor points

1. AMENDMENT RATIONALE

The purpose of this amendment is mainly to clarify some points of the protocol regarding the management of vitamin K antagonist (VKA) treatment and to decrease constraints of the study for patients.

This amendment relates also to a precision regarding the primary efficacy criterion, to an adjustment of some selection criteria in order to improve the feasibility of the study and relates to minor changes as typographical errors or style.

The clinical study protocol is updated with the following changes:

- Due to a recruitment rate lower than expected the planned end of study is postponed to April 2016.
- In order to have a better harmonization between the centres in the management of treatment with VKA some clarifications are incorporated in Chapter 8.4.6 Coagulation parameters.
- Atrial fibrillation and Atrial flutter are not the same rhythm disorder, but they are very similar and both are the expression of abnormal electrical impulses starting in the atria. So regarding the definition of the primary criterion, the atrial flutter emergence should be considered as having the same meaning as a recurrence in persistent AF. This primary criterion will be more precisely defined by the time to the first Atrial Fibrillation recurrence or Atrial Flutter emergence.
- To reduce constraints of patients follow-up, the number of scheduled visits passes from 9 to 7 and the TTEM will be weekly transmitted from week 6 to the end of the study instead of to be transmitted daily from week 6 to week 8 and then every two days from week 9 to week 24. These changes do not affect the overall risk of the study. The frequency of visits remains what is usually done in daily practice. A weekly TTEM has no impact on patient safety because on one hand patients are treated with an anticoagulant throughout the study and on the other hand a TTEM can be performed at any time in case of AF or atrial flutter symptoms.
- Patients must have a previous history of a first documented persistent Atrial Fibrillation without limitation in time instead of no longer than 3 years. This modification will expand the target population without changing the characteristics of the selected patients by enabling the management of patients who could experience a long period without AF relapse nor atrial flutter emergence.
- Patients must have a systolic heart failure defined by a reduced ventricular ejection fraction and or defined also through other echocardiographic parameters mentioned in the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (2012).
- Regarding previous prohibited treatments by amiodarone or droderanone, the non inclusion criteria of the protocol are adapted as follow:
 - Concomitant treatment with oral amiodarone or dronedarone from selection
 - Concomitant treatment with intravenous amiodarone from selection

Despite the long half life of amiodarone, these time limits relating to its non-use before inclusion should not interfere in a major way with the assessment of the product 6 months after inclusion.

2. CHANGES DESCRIPTION

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<p>CLINICAL RESEARCH ORGANISATIONS</p> <p><u>For Feasibility, Monitoring and Regulatory issues:</u> Pharmaceutical Service Network (PSN) Rufino Gonzalez 28 037 Madrid - SPAIN Phone: +34 91 375 6930 - Fax: +34 91 375 6931 E-mail: www.psnglobal.org</p> <p><u>For refund of patients expenses linked to the study (in France):</u> CLINACT 6-10 rue TROYON 92310 SEVRES – FRANCE Phone: +33 1 46 90 27 27 - Fax: +33 1 46 23 01 56 Email: sebastien.beaumont@clinact.com</p>	<p>CLINICAL RESEARCH ORGANISATIONS</p> <p><u>For Feasibility, Monitoring and Regulatory issues (in Hungary, Czech Republic and Italy):</u> Pharmaceutical Service Network (PSN) Rufino Gonzalez 28 037 Madrid - SPAIN Phone: +34 91 375 6930 - Fax: +34 91 375 6931 E-mail: rzurita@psnglobal.org</p> <p><u>For refund of patients expenses linked to the study (in France):</u> CLINACT 6-10 rue TROYON 92310 SEVRES – FRANCE Phone: +33 1 46 90 27 27 - Fax: +33 1 46 23 01 56 Email: sebastien.beaumont@clinact.com</p>
<p>SYNOPSIS</p> <p>Planned Study Period: January 2013 – January 2015</p> <p>Methodology :</p> <ul style="list-style-type: none"> - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – INR 2-3 (anti-vitamin K should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV • Cardiac monitoring: <ul style="list-style-type: none"> – TTEM: daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and in case of AF symptoms. <p>Study Schedule:</p> <p>9 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of study treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to clinical 	<p>SYNOPSIS</p> <p>Planned Study Period: January 2013 – April 2016</p> <p>Methodology :</p> <ul style="list-style-type: none"> - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> – Ideally INR 2-3 (vitamin K antagonist should be given at least 3 weeks before ECV) – No spontaneous cardioversion before ECV • Cardiac monitoring: <ul style="list-style-type: none"> – TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms. <p>Study Schedule:</p> <p>7 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of study treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to clinical practice of the

PREVIOUS VERSION	MODIFIED VERSION
<p>practice of the centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56 ± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit <p>Diagnosis and Criteria for Inclusion:</p> <p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>[...]</p> <p>3. History of first documented persistent AF less than 3 years.</p> <p>4. History of ischemic or non ischemic heart failure</p> <p>[...]</p> <p>6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion</p> <p>[...]</p>	<p>centre) (installation of the Holter device)</p> <ul style="list-style-type: none"> - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V5/ W8 (D56 ± 7 days): follow-up visit - V6/ W12 (D84 ± 7 days): follow-up visit - V7/ W16 (D112 ± 7 days): follow-up visit - V8/ W20 (D140 ± 7 days): follow-up visit - V9/ W24 (D168 ± 7 days): final study visit <p>Diagnosis and Criteria for Inclusion:</p> <p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>[...]</p> <p>3. Previous history of first documented episode of persistent AF</p> <p>4. Previous history of ischemic or non ischemic heart failure</p> <p>[...]</p> <p>6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) ≥ 30% and ≤ 45% or for patients with a LVEF > 45%:</p> <ul style="list-style-type: none"> • 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 <p>[...]</p>

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<p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <p>1. History of first documented episode of persistent AF more than 3 years</p> <p>[...]</p> <p><i>Criteria related to treatments:</i></p> <p>12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers</p> <p>13. Oral amiodarone:</p> <p>13a Previous treatment with oral amiodarone within 4 months prior to inclusion</p> <p>13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion</p> <p>14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion</p> <p>[...]</p> <p>19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel</p> <p>Exclusion criteria before V3:</p> <p>Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO-TE (trans-esophageal echocardiograph) performed in the same day (before ECV)</p> <p>ECV will be performed in patients without dyskalemia</p>	<p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <p>1. No previous history of first documented episode of persistent AF</p> <p>[...]</p> <p><i>Criteria related to treatments:</i></p> <p>12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, betablockers, calcium-blockers</p> <p>13. Concomitant treatment with oral amiodarone or dronedarone from selection</p> <p>14. Concomitant treatment with intravenous amiodarone from selection</p> <p>[...]</p> <p>19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel</p> <p>Exclusion criteria before V3:</p> <p>Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study.</p> <p>However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>If necessary for obtaining stabilized INR between 2 and 3, the ECV (and following visits) could be postponed by 7 days.</p> <p>[...]</p> <p>Evaluation Criteria:</p> <p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation recurrence defined by the first episode of AF lasting for at least 10 minutes (Follow up of 20 weeks after visit 3 – ECV visit). <p>Handling of AF recurrences: 7-day continuous 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 will be documented using the TTEM: daily transmission from week 6 to week 8. Then, every two days from week 9 to week 24.</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).</p> <p>Moreover, during this TTEM period, if patient experiences any AF symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG traces will be evaluated by a Central Reading Laboratory.</p> <p>[...]</p> <p>Statistical Methods:</p> <p>Sample Size:</p> <p>Assuming an AF recurrence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per</p>	<p>same day (before ECV) and the patient can continue the study.</p> <p>If necessary, for meeting these INR conditions, the ECV (and following visits) could be postponed by 7 days.</p> <p>[...]</p> <p>Evaluation Criteria:</p> <p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation 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). <p>Handling of AF recurrences or atrial flutter emergences: 7-day continuous 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 will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24).</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5).</p> <p>Moreover, during this TTEM period, if patient experiences any AF or atrial flutter symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG (Holter and TTEM) will be evaluated by a Central Reading Laboratory.</p> <p>[...]</p> <p>Statistical Methods:</p> <p>Sample Size:</p> <p>Assuming an AF recurrence or atrial flutter emergence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76</p>

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group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.	randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.
STUDY FLOW CHART Please see flow-chart of previous version in appendix 1	STUDY FLOW CHART Please see flow-chart of modified version in appendix 2
3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY <p>[...]</p> <p>During the study, in case of AF recurrence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped.</p> <p>[...]</p> <p>- ECV in patients with stabilized INR (i.e. values between 2 and 3;sp to) on at least 3 consecutive weekly tests performed. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests performed before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE (trans-esophageal echocardiograph) performed in the same day (before ECV). Patients who do not revert to sinus rhythm or present an early relapse within the observation period after ECV will be withdrawn and the tested product stopped.</p> <p>During the whole study, patients will remain under medical control: visits in cardiology units will be scheduled at least every month. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored between visits using daily, then every 2 days Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.</p> <p>[...]</p>	3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY <p>[...]</p> <p>During the study, in case of AF recurrence or atrial flutter emergence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped.</p> <p>[...]</p> <p>- ECV will be performed in patients with AF and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO–TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Patients who do not revert to sinus rhythm or present an early AF relapse or an early atrial flutter emergence within the observation period after ECV will be withdrawn and the tested product stopped.</p> <p>During the whole study, patients will remain under medical control: visits in cardiology units will be performed throughout the study period. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored once a week between visits using Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading</p>

PREVIOUS VERSION	MODIFIED VERSION
	Laboratory. [...]
<p>4. STUDY DESIGN</p> <p>4.1 OVERALL DESCRIPTION</p> <p>[...]</p> <p>Nine visits are planned for the study:</p> <ul style="list-style-type: none"> - Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit) - Visit 2 (V2): D1: Inclusion visit (start of study treatment) - Visit 3 (V3): W4 (D28 -2/+7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device) - Visit 4 (V4): W5 (D35 -2/+7D): follow-up visit (removing of Holter ECG device and installation of the TTEM) - Visit 5 (V5): W8 (D56 ± 7D): follow-up visit - Visit 6 (V6): W12 (D84 ± 7D): follow-up visit - Visit 7 (V7): W16 (D112 ± 7D) : follow-up visit - Visit 8 (V8): W20 (D140 ± 7D): follow-up visit - Visit 9 (V9): W24 (D168 ± 7D): final study visit <p>[...]</p> <p>4.2. DISCUSSION OF THE STUDY DESIGN</p> <p>4.2.1. Choice of the Study Population</p> <p>[...]</p> <p>The study aim is to investigate the product effect in patients with:</p> <ul style="list-style-type: none"> - Persistent AF history (less than three years) with a duration of the current episode from 7 days to 6 months. - a moderately abnormal systolic heart failure (Left Ventricular Ejection Fraction (LVEF) between 30 to 45% as defined in the report from the American Society of Echocardiography's Guideline). 	<p>4. STUDY DESIGN</p> <p>4.1 OVERALL DESCRIPTION</p> <p>[...]</p> <p>Seven visits are planned for the study:</p> <ul style="list-style-type: none"> - Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit) - Visit 2 (V2): D1: Inclusion visit (start of study treatment) - Visit 3 (V3): W4 (D28 -2/+7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device) - Visit 4 (V4): W5 (D35 -2/+7D): follow-up visit (removing of Holter ECG device and installation of the TTEM) — Visit 5 (V5): W8 (D56 ± 7D): follow-up visit - Visit 6 (V6): W12 (D84 ± 7D): follow-up visit - Visit 7 (V7): W16 (D112 ± 7D) : follow-up visit — Visit 8 (V8): W20 (D140 ± 7D): follow-up visit - Visit 9 (V9): W24 (D168 ± 7D): final study visit <p>[...]</p> <p>4.2. DISCUSSION OF THE STUDY DESIGN</p> <p>4.2.1. Choice of the Study Population</p> <p>[...]</p> <p>The study aim is to investigate the product effect in patients with:</p> <ul style="list-style-type: none"> - Previous history of persistent AF with duration of the current episode from 7 days to 6 months. - A systolic heart failure defined by a reduced left ventricular ejection fraction ($\geq 30\%$ and $\leq 45\%$) or for patients with a LVEF $> 45\%$: <ul style="list-style-type: none"> • an increased left ventricular end-diastolic size (diameter ≥ 60 mm and/or > 32 mm/m² and/or

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<p>[...]</p> <ul style="list-style-type: none"> - a Left Atrial Area (LAA) not severely abnormal (less than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline). <p>4.2.2. Choice of the Study Design</p> <p>[...]</p> <p>According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF since cardioversion.</p> <p>To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.</p> <p>Eligible participants will enter a selection phase in which anticoagulant treatment (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2.0 to 3.0 before ECV. According to guidelines for the management of AF [6], AVK should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.</p> <p>[...]</p> <p>Finally, during the study, patients will be scheduled for a clinical visit every month (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.</p> <p>[...]</p>	<p>volume > 97 ml/m²),</p> <ul style="list-style-type: none"> • 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 [23, 24]. <p>[...]</p> <ul style="list-style-type: none"> - A Left Atrial Area (LAA) not severely abnormal (no greater than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline) [23]. <p>4.2.2. Choice of the Study Design</p> <p>[...]</p> <p>According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF (or emergence of atrial flutter) since cardioversion.</p> <p>To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.</p> <p>Eligible participants will enter a selection phase in which anticoagulant treatment (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) of 2 to 3 before ECV. According to guidelines for the management of AF [6], VKA should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.</p> <p>[...]</p> <p>Finally, during the study, patients will be scheduled for a clinical visit every 4 weeks or 8 weeks (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.</p> <p>[...]</p>

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<p>5. STUDY POPULATION</p> <p>5.1 INCLUSION CRITERIA</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>[...]</p> <p>3. History of first documented persistent AF less than 3 years</p> <p>4. History of ischemic or non ischemic heart failure</p> <p>[...]</p> <p>6. Reduced left ventricular ejection fraction between 30% and 45% inclusive (using the two-dimensional echocardiography biplane Simpson's rule) at selection and at inclusion</p> <p>[...]</p>	<p>5. STUDY POPULATION</p> <p>5.1 INCLUSION CRITERIA</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <p>[...]</p> <p>3. Previous history of first documented episode of persistent AF</p> <p>4. Previous history of ischemic or non ischemic heart failure</p> <p>[...]</p> <p>6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ or for patients with a LVEF $> 45\%$:</p> <ul style="list-style-type: none"> • 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 <p>[...]</p>

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<p>5.2 NON INCLUSION CRITERIA</p> <p><i>Criteria related to pathologies:</i></p> <p>1. History of first documented episode of persistent AF more than 3 years, [...]</p> <p><i>Criteria related to treatments:</i></p> <p>[...]</p> <p>12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except stable dose of digoxin, betablockers, calcium-blockers</p> <p>13. Oral amiodarone:</p> <p>13a Previous treatment with oral amiodarone within 4 months prior to inclusion</p> <p>13b Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion</p> <p>14. Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion [...]</p> <p>19. Patient treated with other anticoagulant treatment than antivitamin K: thrombin inhibitor such as Dabigatran or treated with antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel</p> <p>5.6 WITHDRAWAL CRITERIA</p> <p>[...]</p> <ul style="list-style-type: none"> Erroneous inclusion according to the study protocol. Any inclusion not respecting inclusion/non inclusion criteria will immediately be withdrawn and an appropriate treatment will be given by the investigator 	<p>5.2 NON INCLUSION CRITERIA</p> <p><i>Criteria related to pathologies:</i></p> <p>1. No previous history of first documented episode of persistent Atrial Fibrillation [...]</p> <p><i>Criteria related to treatments:</i></p> <p>[...]</p> <p>12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, betablockers, calcium-blockers</p> <p>13. Concomitant treatment with oral amiodarone or dronedarone from selection</p> <p>14. Concomitant treatment with intravenous amiodarone from selection [...]</p> <p>19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel</p> <p>5.6 WITHDRAWAL CRITERIA</p> <p>[...]</p> <ul style="list-style-type: none"> Erroneous inclusion according to the study protocol. The decision to maintain or not the patient in the study will be taken jointly by the investigator and the sponsor. Erroneous inclusions will not be paid to the

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<p>under his/her responsibility. Erroneous inclusions will not be paid to the investigator.</p> <ul style="list-style-type: none"> Patients who could not be treated with AVK for at least 3 weeks before ECV. Patients who will not have a stabilized INR between 2 and 3 on at least 3 consecutive weekly tests. Patients with only 2 consecutive INR tests between 2 and 3 in the last 3 weeks for whom a trans-oesophageal echocardiography can not be performed before ECV or for whom a trans-oesophageal echocardiography shows a thrombus in the atria. Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early relapse within the observation period after ECV will be considered to have finished follow-up. Occurrence of AF recurrence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance. <p>[...]</p>	<p>investigator.</p> <ul style="list-style-type: none"> Patients who could not be treated with VKA for at least 3 weeks before ECV or who will experience a VKA intolerance during the study. Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be considered to have finished follow-up. Occurrence of AF recurrence or atrial flutter emergence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance. <p>[...]</p>
<p>6. STUDY TREATMENT</p> <p>6.2. PACKAGING AND LABELLING</p> <p>6.2.1. Packaging</p> <p>[...]</p> <p>The Investigator will provide the patient with the treatment according to the following schedule:</p> <p>At Inclusion Visit (V2): a 12-week treatment unit will contain 3 cases, each case containing:</p> <ul style="list-style-type: none"> - 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each. <p>At Visit 6 (V6): a 12-week treatment unit will contain 3 cases, each case containing:</p>	<p>6. STUDY TREATMENT</p> <p>6.2. PACKAGING AND LABELLING</p> <p>6.2.1. Packaging</p> <p>[...]</p> <p>Two 12-week treatment units will contain 3 cases, each case of 4-week treatment containing: 10 blister packs of four 1 g F373280 soft capsules or 1 g placebo soft capsules each.</p> <p>[...]</p>

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<p>- 10 blister packs of four 1 g F373280 soft capsules or placebo soft capsules each.</p> <p>[...]</p> <p>6.4 ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT</p> <p>[...]</p> <p>Practically, once patient's eligibility is confirmed at selection visit (V1):</p> <ul style="list-style-type: none"> • The Investigator: <ul style="list-style-type: none"> – Contacts the IVRS/IWRS – Answers the questions relating to the patient – In return, the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS. <p>[...]</p> <p>The Investigator will dispense to the patient the case which label indicates the treatment number and the administration period.</p> <p>At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment according to the same process as described above.</p>	<p>6.4 ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT</p> <p>[...]</p> <p>At selection visit (V1), practically, once patient's eligibility is confirmed:</p> <ul style="list-style-type: none"> • The Investigator: <ul style="list-style-type: none"> – Contacts the IVRS/IWRS – Answers the questions related to the patient <p>[...]</p> <p>At inclusion visit (V2), the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.</p> <p>At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment according to the same process as described above.</p> <p>The Investigator will dispense to the patient the 4-week treatment cases (one or two according to the visit) which label indicates the treatment number and the administration period.</p>
<p>7. CONCOMITANT TREATMENTS</p> <p>7.1. ANTI-VITAMIN K TREATMENT</p> <p>AVK should be given for at least 3 weeks before ECV and continued for the whole study duration. The AVK used will be left to the decision of the each Investigator according to his/her local practice.</p>	<p>7. CONCOMITANT TREATMENTS</p> <p>7.1. <u>VITAMIN K ANTAGONIST TREATMENT</u></p> <p>VKA should be given for at least 3 weeks before ECV and continued for the whole study duration. However, VKA should be stopped in case of occurrence of VKA intolerance during the study and the patient should be withdrawn from the study. The VKA used will be left to the decision of each Investigator according to his/her local practice.</p>

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<p>7.2. PROHIBITED TREATMENTS</p> <p>[...]</p> <p>Any anticoagulant treatment other than AVK: thrombin inhibitor such as Dabigatran or antiaggregant P2Y12 inhibitors such as Clopidogrel or Prasugrel</p> <p>[...]</p>	<p>7.2. PROHIBITED TREATMENTS</p> <p>[...]</p> <p>Any oral anticoagulant treatment other than VKA: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or irreversible antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel</p> <p>[...]</p>
<p>8. EVALUATION CRITERIA</p> <p>8.1 PRIMARY EFFICACY CRITERIA</p> <p>8.1.1. Time to the first Atrial Fibrillation Recurrence</p> <p>8.1.1.1. Definition</p> <p>Time to first AF recurrence is defined by the first episode of AF (symptomatic or not) lasting for at least 10 minutes.</p> <p>8.1.1.2. Schedule</p> <p>The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF will be assessed after visit 3 (week 5).</p> <p>8.1.1.3. Evaluation Methods</p> <p>[...]</p> <ul style="list-style-type: none"> Trans Telephonic ECG Monitoring: <p>The ECG follow up will be documented using the TTEM: daily transmission from the day after visit 4 (week 6) to visit 5 (week 8). Then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study).</p> <p>Moreover, if patient experiences AF symptoms during this TTEM period, it should be documented using the TTEM.</p> <p>In case of AF recurrence and provided that the patient does not require a cardioversion or an introduction of an anti-</p>	<p>8. EVALUATION CRITERIA</p> <p>8.1 PRIMARY EFFICACY CRITERIA</p> <p>8.1.1. Time to the first Atrial Fibrillation Recurrence or Atrial Flutter Emergence</p> <p>8.1.1.1. Definition</p> <p>Time to first AF recurrence or atrial flutter emergence is defined by the time to first episode of AF or atrial flutter (symptomatic or not) lasting for at least 10 minutes.</p> <p>8.1.1.2. Schedule</p> <p>The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5).</p> <p>8.1.1.3. Evaluation Methods</p> <p>[...]</p> <ul style="list-style-type: none"> Trans Telephonic ECG Monitoring: <p>The ECG follow up will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM.</p> <p>Moreover, if patient experiences AF or atrial flutter symptoms during this TTEM period, it should be documented using the TTEM.</p>

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<p>arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.</p> <p>The TTEM will be centralized by the Central Reading Laboratory. The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM. The TTEM will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be emailed to the site (or per fax on request of the site). The investigator will be asked to review and sign this document.</p> <p>The TTEM process will be fully described in a separate document.</p>	<p>In case of AF recurrence or atrial flutter emergence and provided that the patient does not require a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.</p> <p>• Process of centralisation of ECG (Holter and TTEM)</p> <p>ECG (Holter and TTEM) will be centralized by the Central Reading Laboratory. The ECG will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be emailed to the site (or per fax on request of the site). The investigator will be asked to review and sign these documents.</p> <p>The Holter and TTEM process will be fully described in separate documents.</p>

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<p>8.1.2 Secondary Efficacy Criteria</p> <p>8.1.2.3. Clinical parameters evaluation</p> <p>8.1.2.3.1. EHRA score assessment</p> <p>8.1.2.3.1.3. Evaluation Methods</p> <p>EHRA evaluation will be collected by Central Reading Laboratory during all the study period.</p>	<p>8. 2 SECONDARY EFFICACY CRITERIA</p> <p>8.2.3. Clinical parameters evaluation</p> <p>8.2.3.1. EHRA score assessment</p> <p>8.2.3.1.3. Evaluation Methods</p> <p>EHRA evaluation will be collected by Central Reading Laboratory during TTEM period.</p>
<p>8.1.2.3.2. Number of recurrence of symptomatic AF</p> <p>It consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.</p>	<p>8.2.3.2. Time to first AF recurrence less than 10 minutes</p> <p>Time to first AF recurrence less than 10 minutes will be assessed during TTEM period.</p>
<p>8.1.2.3.2. Number of recurrence of symptomatic AF</p> <p>It consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.</p>	<p>8.2.3.3 Recurrence of symptomatic AF</p> <p>Recurrence of symptomatic AF will be assessed during TTEM period.</p> <p>The number of recurrences of symptomatic AF consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.</p> <p>The time to first symptomatic AF recurrence is defined by the time to first episode of symptomatic AF.</p>
<p>8.2. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA</p> <p>8.2.2 Blood samples</p> <p>8.2.2.2. Technical handling</p> <p>Two blood samples (4 ml) will be collected in EDTA tubes. They will be gently shaken, stored between +2°C/+8°C in a fridge (<u>no freezing will be allowed</u>) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C).</p> <p>[...]</p>	<p>8.3. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA</p> <p>8.3.2 Blood samples</p> <p>8.3.2.2. Technical handling</p> <p>Two blood samples (2 x 4 ml) will be collected in EDTA tubes. They will be homogenized slowly by inverting the tube without shaking, stored between +2°C/+8°C in a fridge (<u>no freezing will be allowed</u>) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C).</p> <p>[...]</p>

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<p>8.3 SAFETY ASSESSMENT</p> <p>8.3.2 Laboratory Investigations</p> <p>8.3.2.2 Technical Procedures and Parameters</p> <p><u>Haematology:</u> <i>hematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and absolute), reticulocytes, platelets.</i></p> <p><u>Chemistry:</u> [...]</p> <p>Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.</p> <p>8.3.3. Global Physical Examination</p> <p>A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.</p> <p>[...]</p> <p>8.3.5. Electrocardiogram (ECG)</p> <p>8.3.5.1. Schedule</p> <p>An ECG will be recorded after at least 10 minutes of rest at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.</p> <p>[...]</p> <p>8.3.6 Coagulation parameters</p> <p>[...]</p> <p>During the pre-cardioversion period, if the anticoagulation by AVK should be initiated, then the INR monitoring will be as follow:</p> <ul style="list-style-type: none"> – INR 2-3 times a week for the first week of treatment 	<p>8.4 SAFETY ASSESSMENT</p> <p>8.4.2 Laboratory Investigations</p> <p>8.4.2.2 Technical Procedures and Parameters</p> <p>[...]</p> <p><u>Haematology:</u> <i>haematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and/or absolute), reticulocytes, platelets.</i></p> <p>Biochemistry [...]</p> <p>Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.</p> <p>8.4.3. Global Physical Examination</p> <p>A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 4, visit 5, visit 6, visit 7, visit 8 and visit 9</p> <p>[...].</p> <p>8.4.5. Electrocardiogram (ECG)</p> <p>8.4.5.1. Schedule</p> <p>An ECG will be recorded after at least 10 minutes of rest at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9 using an usual standardised 12-lead cardiograph.</p> <p>[...]</p> <p>8.4.6 Coagulation parameters</p> <p>[...]</p> <p>The recommendations for the controls of INR are the following [25, 26]:</p> <p>1) During the pre-cardioversion period, if the anticoagulation by VKA has to be initiated, the treatment must be initiated at least 3 weeks prior to</p>

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<ul style="list-style-type: none"> - INR weekly up to ECV - INR every 4 weeks after ECV <p>For patients already treated with AVK, INR monitoring will be as follow:</p> <ul style="list-style-type: none"> - INR weekly up to ECV - INR every 4 weeks after ECV <p>aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.</p> <p>Anti-coagulation by AVK should be given at least 3 weeks before ECV and continued for the whole study duration.</p> <p>The quantity of blood samples collected at each time for coagulation parameters will be 2 mL.</p> <p>Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal or clinically significant results, the Investigator will order laboratory control tests.</p> <p>[...]</p>	<p>cardioversion then the INR will be monitored as follow:</p> <ul style="list-style-type: none"> - The adjustment of the dosage of VKA should be performed stepwise by controlling INR 2 to 3 times a week until stabilization within the target range (2 - 3) on 2 successive tests. - When the INR is within the target range (2 - 3) on 2 successive tests, the dose of VKA should be maintained. Then the controls of INR will be progressively spaced within a few weeks. - When INR is stabilized, at least one test should be performed each week. - In all cases, an INR control must be performed within 24 h before ECV. <p>2) During the pre-cardioversion period, if the anticoagulation by VKA was already initiated, the INR will be monitored as follow:</p> <ul style="list-style-type: none"> - One INR per week up to ECV - An INR control must be performed within 24 h before ECV <p>3) After cardioversion : one INR each month</p> <p>4) Throughout the duration of the study if INR > 3 the advocated actions are:</p> <ul style="list-style-type: none"> - No transesophageal echocardiography before cardioversion - For asymptomatic patients: <ul style="list-style-type: none"> - 3 < INR < 4: no omission of VKA (dose adjustment if required), no vitamin K - 4 ≤ INR < 6: omit one dose of VKA, no vitamin K - 6 ≤ INR < 10: interrupt VKA, vitamin K 2 mg orally - INR ≥ 10: interrupt VKA, vitamin K 5 mg orally <p>For INR ≥ 6, an adverse event has to be reported (asymptomatic overdose).</p> <p>Anti-coagulation by VKA should be given at least 3 weeks before ECV and continued for the whole study duration.</p>

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	<p>aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 5, visit 6, visit 7, visit 8 and visit 9.</p> <p>The quantity of blood samples collected at each time for coagulation parameters will be 2 ml.</p> <p>Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.</p> <p>[...]</p>
<p>8.4 CONCOMITANT TREATMENTS</p> <p>Concomitant treatments will be evaluated at each study visit.</p> <p>Requirements relating to patient's concomitant treatments started before screening visit and continued throughout the trial, or started during the trial, can be found in section 7.</p>	<p>8.5 CONCOMITANT TREATMENTS</p> <p>Concomitant treatments will be evaluated at each study visit.</p> <p>Requirements related to patient's concomitant treatments started before selection visit and continued throughout the trial, or started during the trial, can be found in section 7.</p>
<p>9. STUDY PROCEDURES</p> <p>Visit 1 - Selection Visit (Week - 4 to Week -1):</p> <p>[...]</p> <ul style="list-style-type: none"> The patient will enter the selection period in which anticoagulant (AVK) will be adjusted to achieve an International Normalized Ratio (INR) of 2 to 3 before ECV. <p>[...]</p> <p>The patient will receive from the investigational centre the study card to be kept for the duration of the study.</p> <p>Visit 2 - Inclusion Visit (Day 1)</p> <p>If the patient's behaviour during the selection period and/or the result of complementary examinations, particularly the confirmation of the presence of persistent AF by the</p>	<p>9. STUDY PROCEDURES</p> <p>Visit 1 - Selection Visit (Week - 4 to Week -1):</p> <p>[...]</p> <ul style="list-style-type: none"> The patient will enter the selection and pre-cardioversion periods in which anticoagulant (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) in the range of 2 to 3 before ECV. <p>[...]</p> <p>The patient will receive from the investigational centre the participant card to be kept for all the duration of the study.</p> <p>Visit 2 - Inclusion Visit (Day 1):</p> <p>If the patient's behaviour during the selection period and/or the result of complementary examinations, particularly the confirmation of the presence of persistent AF by the Central</p>

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<p>Central Reading Laboratory during this period, the INR and laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:</p> <p>[...]</p> <p>If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and allocated a treatment number using the IVRS/IWRS.</p> <p>Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.3.6) in order to ensure that the INR is stable (between 2 to 3 before electrical cardioversion).</p> <p>[...]</p> <p>At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period.</p> <p>Vist 3 (Week 4: D28 -2/+7 days) cardioversion</p> <p>[...]</p> <p>Electrocardioversion (ECV): ECV has to be scheduled 4 weeks after randomization and after target International Normalized Ratio levels will be stabilized (between 2 and 3) on at least 3 consecutive weekly tests in patients with AF. Patients not stabilized for INR (i.e. values not between 2 and 3) on at least 3 consecutive weekly tests before ECV will be excluded from the study, unless the presence of atrial thrombosis may be excluded with ECHO –TE performed in the same day (and before ECV). ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia.</p> <p>[...]</p> <p>Patients who will not revert to sinus rhythm or with early relapse within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.</p> <p>[...]</p>	<p>Reading Laboratory during this period, the INR and the laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:</p> <p>[...]</p> <p>If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 2 for the first 12-week period.</p> <p>Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.4.6) in order to fulfil the ECV conditions (refer to paragraph 3).</p> <p>[...]</p> <p>At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period (one case of treatment).</p> <p>Vist 3 (Week 4: D28 -2/+7 days) cardioversion</p> <p>[...]</p> <p>Electrocardioversion (ECV): ECV has to be performed 4 weeks after randomization in patients with AF. ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO–TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study.</p> <p>[...]</p> <p>Patients who will not revert to sinus rhythm or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-</p>

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<p>At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week period.</p> <p>[...]</p> <p>Visit 4 (Week 5: D35 -2/+7 days)</p> <p>[...]</p> <p>The patient will be requested to perform daily transmission from the day after visit 4 (week 6) to visit 5 (week 8), then every two days from the day after visit 5 (week 9) to visit 9 (week 24 – End of study). Moreover, in case of AF symptoms, additional transmissions may be performed.</p> <p>[...]</p> <p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days)</p> <p>[...]</p> <ul style="list-style-type: none"> Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV, the monitoring of INR, aPTT and TCT should be stopped. <p>[...]</p> <ul style="list-style-type: none"> The cardiac monitoring will be continued using a TTEM device. The device will be given to the patient who will be requested to perform daily transmission from the day after visit 4 (week 6) to visit 5 (week 8), then every two days from the day after visit 5 (week 	<p>up.</p> <p>[...]</p> <p>The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.</p> <p>At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 8-week period (two cases of treatment).</p> <p>[...]</p> <p>Visit 4 (Week 5: D35 -2/+7 days)</p> <p>[...]</p> <p>The patient will be requested to perform one transmission per week from this visit (initial call to perform with the patient) to the visit 9 (week 24 – end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.</p> <p>[...]</p> <p>Visit 5 (Week 8: D56 ± 7 days) – Visit 6 (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) - Visit 8 (Week 20: D140 ± 7 days):</p> <p>[...]</p> <ul style="list-style-type: none"> Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV due to occurrence of VKA intolerance, the monitoring of INR, aPTT and TCT should be stopped. <p>[...]</p> <ul style="list-style-type: none"> The cardiac monitoring will be continued using the TTEM device through one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may

PREVIOUS VERSION	MODIFIED VERSION
<p>9) to visit 9 (week 24 – End of study). Moreover, in case of AF symptoms, additional transmissions may be performed.</p> <p>[...]</p> <p>The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.</p> <p>At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 4-week treatment period.</p> <p>In addition, :</p> <p>- at visit 6:</p> <ul style="list-style-type: none"> • the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period. • an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured. <p>[...]</p> <p>End-of-Study Visit - Visit 9 (Week 24: D168 ± 7 days):</p> <p>[...]</p> <p>The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules</p> <p>[...]</p>	<p>be performed.</p> <p>[...]</p> <p>The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.</p> <p>In addition, at visit 6:</p> <ul style="list-style-type: none"> • the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period. • an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured. <p>At the end of each visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next treatment period: one case at visit 6 and two cases at visit 7.</p> <p>[...]</p> <p><u>Visit 9 - End-of-Study</u> Visit (Week 24: D168 ± 7 days):</p> <p>[...]</p> <p>The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.</p> <p>The total volume of blood collected should be about 90 mL for the study duration (30 mL for the total volume of haematology and biochemistry, 2 mL for each blood samples for coagulations parameters and 4 mL for each blood samples of DHA).</p> <p>[...]</p>

PREVIOUS VERSION	MODIFIED VERSION
<p>13. STATISTICAL ANALYSIS</p> <p>13.2. SAMPLE SIZE</p> <p>Assuming an AF recurrence or flutter emergence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.</p>	<p>13. STATISTICAL ANALYSIS</p> <p>13.2. SAMPLE SIZE</p> <p>Assuming an AF recurrence or atrial flutter emergence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.</p>
<p>13.7. EFFICACY ANALYSIS</p> <p>13.7.1. Primary Criterion</p> <p>13.7.1.1. Primary Analysis</p> <p>The primary criteria, time to first recurrence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model. [...]</p> <p>13.7.2. Secondary Criteria</p> <p>13.7.2.1. Numbers of Atrial Fibrillation Episodes [...]</p> <p>13.7.2.2. Duration of Atrial Fibrillation Episodes [...]</p>	<p>13.7. EFFICACY ANALYSIS</p> <p>13.7.1. Primary Criterion</p> <p>13.7.1.1. Primary Analysis</p> <p>The primary criteria, time to first recurrence of AF or atrial flutter emergence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model. [...]</p> <p>13.7.2. Secondary Criteria</p> <p>13.7.2.1. Numbers of Atrial Fibrillation Episodes <u>in the first week following V3</u> [...]</p> <p>13.7.2.2. Duration of Atrial Fibrillation Episodes <u>in the first week following V3</u> [...]</p>
	<p>16. REFERENCES</p> <p>3 added references:</p> <p>[24]. JOHN J.V. MCMURRAY, STAMATIS ADAMOPOULOS, STEFAN D. ANKER, ANGELO AURICCHIO, MICHAEL BÖHM, KENNETH DICKSTEIN, VOLKMAR FALK, GERASIMOS FILIPPATOS, CÂNDIDA FONSECA, MIGUEL ANGEL GOMEZ-SANCHEZ, TINY JAARMSA, LARS KØBER, GREGORY Y.H. LIP, ALDO PIETRO MAGGIONI, ALEXANDER PARKHOMENKO, BURKERT M. PIESKE, BOGDAN A. POPESCU, PER K. RØNNEVIK, FRANS H. RUTTEN, JUERG SCHWITTER, PETAR SEFEROVIC, JANINA STEPINSKA, PEDRO T.</p>

PREVIOUS VERSION	MODIFIED VERSION
	<p data-bbox="935 338 1501 394">TRINDADE, ADRIAAN A. VOORS, FAIEZ ZANNAD, ANDREAS ZEIHNER</p> <p data-bbox="935 409 1501 495">ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 <i>European Heart Journal</i> (2012) 33, 1787–1847</p> <p data-bbox="855 546 1458 631">[25]. AGENCE NATIONALE DE SECURITE DU MEDICAMENT ET DES PRODUITS DE SANTE (ANSM).</p> <p data-bbox="935 647 1436 703">Bon usage des médicaments antivitamin K (AVK) <i>Actualisation – Juillet 2012</i></p> <p data-bbox="855 730 1445 786">[26]. GILLES PERNOD, ANNE GODIER, CLAIRE GOZALO, BENJAMIN TREMEY, PIERRE SIE</p> <p data-bbox="935 801 1493 909">French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding) <i>Thrombosis Research</i> 126 (2010) e167–e174</p>

ANNEXE 1

STUDY FLOW-CHART FROM PROTOCOL VERSION 7

F373280 CA 201

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)	W8 (56+/-7D)	W12 (84+/-7D)	W16 (112+/-7D)	W20 (140+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	←	→	(2)		X	X	X	X	X
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Hematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		←	→						→
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	← (4)		← (5)	→					
TTEM (6)				←	→				→

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of AVK introduction: INR 2 to 3 times a week, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: everyday from week 6 to week 8; then every 2 days from week 9 to week 24; at any time in case of AF symptoms.

In case of AF recurrence for at least 10 minutes and if the patient does not stop the study treatment, then TTEM once a week

ANNEXE 2
STUDY FLOW-CHART FROM PROTOCOL VERSION 8

F373280 CA 201							
	V1	V2	V3	V4	V6	V7	V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)	W12 (84+/-7D)	W16 (112+/-7D)	W24 (168+/-7D)
Outpatient or Hospitalization (1)			X				
Informed consent	X						
Demographic characteristics	X						
Medico-surgical history	X						
Concomitant disease	X						
Concomitant treatment	X	X	X	X	X	X	X
Habits	X						
Global physical examination (body weight)	X	X	X		X	X	X
Echocardiography	X	X		X	X		X
Eligibility criteria check	X	X					
Blood pressure, heart rate	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X
INR							(2)
aPTT, TCT	X	X	X		X	X	X
Biochemistry	X						X
Haematology	X		X		X		X
Urinary pregnancy test		X					X
Red Blood Cell concentrations of DHA		X	X		X		X
Treatment number allocation		X			X		
IVRS/IWRS	X	X			X		
ECV (3)			X				
Drug administration							
Adverse events recording		X	X	X	X	X	X
Holter ECG	(4)		(5)				
TTEM (6)							

⁽¹⁾ Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of VKA introduction: INR 2 to 3 times a week until stabilization, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) **24-hour Holter ECG**

(5) 7-day Holter ECG

(6) TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms. TTEM once a week even in case of AF recurrence or atrial flutter emergence for at least 10 minutes.

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

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Version 8 – 22OCT2014

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Phone: +33 (0)4 97 02 07 07 - Fax: +33 (0)4 97 10 08 78
E-mail: chantal.raffy@theradis.pharma.com

Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 8 – 22OCT2014

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Medical Director:
Richard ROCHE, MD

Date: 22/10/2014

Signature:

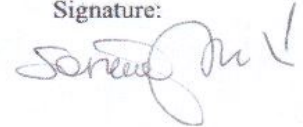


Study Coordinating Investigator:
Savina NODARI, MD

Date:

22 October 2014

Signature:



Protocol F 373280 CA 2 01

COUNTRY COORDINATING INVESTIGATOR

SIGNATURE FORM

Protocol Version 8 – 22OCT2014

Country:

Country Coordinating Investigator:

"Name"	Date:	Signature:
<hr/>		
<hr/>		

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 8 – 22OCT2014

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 22OCT2014 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PolyUnsaturated Fatty Acid (PUFA) has been proven in the following conditions:</p> <ul style="list-style-type: none"> - prevention of AF recurrence in patients with persistent AF, in co-administration with amiodarone (add on therapy) [2] - Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2016	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> - Ideally INR 2-3 (vitamin K antagonist should be given at least 3 weeks before ECV) - No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: 	

	<ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms. <p>- Treatment duration: 24 weeks</p>
Study Schedule:	<p>7 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of study treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter device) - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V6/ W12* (D84 ± 7 days): follow-up visit <p>*see amendment PA05 dated 22OCT2014</p> <ul style="list-style-type: none"> - V7/ W16 (D112 ± 7 days): follow-up visit - V9/ W24* (D168 ± 7 days): final study visit <p>*see amendment PA05 dated 22OCT2014</p>
Number of Patients:	76 x 2 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive) 2. Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. Previous history of first documented episode of persistent AF. 4. Previous history of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ or for patients with a LVEF $> 45\%$: <ul style="list-style-type: none"> • 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 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area ≤ 40 cm² at selection and at inclusion 9. Patients treated or having to be treated by vitamin K antagonist 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> • In all the countries except Italy: <ul style="list-style-type: none"> - Use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - Documented as surgically sterilized • In Italy only: <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - Use of double barrier contraception method (use of effective medical contraception

	<p>method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or</p> <ul style="list-style-type: none"> - Documented as surgically sterilized <p>11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion</p> <p>12. For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study. <p><i>Ethical / legal considerations:</i></p> <p>13. Having signed his/her written informed consent,</p> <p>14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation)</p> <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. No previous history of first documented episode of persistent AF 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 ml/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, betablockers, calcium-blockers 13. Concomitant treatment with oral amiodarone or dronedarone from selection 14. Concomitant treatment with intravenous amiodarone from selection 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω 3 or ω 6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible
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	<p>antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel</p> <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study.</p> <p>However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study.</p> <p>If necessary, for meeting these INR conditions, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280 Soft Capsules
Dose:	Arm with 1g of F373280
Mode of Administration:	Oral, one capsule each evening with dinner.
Duration of Treatment:	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Reference Therapy	Placebo soft capsules Placebo will be administered in the same conditions as the tested product.
Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation 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). <p>Handling of AF recurrences or atrial flutter emergences: 7-day continuous 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 will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24).</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5). Moreover, during this TTEM period, if patient experiences any AF or atrial flutter symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG (Holter and TTEM) will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p> <p>During the 7-day continuous ECG monitoring,</p>

	<ul style="list-style-type: none"> Numbers of AF episodes Duration of AF episodes <p><u>Clinical parameters:</u></p> <p>During the whole study:</p> <ul style="list-style-type: none"> Number of recurrence of symptomatic AF episodes EHRA score Hospitalization for cardiovascular events Hospitalization for thromboembolic stroke All causes of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> Assessment of spontaneous cardioversion Assessment of successful cardioversion Shocks distribution (1, 2 or 3 shocks) Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> Evolution of echocardiographic parameters (at V4, V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (ml), Left atrial volume/BSA (ml/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (ml/m²), Left ventricular end systolic volume/BSA(ml/m²), 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> Adverse events (observed and / or spontaneously reported) Vital signs (Blood pressure (supine and standing), heart rate) Physical examination (body weight, body surface area) Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns (ECG not centralized) Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (<i>PT</i>). <p>Concomitant treatments</p> <p>Compliance</p>
Statistical Methods:	<p>Sample Size:</p> <p>Assuming an AF recurrence or atrial flutter emergence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis</p>

	<p>The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses</p> <p>All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses</p> <p>Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment).</p>
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STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4		V6	V7		V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)		W12 (84+/-7D)	W16 (112+/-7D)		W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	← (2) →								
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Haematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment number allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		← →							
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	↔ (4)		← → (5)						
TTEM (6)				← →					→

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of VKA introduction: INR 2 to 3 times a week until stabilization, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms.

TTEM once a week even in case of AF recurrence or atrial flutter emergence for at least 10 minutes.

LIST OF ABBREVIATIONS

aPTT	: Activated partial thromboplastin time
AE	: Adverse event
AF	: Atrial fibrillation
ALA	: Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body Surface Area
CEP	: Protocol evaluation committee
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	: Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	: Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	: Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	: Transesophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	: European heart rhythm association
EPA	: Eicosapentaenoic acid
e-CRF	: Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate
HBs	: Hepatitis B antigen
HCV	: Hepatitis C virus
HDL	: High density lipoprotein

HF	:	Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR	:	International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS	:	Interactive voice response system
LAA	:	Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL	:	Low density lipoprotein
LOQ	:	Limit of quantification
LVEF	:	Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR	:	Mineralocorticoid receptor
MR perfusion	:	Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA	:	New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
PSC	:	Potentially Clinically Significant Change
PSCV	:	Potentially Clinically Significant Value
PUFA	:	PolyUnsaturated fatty acid
p.o.	:	Per os
PP	:	Per protocol data set
QTcB	:	QT interval using Bazett’s correction formula
QTcF	:	QT interval using Fridericia’s correction formula
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT	:	Thrombin clotting time
TEAEs	:	Treatment emergent adverse events
TTEM	:	TransTelephonic ECG monitoring
VKA	:	Vitamin K Antagonist
WBC	:	White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of AF in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the Polyunsaturated Fatty Acids (PUFAs) constitute one emerging antiarrhythmic therapy. These compounds potently address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or AF.

The potential anti-arrhythmic effects of a PUFA were previously developed in AF: nicotinyl ester of DHA (pro-drug based on DHA delivery) was assessed in a two-week ventricular tachypaced

canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of AF induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll [2] assessed n-3 PUFAs in the prevention of AF recurrences after electrical cardioversion (ECV). All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct ECV 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFAs on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than in the placebo group at 1 month (3.3% vs 10%; $p = 0.043$), at 3 months (10% vs 25%; $p = 0.004$) and at 6 months (13.3% vs 40%; $p < 0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effects of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage

of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 ± 0.33 to 1.61 ± 0.49 and increased from 1.83 ± 0.38 to 2.14 ± 0.65 , respectively).

The hospitalization rates for patients with HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and $\text{LVEF} < 35\%$). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA ($n = 14$), 4 g/d n3-PUFA ($n = 13$), or placebo ($n = 16$)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($p = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: $24\% \pm 7\%$ vs $29\% \pm 8\%$, $p = 0.005$) and 1 g/d treatment groups ($24\% \pm 8\%$ vs $27\% \pm 8\%$, $p = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent AF and heart failure in the maintenance of sinus rhythm after ECV.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of AF.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

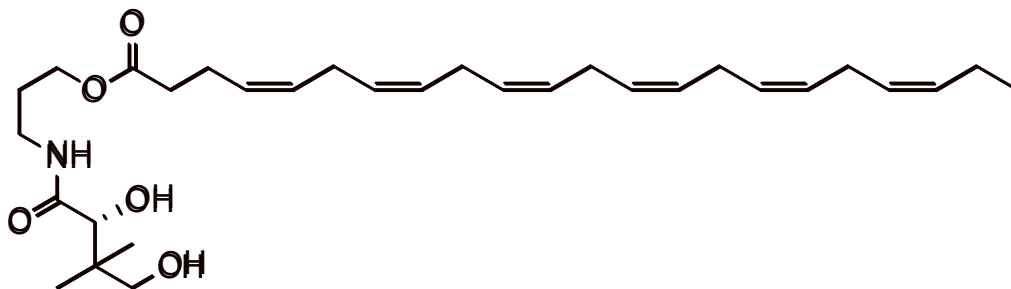
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. Pharmacological profile

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased atrial effective refractory period (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $p < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the electrocardiogram (ECG) intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing-induced congestive heart failure provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses congestive heart failure-induced AF-promotion and fibrosis in the ventricular tachypacing canine model. Nicotinyl ester of DHA was tested in this model, at 1 g/day and 5 g/day, during 4 weeks, to prevent congestive heart failure-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in AF duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1 g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5 g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280 similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 mg/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies, no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: Single dose

Six consecutive single ascending doses were tested (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events (SAE) occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of

an alternative explanation, 3 TEAEs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotension without loss of consciousness) and 4 in the group of F373280 at the dosage of 16 g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events (AE) were reported in the groups of F373280 at the dosages of 0.5 g, 1 g, 2 g, 4 g and 8 g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5 g to 16 g in 36 young healthy male subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16 g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1 g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding Pharmacokinetics parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16 g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple doses

Three consecutive repeated ascending doses (1, 2 and 4 g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280, 5/9 TEAEs were classified according the System Organ Class in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAEs have already been reported with PUFAs and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** C_{max} and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after ECV in persistent AF patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing [1].

Moreover, the effectiveness of PUFAs has been proven in the following conditions:

- Prevention of AF recurrence in patients with persistent AF in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent AF and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after ECV in patients with persistent AF and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1 g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor® [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations:
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:

Very rare: nasal dryness

- Gastrointestinal disorders:

Common: dyspepsia, nausea

Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper

Rare: gastrointestinal pain

Very rare: lower gastrointestinal haemorrhage

- Hepatobiliary disorders:

Rare: hepatic disorders

- Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

- General disorders and administration site conditions:

Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1 g and 4 g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after

administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in AF studies [2, 8]. The range of PUFAs doses tested was between 2 g to 3 g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in HF patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1 g to 5 g (1 g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent form. A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on AF and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of AF and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (vitamin K antagonist, VKA), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence or atrial flutter emergence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication
- Anticoagulation with vitamin K antagonist (VKA) for at least 3 weeks before ECV
- ECV will be performed in patients with AF and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last

tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Patients who do not revert to sinus rhythm or present an early AF relapse or an early atrial flutter emergence within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be performed throughout the study period. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored once a week between visits using Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent AF and chronic heart failure.

After a 1 to 4-week of run-in period without study treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Seven visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of study treatment)
- Visit 3 (V3): W4 (D28-2/+7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)

- Visit 4 (V4): W5 (D35 -2/+7D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 6* (V6): W12 (D84 ± 7D): follow-up visit
*see amendment PA05 dated 22OCT2014
- Visit 7 (V7): W16 (D112 ± 7D) : follow-up visit
- Visit 9* (V9): W24 (D168 ± 7D): final study visit
*see amendment PA05 dated 22OCT2014

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent AF and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent AF with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- Previous history of persistent AF with duration of the current episode from 7 days to 6 months.
- A systolic heart failure defined by a reduced left ventricular ejection fraction ($\geq 30\%$ and $\leq 45\%$) 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 [23, 24].

According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.

- A Left Atrial Area (LAA) not severely abnormal (no greater than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline) [23]. According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of ECV, patients should have a stable medical treatment of heart failure and should not have any myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on antiarrhythmics in AF (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, antiarrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF (or emergence of atrial flutter) since cardioversion.

To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) of 2 to 3 before ECV. According to guidelines for the management of AF [6], VKA should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodari's study [2], the duration of pre-treatment with PUFAs before cardioversion appears to be a contributing factor in success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of AF recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of AF recurrences occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using an easier device to carry and to use, i.e. a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every 4 weeks or 8 weeks (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with AF [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of AF after cardioversion. Moreover, PUFAs at dosage of 1 g and 2 g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1 g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95 mg/ml and 60 to 90 mg/ml, respectively) (phase I study of F373280 and [16]). With regard to the rhythm of administration, mean peak/trough

fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a 1 g daily dose of F373280 is considered to be appropriate for this proof of concept study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive)
2. Patient with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted
3. Previous history of first documented episode of persistent AF
4. Previous history of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ 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
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers

8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by vitamin K antagonist
10. For female patient of child-bearing potential:
 - **In all the countries except Italy:**
 - Use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - Documented as surgically sterilized
 - **In Italy only:**
 - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - Use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - Documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or
 - Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,

14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation)

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. No previous history of first documented episode of persistent Atrial Fibrillation
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 ml/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, beta-blockers, calcium-blockers.
13. Concomitant treatment with oral amiodarone or dronedarone from selection
14. Concomitant treatment with intravenous amiodarone from selection
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months

16. Treatment with any Polyunsaturated Fatty Acid within the last 3 months
17. Dietary supplement with $\omega 3$ or $\omega 6$ according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENT IDENTIFICATION

Patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

Reasons for a patient's premature withdrawal from the study may be the following:

- Patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- Investigator's decision in the patient's interest, particularly if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.
- Erroneous inclusion according to the study protocol. The decision to maintain or not the patient in the study will be taken jointly by the investigator and the sponsor. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with VKA for at least 3 weeks before ECV or who will experience a VKA intolerance during the study.
- Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal

echocardiography) performed on the same day (before ECV) and the patient can continue the study.

- Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be considered to have finished follow-up.
- Occurrence of AF recurrence or atrial flutter emergence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate in another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit:

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.
- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the Institut de Recherche Pierre Fabre (IRPF) will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- **F373280**

Formulation of F373280, 1 g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- **Placebo**

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the IRPF according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

Two 12-week treatment units will contain 3 cases, each case of 4-week treatment containing: 10 blister packs of four 1 g F373280 soft capsules or 1 g placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number
- c) packaging batch number
- d) treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:

-“for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”

On the treatment unit, another label will be affixed with the mention of the Investigator’s name and patient’s code (completed by the Investigator).

In addition, on each case will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the IRPF will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient’s selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion visit (V2) and another one at visit 6.

For each patient, the treatment number given at visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

At selection visit (V1), practically, once patient's eligibility is confirmed:

- The Investigator:
 - Contacts the IVRS/IWRS

- Answers the questions related to the patient
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

At inclusion visit (V2), the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.

At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment.

The Investigator will dispense to the patient the 4-week treatment cases (one or two according to the visit) which label indicates the treatment number and the administration period.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure to F373280 or placebo will be 24 weeks.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator in collaboration with the Sponsor's representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (at selection visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the electronic Case Report Forms (e-CRF). All treatments should be evaluated by the Investigator at patient's selection, and treatment prolongation or stop during the study should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. VITAMIN K ANTAGONIST TREATMENT

VKA should be given for at least 3 weeks before ECV and continued for the whole study duration. However, VKA should be stopped in case of occurrence of VKA intolerance during the study and the patient should be withdrawn from the study. The VKA used will be left to the decision of each Investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:

- Class I:
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
- Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.

- Ranolazine

- Any PUFA

- Any oral anticoagulant treatment other than VKA: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or irreversible antiplatelet agents P2Y₁₂ inhibitors such as ticlopidine, clopidogrel or prasugrel

- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the e-CRF. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION

8.1.1. Time to the first Atrial Fibrillation Recurrence or Atrial Flutter Emergence

8.1.1.1. *Definition*

Time to first AF recurrence or atrial flutter emergence is defined by the time to first episode of AF or atrial flutter (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring, the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM).

- Trans Telephonic ECG Monitoring:

The ECG follow up will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM.

Moreover, if patient experiences AF or atrial flutter symptoms during this TTEM period, it should be documented using the TTEM.

In case of AF recurrence or atrial flutter emergence and provided that the patient does not require a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

- Process of centralisation of ECG (Holter and TTEM)

ECG (Holter and TTEM) will be centralized by the Central Reading Laboratory. The ECG will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be emailed to the site (or per fax on request of the site). The investigator will be asked to review and sign these documents.

The Holter and TTEM process will be fully described in separate documents.

8.2. SECONDARY EFFICACY CRITERIA

8.2.1. Numbers of AF episodes in the first week following visit 3 (ECV visit)

8.2.1.1. Definition

Number of AF episodes will consist in the assessment of AF episodes with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the study visit 4.

8.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.2.2. Duration of AF episodes in the first week following visit 3 (ECV visit)

8.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episode.

8.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the follow up study visit (visit 4).

8.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.2.3. Clinical parameters evaluation

8.2.3.1. *EHRA score assessment*

8.2.3.1.1. *Definition*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily.

8.2.3.1.2. *Schedule*

EHRA evaluation will be performed in case of evocative symptoms of arrhythmia.

8.2.3.1.3. *Evaluation Methods*

EHRA evaluation will be collected by Central Reading Laboratory during TTEM period.

8.2.3.2. *Time to first AF recurrence less than 10 minutes*

Time to first AF recurrence less than 10 minutes will be assessed during TTEM period.

8.2.3.3. *Recurrence of symptomatic AF*

Recurrence of symptomatic AF will be assessed during TTEM period.

The number of recurrences of symptomatic AF consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.

The time to first symptomatic AF recurrence is defined by the time to first episode of symptomatic AF.

8.2.3.4. *Number and duration of hospitalizations*

- Number and duration of hospitalizations for cardiovascular events
 - Hospitalization for AF treatment

- Hospitalization for worsening of heart failure
- Hospitalization for myocardial infarction
- All cause of hospitalization
- Number and duration of hospitalizations for thromboembolic stroke

8.2.4. Cardioversion assessment

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shocks distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.2.5. Evolution of echocardiographic parameters

8.2.5.1. Definition

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (ml), Left atrial volume/BSA (ml/m²), LVEF (%), Left ventricular end diastolic volume/BSA (ml/m²), Left ventricular end systolic volume/BSA (ml/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (ml), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (ml).

8.2.5.2. Schedule

Measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

Measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.2.5.3. Evaluation method

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European

Association of Echocardiography [23]. So, the recommended method for volume measurements is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.3. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.3.1. Definition

Because of the limited human tissue accessibility for biopsy, red blood cell DHA contents is a marker of tissue DHA concentration [13], [14].

8.3.2. Blood samples

8.3.2.1. Collection schedule

Blood samples will be collected to determine the red blood cells (RBC) concentrations of DHA.

Blood samples will be performed at visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the e-CRFs.

8.3.2.2. Technical handling

Two blood samples (2 x 4 ml) will be collected in EDTA tubes. They will be homogenized slowly by inverting the tube without shaking, stored between +2°C/+8°C in a fridge (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.3.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent)

and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock) in a separate file.

8.4. SAFETY ASSESSMENT

8.4.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of AEs since the last visit will be based on the patient's spontaneous reporting, the Investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.4.2. Laboratory Investigations

8.4.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kalemia will be checked before electrical cardioversion at visit 3.

The total volume of blood samples taken for haematology and biochemistry analysis should not exceed 30 ml.

8.4.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *haematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and/or absolute), reticulocytes, platelets.*

Biochemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula:

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})]$$

in women:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})] \times 0.85$$

- with serum creatinine expressed as $\mu\text{mol/l}$:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / \text{serum creatinine in } \mu\text{mol/l}] \times k, \text{ where } k = 1.23 \text{ for men, } 1.04 \text{ for women.}$$

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.

8.4.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9.

The Body surface area (BSA) will be calculated at the same visits using Mostellers' formula:

$$BSA = [(Weight \times Height)/3600]^{1/2}$$

(Weight in kg, height in cm)

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.4.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.4.4.1. *Schedule*

Vital signs will be measured at each visit.

8.4.4.2. *Technical Procedure and Parameters*

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation by counting the beats for at least 30 seconds, after at least 5 minutes in supine position and after 2 minutes in standing position.

Bodyweight will be measured with patient in underwear and with the same balance at each visit.

8.4.5. Electrocardiogram (ECG)

8.4.5.1. *Schedule*

An ECG will be recorded after at least 10 minutes of rest at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9 using a usual standardised 12-lead cardiograph.

8.4.5.2. *Technical Procedure and Parameters*

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns will be reported in the

e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent AF.

8.4.6. Coagulation parameters

Coagulation assessment will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

The recommendations for the controls of INR are the following [25, 26]:

1) During the pre-cardioversion period, if the anticoagulation by VKA has to be initiated, the treatment must be initiated at least 3 weeks prior to cardioversion then the INR will be monitored as follow:

- The adjustment of the dosage of VKA should be performed stepwise by controlling INR 2 to 3 times a week until stabilization within the target range (2 - 3) on 2 successive tests.
- When the INR is within the target range (2 - 3) on 2 successive tests, the dose of VKA should be maintained. Then the controls of INR will be progressively spaced within a few weeks.
- When INR is stabilized, at least one test should be performed each week.
- In all cases, an INR control must be performed within 24 h before ECV.

2) During the pre-cardioversion period, if the anticoagulation by VKA was already initiated, the INR will be monitored as follow:

- One INR per week up to ECV
- An INR control must be performed within 24 h before ECV

3) After cardioversion : one INR every 4 weeks

4) Throughout the duration of the study if $INR > 3$ the advocated actions are:

- No transesophageal echocardiography before cardioversion
- For asymptomatic patients:
 - $3 < \text{INR} < 4$: no omission of VKA (dose adjustment if required), no vitamin K
 - $4 \leq \text{INR} < 6$: omit one dose of VKA, no vitamin K
 - $6 \leq \text{INR} < 10$: interrupt VKA, vitamin K 2 mg orally
 - $\text{INR} \geq 10$: interrupt VKA, vitamin K 5 mg orally

For $\text{INR} \geq 6$, an adverse event has to be reported (asymptomatic overdose).

Anti-coagulation by VKA should be given at least 3 weeks before ECV and continued for the whole study duration.

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9.

The quantity of blood samples collected at each time for coagulation parameters will be 2 ml.

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.

8.5. CONCOMITANT TREATMENTS

Concomitant treatments will be evaluated at each study visit.

Requirements related to patient's concomitant treatments started before selection visit and continued throughout the trial, or started during the trial, can be found in section 7.

8.6. COMPLIANCE

The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.

At each visit (except at visit 4), the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week - 4 to Week -1):

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If the patient accepts to participate in the study, he/she will sign the informed consent form and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and AF characteristics
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria:

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory. The Central Reading Laboratory will send his/her assessment regarding the confirmation of persistent AF within 2 working days to the Investigator.

- The patient will enter the selection and pre-cardioversion periods in which anticoagulant (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) in the range of 2 to 3 before ECV.

At the end of the visit, the Investigator will contact the IVRS/IWRS to confirm the patient selection (which will automatically order the treatment delivery) and organise the appointment for the next visit.

The patient will receive from the investigational centre the participant card to be kept for all the duration of the study.

Visit 2 - Inclusion Visit (Day 1):

If the patient's behaviour during the selection period and/or the result of complementary examinations, particularly the confirmation of the presence of persistent AF by the Central Reading Laboratory during this period and the laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 2 for the first 12-week period.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.4.6) in order to fulfil the ECV conditions (refer to paragraph 3).

At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period (one case of treatment).

Visit 3 (Week 4: D28 -2/+7 days) cardioversion:

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, RBC concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be performed 4 weeks after randomization in patients with AF. ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge.

Patients who will not revert to sinus rhythm or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 8-week period (two cases of treatment).

Visit 4 (Week 5: D35 -2/+7 days):

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of AE
- Concomitant treatments (authorised, disallowed)
- Bodyweight (bodyweight measured at V3 to be used)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to perform one transmission per week from this visit (initial call to perform with the patient) to the visit 9 (week 24 – end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.

Visit 6* (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) :

*see amendment PA05 dated 22OCT2014

Patient will be assessed for the following criteria:

- Adverse events

- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV due to occurrence of VKA intolerance, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using the TTEM device through one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

In addition, at visit 6:

- the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period.
- an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.

At the end of each visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next treatment period: one case at visit 6 and two cases at visit 7.

Visit 9* - End-of-Study Visit (Week 24: D168 ± 7 days):

*see amendment PA05 dated 22OCT2014

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight

- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT), Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.

The total volume of blood collected should be about 90 ml for the study duration (30 ml for the total volume of haematology and biochemistry, 2 ml for each blood samples for coagulations parameters and 4 ml for each blood samples of DHA).

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An AE is any adverse change from the patient's baseline condition, i.e. any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

AE includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

10.1.3. Reporting of Adverse Events

The records of AE in the e-CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A SAE includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect

Other events such as cancer and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure
- preparation for routine health assessment/procedure (e.g. routine colonoscopy)
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required)
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by FAX at the following number:

+ 33 1 49 10 80 90

In case of non-inclusion, the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial, an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose and associated adverse event if any, are reported only on the Adverse Event page of the e-CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must also be transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the Sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and must be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is withdrawn from the study.

The Investigator must report to the Sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The Investigator must immediately notify the Sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the Investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the Sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING

PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An e-CRF will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files that will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and should include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF. Training sessions will be held by the subcontractor for all participants using this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRFs (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. Follow-up Visits

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of primary end point measures, the safety data. The IDMC will thereafter recommend to the Sponsor whether to continue, modify, or stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on the e-CRFs.

The e-CRFs used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate the coding.

12.4. DATA STORAGE

Computer data files as well as their modifications will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e. data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by PFB or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence or atrial flutter emergence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients

per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 3 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety.
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol

deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence of AF or atrial flutter emergence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes in the first week following V3

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes in the first week following V3

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAEs
- With at least three TEAEs
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.

Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:

- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TEAE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patients).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

SAE will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

CNALV (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and HR in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. Individual Patient Changes

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) minus number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days)

13.11. INTERIM ANALYSIS AND DATA MONITORING

No analyses of efficacy data are planned for IDMC that ensures that the overall probability of type I error is controlled. No Type I error and sample size adjustments are necessary. Any recommendations of the IDMC to alter study conduct will be based on safety, so IDMC monitoring of the study will not affect the statistical operating characteristics of the final analysis.

The IDMC will review, three times during the study period (after the first 30 subjects will have been randomized, when the first 80 subjects will have terminated their study participation and when 130 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor Pierre Fabre Médicament, has an insurance policy intended to guarantee against possible damage resulting from the research. The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Médicament are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities.

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not.

- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents.
- Authorises direct access to source documents for monitoring, audits and inspections.
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. Early Study Termination Decided by the Competent Authorities

The Competent Authorities may suspend or prohibit a study if they consider that either the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both its representatives (Study Manager, CRA...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at Pierre Fabre Médicament and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed in writing with the Study Manager, the Investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the Sponsor's responsibility.

Upon data analysis completion, a final report including a review of the objectives and methods, a presentation and a discussion of the results is drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the Investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow the use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The Investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) Investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all Investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1]. **F373280 INVESTIGATOR'S BROCHURE**, version October 2013
- [2]. NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3]. NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57;870-879
- [4]. MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5]. GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6]. CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7]. KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8]. BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9]. **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10]. **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11]. TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedaron for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12]. LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedaron versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13]. **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14]. **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15]. **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16]. SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.
- [17]. LEGRAND P., SCHMITT B., MOUROT J., CATHELINE D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.

The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human.

Lipids, 2010, 45, 11-19.

- [18]. HARRIS WS, VON SCHACKY C.
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19]. ABSTRACT: P5161.
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M, DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20]. **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21]. **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22]. **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23]. ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108
- [24]. JOHN J.V. McMURRAY, STAMATIS ADAMOPOULOS, STEFAN D. ANKER, ANGELO AURICCHIO, MICHAEL BÖHM, KENNETH DICKSTEIN, VOLKMAR FALK, GERASIMOS FILIPPATOS, CÂNDIDA FONSECA, MIGUEL ANGEL GOMEZ-SANCHEZ, TINY JAARSMA, LARS KØBER, **GREGORY Y.H. LIP, ALDO PIETRO MAGGIONI, ALEXANDER PARKHOMENKO, BURKERT**

M. PIESKE, BOGDAN A. POPESCU, PER K. RØNNEVIK, FRANS H. RUTTEN, JUERG SCHWITTER, PETAR SEFEROVIC, JANINA STEPINSKA, PEDRO T. TRINDADE, ADRIAAN A. VOORS, FAIEZ ZANNAD, ANDREAS ZEIHNER
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012
European Heart Journal (2012) 33, 1787–1847

- [25]. AGENCE NATIONALE DE SECURITE DU MEDICAMENT ET DES PRODUITS DE SANTE (ANSM).
Bon usage des médicaments antivitamin K (AVK)
Actualisation – Juillet 2012
- [26]. GILLES PERNOD, ANNE GODIER, CLAIRE GOZALO, BENJAMIN TREMEY, PIERRE SIE
French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding)
Thrombosis Research 126 (2010) e167–e174

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity,

integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be

enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

**NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY
TO PIERRE FABRE CORPORATE VIGILANCES DIVISION**

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION BY E-MAIL WITHIN 24H TO HQ.pharmacovigilance@pierre-fabre.com OR BY FAX WITHIN 24H – Fax N°: 33 (0) 1.49.10.80.90

Transmission date (ddmmyyyy) Country :
SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ **SUBJECT CHARACTERISTICS**

Gender	<input type="checkbox"/> 1=M, 2=F	Height	<input type="text"/> <input type="text"/> <input type="text"/> cm	Birth date	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Weight	<input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg
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➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) : 	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ MEASURES TAKEN FOLLOWING THE SAE

• Study treatment

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readadministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• The event led to :

- ☐ Prescription of corrective or symptomatic treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Discontinuation of concomitant treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Others, specify :

➤ OUTCOME

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)

Study drug: Related to study protocol:

☐ Not Suspected ☐ Suspected ☐ Not Suspected ☐ Suspected

Comments:

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(⊞)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(⊞) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		<ul style="list-style-type: none"> • < 1 500/mm³ whatever the baseline value
WBC (if missing value for neutrophils)		<ul style="list-style-type: none"> • < 3 000/mm³ whatever the baseline value
PLATELETS		<ul style="list-style-type: none"> • < 100 000/mm³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology :Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

***16.1.1.9. Protocol amendment n° PA06
General and non-substantial dated on 06 June 2016)***

**CLINICAL STUDY PROTOCOL AMENDMENT n° PA06
(GENERAL – Non Substantial)**

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

CLINICAL STUDY PROTOCOL AMENDMENT n° PA06

(GENERAL – Non-Substantial)

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code: F373280 CA 2 01

EudraCT Number or equivalent: 2012-003487-48

Sponsor's Representative: **Karim KEDDAD**
INSTITUT DE RECHERCHE PIERRE FABRE
Centre de R&D Pierre Fabre - BP 13562
3 avenue Hubert Curien
31035 TOULOUSE Cedex 1, FRANCE

Study Coordinating Investigator: **Pr 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
c/o Spedali Civili di Brescia
Piazzale Spedali Civili, 1
25123 - BRESCIA, ITALY

Date of amendment PA06: 06JUN2016

The information contained in this document is confidential and is the property of the sponsor Pierre Fabre Médicament. This information is given for the needs of the trial and must not be disclosed without prior written consent of the sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the trial must be informed that it is confidential and must be disclosed.

APPROVAL FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA06

(GENERAL – Non-Substantial)

Dated: 06JUN2016

Sponsor's representative(s)

• Head of Medical Unit

Date:

Signature:

Dr Karim KEDDAD


10 JUNE 2016



Study Coordinating Investigator:

Date: 20/06/2016 Signature:

Pr Savina NODARI



COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

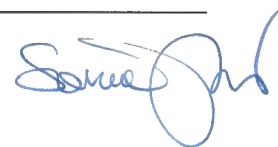
Clinical Study Protocol Amendment n° PA06

(GENERAL – Non-Substantial)

Dated: 06JUN2016

Country Coordinating Investigator:

Date: 20/06/2016 Signature:



INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA06

(GENERAL – Non-Substantial)

Dated: 06JUN2016

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA06 and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF AMENDMENTS

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
NA	NA	General	NA	<p><u>Corresponding to Protocol Version 2:</u></p> <p>Following French CA request (ANSM) and leading to protocol version 2:</p> <ul style="list-style-type: none"> - Add of a non inclusion criteria: "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6
PA01	Substantial	Local (Italy)	01MAR2013	<p><u>Corresponding to Protocol Version 3:</u></p> <ul style="list-style-type: none"> - Integration of the modification included in the protocol version 2 - Harmonisation of the protocol and the Informed Consent Form: <ul style="list-style-type: none"> • adjustment of the selection criteria n°10 related to the contraception method • addition of a letter that is given by the patient to his/her GENERAL practitioner (GP) • precision that the sponsor can not collect a copy of the Informed Consent Form • precision that the patient card is in Italian language only (without any English mention)
PA02	Non Substantial	General	28MAR2013	<p><u>Corresponding to Protocol Version 4 :</u></p> <ul style="list-style-type: none"> - change of Sponsor's Representative (Clinical Study Manager), - modification of the technical handling of the blood samples for determination of red blood cells concentration of DHA: the centrifugation is no more needed, - precision on the function and address of the International Study Coordinator Pr Nodari, - add of address and contacts details of two CRO newly involved in the study: Theradis (in charge of transportation of blood samples to the Analytical centre and material supply) and "Clinact" (in charge of refund of patients expenses linked to the study), - adjustment of the wording, in agreement with the commitment to the French Ethics Committee. In the paragraphe 8.3.2.1, the wording "hematology examination" is replaced by "standard hematologic dosage", - precision of the full title in the study synopsis (in agreement with the commitment to the Spanish Ethics Committee), - correction of a mistake in section 8.1.1.3 (related to TTEM transmission) and sections 3, 9 and study synopsis (related to the definition of INR not stabilized). - addition of the changes included in the local italian

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
				substantial protocol amendment (i.e: contraception method, letter to GENERAL Practitioner, patient card in Italian and no collection of the consent form by the sponsor in Italy).
PA03	Substantial	General	23OCT2013	<p><u>Corresponding to Protocol Version 5:</u></p> <ul style="list-style-type: none"> - Fax modification of the sponsor's representatives - Planned end of study postponed to January 2015. - The authorized history of the first documented persistent atrial fibrillation is less than 3 years. - At selection a hyperkalemia or a hypokalemia is better defined by the standards of the local laboratories. - Regarding previous treatments by amiodarone the non inclusion criteria of the protocol are adapted as follow: <ul style="list-style-type: none"> • Previous treatment with oral amiodarone within 4 months prior to inclusion • Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion • Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion. - For male with a child-bearing potential partner (in Italy only): taking into account the duration of spermatogenesis the absolute abstention from sexual intercourse or the use of double barrier contraception method are extended to 3 months after the end of the study. - Ranolazine is an antiarrhythmic treatment added to the prohibited treatments. - Update of Serious Adverse Events (SAEs) form: Main change is the SAE sending: SAEs have to be reported to the Corporate Vigilance Department, and not anymore to the clinical study manager. Also SAEs can be sent by e-mail and by fax. - Addition of Alpha Bioresearch as CRO involved for Feasibility, Monitoring and Regulatory issues in Spain. - Correction of some minor typographic errors
PA04	Non Substantial	General	03JUN2014	<p><u>Corresponding to protocol V7:</u></p> <ul style="list-style-type: none"> - Precision on the temperature storage of DHA samples - Precision on the BSA formula - Addition of QTcB and QTcF - Precision on TTEM recording timelines - Clarification of the section Interim analysis and data monitoring (13.11) - Clarifications and specifications on some

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
				minor points
PA05	Substantial	General	22OCT2014	<p><u>Corresponding to protocol V8:</u></p> <ul style="list-style-type: none"> - Planned end of study postponed to April 2016 - Clarifications regarding the management of VKA treatment - Precision regarding the primary efficacy criterion (the time to the first Atrial Fibrillation recurrence or Atrial Flutter emergence) - Deletion of Visit 5 and Visit 8 - Previous history of a first documented persistent Atrial Fibrillation without limitation in time instead of no longer than 3 years - Patients must have a systolic heart failure defined by a reduced ventricular ejection fraction and or defined also through other echocardiographic parameters mentioned in the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) - Regarding previous prohibited treatments by amiodarone or droderanone, the non inclusion criteria of the protocol are adapted as follow: <ul style="list-style-type: none"> • Concomitant treatment with oral amiodarone or dronedarone from selection • Concomitant treatment with intravenous amiodarone from selection

1. AMENDMENT RATIONALE

This amendment is written to update the Sponsor Personnel list following changes in the Clinical team and to extend the planned end date of the study:

- The previous Clinical Study Manager left the team: Gaëlle Alcaraz, and one new Clinical Study Manager has joined the team: Marine Fagard
- Dr Richard Roche (Medical Director) is replaced by Dr Karim Keddad (Head of medical Unit)
- Due to a recruitment rate lower than expected the planned end of study is postponed to September 2017.

2. CHANGES DESCRIPTION

PREVIOUS VERSION	MODIFIED VERSION
<i>Sponsor Personnel, page 2 & page 3</i> <u>Clinical Study Manager (Monitor)</u> Gaëlle ALCARAZ Institut de Recherche Pierre Fabre Centre de R&D Pierre Fabre BP 13 562 3, Avenue Hubert Curien 31035 TOULOUSE Cedex 1, France Phone: +33 5 34 50 62 16 Fax: + 33 5 34 50 69 69 E-mail: gaelle.alcaraz@pierre-fabre.com <i>Sponsor Personnel, page 2, page 3 & page 5</i> <u>Medical Director</u> Richard ROCHE, MD Institut de Recherche Pierre Fabre Centre de R&D Pierre Fabre BP 13 562 3, Avenue Hubert Curien 31035 TOULOUSE Cedex 1, France Phone: +33 5 34 50 61 94 Fax: +33 5 34 50 69 69	<u>Clinical Study Manager (Monitor)</u> <u>Marine FAGARD</u> Institut de Recherche Pierre Fabre Centre de R&D Pierre Fabre BP 13 562 3, Avenue Hubert Curien 31035 TOULOUSE Cedex 1, France Phone: +33 (0)5 34 50 63 54 Fax: +33 (0)5 34 50 65 92 E-mail: marine.fagard@pierre-fabre.com <u>Head of Medical Unit</u> <u>Karim KEDDAD, MD, PhD</u> Institut de Recherche Pierre Fabre Centre de R&D Pierre Fabre BP 13 562 3, Avenue Hubert Curien 31035 TOULOUSE Cedex 1, France Phone: +33 5 34 50 61 69 Fax: +33 (0)5 34 50 65 92

PREVIOUS VERSION	MODIFIED VERSION
<p>E-mail: richard.roche@pierre-fabre.com</p> <p><i>SYNOPSIS, page 13</i></p> <p>Planned Study Period: January 2013 – April 2016</p>	<p>E-mail: <u>karim.keddad@pierre-fabre.com</u></p> <p>Planned Study Period: January 2013 – September 2017</p>

***16.1.1.10. Protocol amendment n° PA07
General and substantial dated on 28 September 2016
linked to Protocol and appendices
(version 9: 28 September 2016)***

**CLINICAL STUDY PROTOCOL AMENDMENT n° PA07
(GENERAL –SUBSTANTIAL)**

Pierre Fabre Médicament
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CLINICAL STUDY PROTOCOL AMENDMENT n° PA07
(GENERAL – SUBSTANTIAL)

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

Pierre Fabre Study Code: F373280 CA 2 01

EudraCT Number or equivalent: 2012-003487-48

Sponsor's Representative: **Karim KEDDAD**
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Date of amendment PA07: 28SEP16

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APPROVAL FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA07

(GENERAL – SUBSTANTIAL)

Dated: 28SEP16

Sponsor's representative(s)

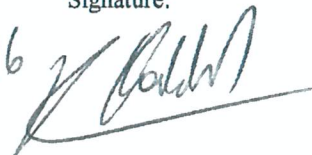
• Head of Medical Unit

Dr Karim KEDDAD

Date:

29/09/2016

Signature:



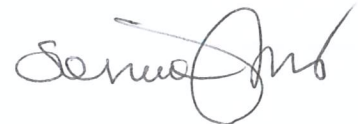
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Pr Savina NODARI

Date:

10/10/2016

Signature:



COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

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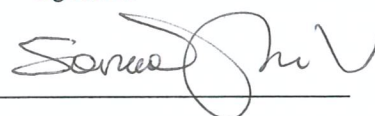
Dated: 28SEP16

Country Coordinating Investigator:

Date:

Signature:

10/10/2016



INVESTIGATOR SIGNATURE FORM

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.

International, multicentric, randomised, double-blind, placebo controlled study

Clinical Study Protocol Amendment n° PA07

(GENERAL –SUBSTANTIAL)

Dated: 28SEP16

By my signature below, I, Dr _____, hereby confirm that I have read, taken note of (and will apply) the modifications brought by the protocol amendment n° PA07 and I will conduct the trial according to these new modalities.

Date:

Signature:

HISTORY OF AMENDMENTS

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
NA	NA	General	NA	<p><u>Corresponding to Protocol Version 2:</u></p> <p>Following French CA request (ANSM) and leading to protocol version 2:</p> <ul style="list-style-type: none"> - Add of a non inclusion criteria: "Breast-feeding female patient" - Add of haematology examination at visit 3 and 6
PA01	Substantial	Local (Italy)	01MAR2013	<p><u>Corresponding to Protocol Version 3:</u></p> <ul style="list-style-type: none"> - Integration of the modification included in the protocol version 2 - Harmonisation of the protocol and the Informed Consent Form: <ul style="list-style-type: none"> • adjustment of the selection criteria n°10 related to the contraception method • addition of a letter that is given by the patient to his/her GENERAL practitioner (GP) • precision that the sponsor can not collect a copy of the Informed Consent Form • precision that the patient card is in Italian language only (without any English mention)
PA02	Non Substantial	General	28MAR2013	<p><u>Corresponding to Protocol Version 4 :</u></p> <ul style="list-style-type: none"> - change of Sponsor's Representative (Clinical Study Manager), - modification of the technical handling of the blood samples for determination of red blood cells concentration of DHA: the centrifugation is no more needed, - precision on the function and address of the International Study Coordinator Pr Nodari, - add of address and contacts details of two CRO newly involved in the study: Theradis (in charge of transportation of blood samples to the Analytical centre and material supply) and "Clinact" (in charge of refund of patients expenses linked to the study), - adjustment of the wording, in agreement with the commitment to the French Ethics Committee. In the paragraphe 8.3.2.1, the wording "hematology examination" is replaced by "standard hematologic dosage", - precision of the full title in the study synopsis (in agreement with the commitment to the Spanish Ethics Committee), - correction of a mistake in section 8.1.1.3 (related to TTEM transmission) and sections 3, 9 and study synopsis (related to the definition of INR not stabilized). - addition of the changes included in the local italian

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
				substantial protocol amendment (i.e: contraception method, letter to GENERAL Practionner, patient card in Italian and no collection of the consent form by the sponsor in Italy).
PA03	Substantial	General	23OCT2013	<p><u>Corresponding to Protocol Version 5:</u></p> <ul style="list-style-type: none"> - Fax modification of the sponsor's representatives - Planned end of study postponed to January 2015. - The authorized history of the first documented persistent atrial fibrillation is less than 3 years. - At selection a hyperkalemia or a hypokalemia is better defined by the standards of the local laboratories. - Regarding previous treatments by amiodarone the non inclusion criteria of the protocol are adapted as follow: <ul style="list-style-type: none"> • Previous treatment with oral amiodarone within 4 months prior to inclusion • Intake of oral amiodarone for more than 1 month within 4 to 12 months before inclusion • Previous treatment with intravenous amiodarone within 4 weeks prior to inclusion. - For male with a child-bearing potential partner (in Italy only): taking into account the duration of spermatogenesis the absolute abstention from sexual intercourse or the use of double barrier contraception method are extended to 3 months after the end of the study. - Ranolazine is an antiarrhythmic treatment added to the prohibited treatments. - Update of Serious Adverse Events (SAEs) form: Main change is the SAE sending: SAEs have to be reported to the Corporate Vigilance Department, and not anymore to the clinical study manager. Also SAEs can be sent by e-mail and by fax. - Addition of Alpha Bioresearch as CRO involved for Feasibility, Monitoring and Regulatory issues in Spain. - Correction of some minor typographic errors
PA04	Non Substantial	General	03JUN2014	<p><u>Corresponding to protocol V7:</u></p> <ul style="list-style-type: none"> - Precision on the temperature storage of DHA samples - Precision on the BSA formula - Addition of QTcB and QTcF - Precision on TTEM recording timelines - Clarification of the section Interim analysis and data monitoring (13.11) - Clarifications and specifications on some

N°	TYPE	APPLICATION AREA	DATE	MODIFICATIONS
				minor points
PA05	Substantial	General	22OCT2014	<p><u>Corresponding to protocol V8:</u></p> <ul style="list-style-type: none"> - Planned end of study postponed to April 2016 - Clarifications regarding the management of VKA treatment - Precision regarding the primary efficacy criterion (the time to the first Atrial Fibrillation recurrence or Atrial Flutter emergence) - Deletion of Visit 5 and Visit 8 - Previous history of a first documented persistent Atrial Fibrillation without limitation in time instead of no longer than 3 years - Patients must have a systolic heart failure defined by a reduced ventricular ejection fraction and or defined also through other echocardiographic parameters mentioned in the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) - Regarding previous prohibited treatments by amiodarone or droderanone, the non inclusion criteria of the protocol are adapted as follow: <ul style="list-style-type: none"> • Concomitant treatment with oral amiodarone or dronedarone from selection • Concomitant treatment with intravenous amiodarone from selection
PA06	Non substantial	General	06JUN2016	<p><u>Corresponding to protocol V8</u></p> <ul style="list-style-type: none"> - Change of sponsor Clinical Study Manager and Clinical Development Physician - Planned end of study postponed to September 2017

1. AMENDMENT RATIONALE

The F373280 CA 201 planned initially to recruit 152 patients over 6 months across 50 sites in Europe.

Since May 2013, only 134 patients have been randomised and 1 patient is currently enrolled. Due to very slow recruitment over more than 3 years, and, in the absence of any possibility to plan a reliable date for completion of recruitment, the Sponsor has decided to stop the recruitment of patients as of September 23, 2016. This population of maximum 135 randomised patients will be taken into account for efficacy and safety analyses. Despite the loss of power, statistical analyses planned in the protocol are maintained.

There is no unexpected safety signal on the current population, therefore, enrolled patients may continue receiving treatment and participate in the study, as planned by the protocol.

In this context, the purpose of this amendment is limited to the change of the number of patients, the number of IDMC meetings and the planned study period.

This change does apply to all relevant sections of the protocol. Furthermore, all enrolled patients will be informed of this change of recruited patient number.

2. CHANGES DESCRIPTION

PREVIOUS VERSION	MODIFIED VERSION
<p>Synopsis Planned Study Period: January 2013 – September 2017 (according to amendment PA06) Number of Patients: 76 x 2 patients</p> <p>13.11 INTERIM ANALYSIS AND DATA MONITORING The IDMC will review, three times during the study period (after the first 30 subjects will have been randomized, when the first 80 subjects will have terminated their study participation and when 130 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.</p>	<p>Synopsis Planned Study Period: January 2013 – April 2017 Number of Patients: maximum 135 patients</p> <p>13.11 INTERIM ANALYSIS AND DATA MONITORING The IDMC will review, two times during the study period (after the first 30 subjects will have been randomized and when the first 80 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.</p>

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

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Version 9 – 28SEP2016

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Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 9 – 28SEP2016

Sponsor's Representative:

Head of Medical Unit:

Karim KEDDAD, MD, PhD

Date:

29/09/2016

Signature:



Study Coordinating Investigator:

Savina NODARI, MD

Date:

10/10/2016

Signature:



<p>Protocol F 373280 CA 2 01</p> <p>COUNTRY COORDINATING INVESTIGATOR</p> <p>SIGNATURE FORM</p> <p>Protocol Version 9 – 28SEP2016</p>

Country:ITALY.....

Country Coordinating Investigator:

"Name"
SAVINA NODARI

10/10/2016
Date:


Signature:

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 9 – 28SEP2016

By my signature below, I, Dr / Pr "

", hereby confirm that I agree:

- ♦ to conduct the trial described in the protocol F 373280 CA 2 01, dated 28SEP2016 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- ♦ to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- ♦ to comply with the procedure for data recording and reporting;
- ♦ to allow monitoring, auditing and inspection;
- ♦ to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- ♦ to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- ♦ to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- ♦ that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

Signature:

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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PolyUnsaturated Fatty Acid (PUFA) has been proven in the following conditions:</p> <ul style="list-style-type: none"> - prevention of AF recurrence in patients with persistent AF, in co-administration with amiodarone (add on therapy) [2] - Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2017	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> - Ideally INR 2-3 (vitamin K antagonist should be given at least 3 weeks before ECV) - No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: 	

	<ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms. <p>- Treatment duration: 24 weeks</p>
Study Schedule:	<p>7 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of study treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter device) - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V6/ W12* (D84 ± 7 days): follow-up visit <p>*see amendment PA05 dated 22OCT2014</p> <ul style="list-style-type: none"> - V7/ W16 (D112 ± 7 days): follow-up visit - V9/ W24* (D168 ± 7 days): final study visit <p>*see amendment PA05 dated 22OCT2014</p>
Number of Patients:	Maximum 135 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive) 2. Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. Previous history of first documented episode of persistent AF. 4. Previous history of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ or for patients with a LVEF $> 45\%$: <ul style="list-style-type: none"> • 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 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area ≤ 40 cm² at selection and at inclusion 9. Patients treated or having to be treated by vitamin K antagonist 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> • In all the countries except Italy: <ul style="list-style-type: none"> - Use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - Documented as surgically sterilized • In Italy only: <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - Use of double barrier contraception method (use of effective medical contraception

	<p>method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or</p> <ul style="list-style-type: none"> - Documented as surgically sterilized <p>11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion</p> <p>12. For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study. <p><i>Ethical / legal considerations:</i></p> <p>13. Having signed his/her written informed consent,</p> <p>14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation)</p> <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. No previous history of first documented episode of persistent AF 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 ml/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, betablockers, calcium-blockers 13. Concomitant treatment with oral amiodarone or dronedarone from selection 14. Concomitant treatment with intravenous amiodarone from selection 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω 3 or ω 6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible
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	<p>antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel</p> <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study.</p> <p>However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study.</p> <p>If necessary, for meeting these INR conditions, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280 Soft Capsules
Dose:	Arm with 1g of F373280
Mode of Administration:	Oral, one capsule each evening with dinner.
Duration of Treatment:	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Reference Therapy	Placebo soft capsules Placebo will be administered in the same conditions as the tested product.
Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation 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). <p>Handling of AF recurrences or atrial flutter emergences: 7-day continuous 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 will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24).</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5). Moreover, during this TTEM period, if patient experiences any AF or atrial flutter symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG (Holter and TTEM) will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p> <p>During the 7-day continuous ECG monitoring,</p>

	<ul style="list-style-type: none"> • Numbers of AF episodes • Duration of AF episodes <p><u>Clinical parameters:</u></p> <p>During the whole study:</p> <ul style="list-style-type: none"> • Number of recurrence of symptomatic AF episodes • EHRA score • Hospitalization for cardiovascular events • Hospitalization for thromboembolic stroke • All causes of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> • Assessment of spontaneous cardioversion • Assessment of successful cardioversion • Shocks distribution (1, 2 or 3 shocks) • Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> • Evolution of echocardiographic parameters (at V4, V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (ml), Left atrial volume/BSA (ml/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (ml/m²), Left ventricular end systolic volume/BSA(ml/m²), 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> • Adverse events (observed and / or spontaneously reported) • Vital signs (Blood pressure (supine and standing), heart rate) • Physical examination (body weight, body surface area) • Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns (ECG not centralized) • Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets • Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) • Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (<i>PT</i>). <p>Concomitant treatments</p> <p>Compliance</p>
Statistical Methods:	<p>Sample Size:</p> <p>Assuming an AF recurrence or atrial flutter emergence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis</p>

	<p>The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses</p> <p>All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses</p> <p>Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment).</p>
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STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4		V6	V7		V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)		W12 (84+/-7D)	W16 (112+/-7D)		W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR					X			X	(2)
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Haematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment number allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration									
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	(4)			(5)					
TTEM (6)									

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of VKA introduction: INR 2 to 3 times a week until stabilization, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms.
TTEM once a week even in case of AF recurrence or atrial flutter emergence for at least 10 minutes.

LIST OF ABBREVIATIONS

aPTT	: Activated partial thromboplastin time
AE	: Adverse event
AF	: Atrial fibrillation
ALA	: Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body Surface Area
CEP	: Protocol evaluation committee
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	: Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	: Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	: Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	: Transesophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	: European heart rhythm association
EPA	: Eicosapentaenoic acid
e-CRF	: Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate
HBs	: Hepatitis B antigen
HCV	: Hepatitis C virus
HDL	: High density lipoprotein

HF	:	Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR	:	International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS	:	Interactive voice response system
LAA	:	Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL	:	Low density lipoprotein
LOQ	:	Limit of quantification
LVEF	:	Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR	:	Mineralocorticoid receptor
MR perfusion	:	Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA	:	New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
PSC	:	Potentially Clinically Significant Change
PSCV	:	Potentially Clinically Significant Value
PUFA	:	PolyUnsaturated fatty acid
p.o.	:	Per os
PP	:	Per protocol data set
QTcB	:	QT interval using Bazett’s correction formula
QTcF	:	QT interval using Fridericia’s correction formula
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT	:	Thrombin clotting time
TEAEs	:	Treatment emergent adverse events
TTEM	:	TransTelephonic ECG monitoring
VKA	:	Vitamin K Antagonist
WBC	:	White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of AF in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the Polyunsaturated Fatty Acids (PUFAs) constitute one emerging antiarrhythmic therapy. These compounds potentially address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or AF.

The potential anti-arrhythmic effects of a PUFA were previously developed in AF: nicotinyl ester of DHA (pro-drug based on DHA delivery) was assessed in a two-week ventricular tachypaced

canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of AF induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll [2] assessed n-3 PUFAs in the prevention of AF recurrences after electrical cardioversion (ECV). All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct ECV 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFAs on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than in the placebo group at 1 month (3.3% vs 10%; $p = 0.043$), at 3 months (10% vs 25%; $p = 0.004$) and at 6 months (13.3% vs 40%; $p < 0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effects of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs (n=67) or placebo (n=66) at a dosage

of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 ± 0.33 to 1.61 ± 0.49 and increased from 1.83 ± 0.38 to 2.14 ± 0.65 , respectively).

The hospitalization rates for patients with HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and $\text{LVEF} < 35\%$). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA ($n = 14$), 4 g/d n3-PUFA ($n = 13$), or placebo ($n = 16$)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($p = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: $24\% \pm 7\%$ vs $29\% \pm 8\%$, $p = 0.005$) and 1 g/d treatment groups ($24\% \pm 8\%$ vs $27\% \pm 8\%$, $p = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent AF and heart failure in the maintenance of sinus rhythm after ECV.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of AF.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

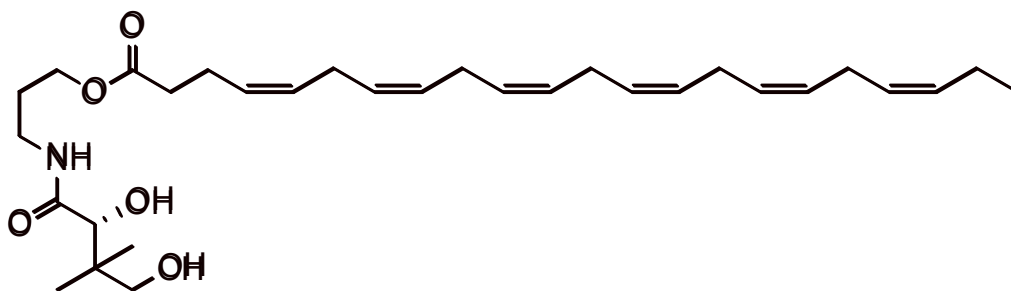
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. Pharmacological profile

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased atrial effective refractory period (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $p < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the electrocardiogram (ECG) intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing-induced congestive heart failure provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses congestive heart failure-induced AF-promotion and fibrosis in the ventricular tachypacing canine model. Nicotinyl ester of DHA was tested in this model, at 1 g/day and 5 g/day, during 4 weeks, to prevent congestive heart failure-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in AF duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1 g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5 g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280 similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 mg/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies, no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: Single dose

Six consecutive single ascending doses were tested (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events (SAE) occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of

an alternative explanation, 3 TEAEs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotension without loss of consciousness) and 4 in the group of F373280 at the dosage of 16 g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events (AE) were reported in the groups of F373280 at the dosages of 0.5 g, 1 g, 2 g, 4 g and 8 g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5 g to 16 g in 36 young healthy male subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16 g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1 g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding Pharmacokinetics parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16 g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple doses

Three consecutive repeated ascending doses (1, 2 and 4 g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280, 5/9 TEAEs were classified according the System Organ Class in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAEs have already been reported with PUFAs and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** C_{max} and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after ECV in persistent AF patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing [1].

Moreover, the effectiveness of PUFAs has been proven in the following conditions:

- Prevention of AF recurrence in patients with persistent AF in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent AF and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after ECV in patients with persistent AF and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1 g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor® [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations:
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:

Very rare: nasal dryness

- Gastrointestinal disorders:

Common: dyspepsia, nausea

Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper

Rare: gastrointestinal pain

Very rare: lower gastrointestinal haemorrhage

- Hepatobiliary disorders:

Rare: hepatic disorders

- Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

- General disorders and administration site conditions:

Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1 g and 4 g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after

administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in AF studies [2, 8]. The range of PUFAs doses tested was between 2 g to 3 g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in HF patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1 g to 5 g (1 g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent form. A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on AF and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of AF and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (vitamin K antagonist, VKA), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence or atrial flutter emergence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication
- Anticoagulation with vitamin K antagonist (VKA) for at least 3 weeks before ECV
- ECV will be performed in patients with AF and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last

tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Patients who do not revert to sinus rhythm or present an early AF relapse or an early atrial flutter emergence within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be performed throughout the study period. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored once a week between visits using Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 152 patients suffering from persistent AF and chronic heart failure.

After a 1 to 4-week of run-in period without study treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Seven visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of study treatment)
- Visit 3 (V3): W4 (D28-2/+7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)

- Visit 4 (V4): W5 (D35 -2/+7D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 6* (V6): W12 (D84 ± 7D): follow-up visit
*see amendment PA05 dated 22OCT2014
- Visit 7 (V7): W16 (D112 ± 7D) : follow-up visit
- Visit 9* (V9): W24 (D168 ± 7D): final study visit
*see amendment PA05 dated 22OCT2014

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent AF and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent AF with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- Previous history of persistent AF with duration of the current episode from 7 days to 6 months.
- A systolic heart failure defined by a reduced left ventricular ejection fraction ($\geq 30\%$ and $\leq 45\%$) 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 [23, 24].

According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.

- A Left Atrial Area (LAA) not severely abnormal (no greater than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline) [23]. According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of ECV, patients should have a stable medical treatment of heart failure and should not have any myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on antiarrhythmics in AF (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, antiarrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF (or emergence of atrial flutter) since cardioversion.

To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) of 2 to 3 before ECV. According to guidelines for the management of AF [6], VKA should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodari's study [2], the duration of pre-treatment with PUFAs before cardioversion appears to be a contributing factor in success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of AF recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of AF recurrences occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using an easier device to carry and to use, i.e. a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every 4 weeks or 8 weeks (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with AF [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of AF after cardioversion. Moreover, PUFAs at dosage of 1 g and 2 g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1 g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95 mg/ml and 60 to 90 mg/ml, respectively) (phase I study of F373280 and [16]). With regard to the rhythm of administration, mean peak/trough

fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a 1 g daily dose of F373280 is considered to be appropriate for this proof of concept study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive)
2. Patient with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted
3. Previous history of first documented episode of persistent AF
4. Previous history of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ 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
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers

8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by vitamin K antagonist
10. For female patient of child-bearing potential:
 - **In all the countries except Italy:**
 - Use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - Documented as surgically sterilized
 - **In Italy only:**
 - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - Use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - Documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or
 - Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,

14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation)

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. No previous history of first documented episode of persistent Atrial Fibrillation
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 ml/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, beta-blockers, calcium-blockers.
13. Concomitant treatment with oral amiodarone or dronedarone from selection
14. Concomitant treatment with intravenous amiodarone from selection
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months

16. Treatment with any Polyunsaturated Fatty Acid within the last 3 months
17. Dietary supplement with $\omega 3$ or $\omega 6$ according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

76 x 2 patients (taking into account 15 % of non evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENT IDENTIFICATION

Patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

Reasons for a patient's premature withdrawal from the study may be the following:

- Patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- Investigator's decision in the patient's interest, particularly if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.
- Erroneous inclusion according to the study protocol. The decision to maintain or not the patient in the study will be taken jointly by the investigator and the sponsor. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with VKA for at least 3 weeks before ECV or who will experience a VKA intolerance during the study.
- Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal

echocardiography) performed on the same day (before ECV) and the patient can continue the study.

- Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be considered to have finished follow-up.
- Occurrence of AF recurrence or atrial flutter emergence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate in another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit:

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.
- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the Institut de Recherche Pierre Fabre (IRPF) will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- **F373280**

Formulation of F373280, 1 g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- **Placebo**

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the IRPF according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

Two 12-week treatment units will contain 3 cases, each case of 4-week treatment containing: 10 blister packs of four 1 g F373280 soft capsules or 1 g placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number
- c) packaging batch number
- d) treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:

-“for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”

On the treatment unit, another label will be affixed with the mention of the Investigator’s name and patient’s code (completed by the Investigator).

In addition, on each case will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the IRPF will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient’s selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion visit (V2) and another one at visit 6.

For each patient, the treatment number given at visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

At selection visit (V1), practically, once patient's eligibility is confirmed:

- The Investigator:
 - Contacts the IVRS/IWRS

- Answers the questions related to the patient
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

At inclusion visit (V2), the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.

At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment.

The Investigator will dispense to the patient the 4-week treatment cases (one or two according to the visit) which label indicates the treatment number and the administration period.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure to F373280 or placebo will be 24 weeks.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator in collaboration with the Sponsor's representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (at selection visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the electronic Case Report Forms (e-CRF). All treatments should be evaluated by the Investigator at patient's selection, and treatment prolongation or stop during the study should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. VITAMIN K ANTAGONIST TREATMENT

VKA should be given for at least 3 weeks before ECV and continued for the whole study duration. However, VKA should be stopped in case of occurrence of VKA intolerance during the study and the patient should be withdrawn from the study. The VKA used will be left to the decision of each Investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:

- Class I:
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
- Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.

- Ranolazine

- Any PUFA

- Any oral anticoagulant treatment other than VKA: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or irreversible antiplatelet agents P2Y₁₂ inhibitors such as ticlopidine, clopidogrel or prasugrel

- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the e-CRF. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION

8.1.1. Time to the first Atrial Fibrillation Recurrence or Atrial Flutter Emergence

8.1.1.1. *Definition*

Time to first AF recurrence or atrial flutter emergence is defined by the time to first episode of AF or atrial flutter (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring, the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM).

- Trans Telephonic ECG Monitoring:

The ECG follow up will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM.

Moreover, if patient experiences AF or atrial flutter symptoms during this TTEM period, it should be documented using the TTEM.

In case of AF recurrence or atrial flutter emergence and provided that the patient does not require a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

- Process of centralisation of ECG (Holter and TTEM)

ECG (Holter and TTEM) will be centralized by the Central Reading Laboratory. The ECG will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be emailed to the site (or per fax on request of the site). The investigator will be asked to review and sign these documents.

The Holter and TTEM process will be fully described in separate documents.

8.2. SECONDARY EFFICACY CRITERIA

8.2.1. Numbers of AF episodes in the first week following visit 3 (ECV visit)

8.2.1.1. Definition

Number of AF episodes will consist in the assessment of AF episodes with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the study visit 4.

8.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.2.2. Duration of AF episodes in the first week following visit 3 (ECV visit)

8.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episode.

8.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the follow up study visit (visit 4).

8.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.2.3. Clinical parameters evaluation

8.2.3.1. *EHRA score assessment*

8.2.3.1.1. *Definition*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily.

8.2.3.1.2. *Schedule*

EHRA evaluation will be performed in case of evocative symptoms of arrhythmia.

8.2.3.1.3. *Evaluation Methods*

EHRA evaluation will be collected by Central Reading Laboratory during TTEM period.

8.2.3.2. *Time to first AF recurrence less than 10 minutes*

Time to first AF recurrence less than 10 minutes will be assessed during TTEM period.

8.2.3.3. *Recurrence of symptomatic AF*

Recurrence of symptomatic AF will be assessed during TTEM period.

The number of recurrences of symptomatic AF consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.

The time to first symptomatic AF recurrence is defined by the time to first episode of symptomatic AF.

8.2.3.4. *Number and duration of hospitalizations*

- Number and duration of hospitalizations for cardiovascular events
 - Hospitalization for AF treatment

- Hospitalization for worsening of heart failure
- Hospitalization for myocardial infarction
- All cause of hospitalization
- Number and duration of hospitalizations for thromboembolic stroke

8.2.4. Cardioversion assessment

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shocks distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.2.5. Evolution of echocardiographic parameters

8.2.5.1. Definition

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (ml), Left atrial volume/BSA (ml/m²), LVEF (%), Left ventricular end diastolic volume/BSA (ml/m²), Left ventricular end systolic volume/BSA (ml/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (ml), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (ml).

8.2.5.2. Schedule

Measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

Measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.2.5.3. Evaluation method

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European

Association of Echocardiography [23]. So, the recommended method for volume measurements is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.3. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.3.1. Definition

Because of the limited human tissue accessibility for biopsy, red blood cell DHA contents is a marker of tissue DHA concentration [13], [14].

8.3.2. Blood samples

8.3.2.1. *Collection schedule*

Blood samples will be collected to determine the red blood cells (RBC) concentrations of DHA.

Blood samples will be performed at visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the e-CRFs.

8.3.2.2. *Technical handling*

Two blood samples (2 x 4 ml) will be collected in EDTA tubes. They will be homogenized slowly by inverting the tube without shaking, stored between +2°C/+8°C in a fridge (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.3.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent)

and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock) in a separate file.

8.4. SAFETY ASSESSMENT

8.4.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of AEs since the last visit will be based on the patient's spontaneous reporting, the Investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.4.2. Laboratory Investigations

8.4.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kalemia will be checked before electrical cardioversion at visit 3.

The total volume of blood samples taken for haematology and biochemistry analysis should not exceed 30 ml.

8.4.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *haematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and/or absolute), reticulocytes, platelets.*

Biochemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula:

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})]$$

in women:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})] \times 0.85$$

- with serum creatinine expressed as $\mu\text{mol/l}$:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / \text{serum creatinine in } \mu\text{mol/l}] \times k, \text{ where } k = 1.23 \text{ for men, } 1.04 \text{ for women.}$$

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.

8.4.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9.

The Body surface area (BSA) will be calculated at the same visits using Mostellers' formula:

$$BSA = [(Weight \times Height)/3600]^{1/2}$$

(Weight in kg, height in cm)

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.4.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.4.4.1. *Schedule*

Vital signs will be measured at each visit.

8.4.4.2. *Technical Procedure and Parameters*

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation by counting the beats for at least 30 seconds, after at least 5 minutes in supine position and after 2 minutes in standing position.

Bodyweight will be measured with patient in underwear and with the same balance at each visit.

8.4.5. Electrocardiogram (ECG)

8.4.5.1. *Schedule*

An ECG will be recorded after at least 10 minutes of rest at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9 using a usual standardised 12-lead cardiograph.

8.4.5.2. *Technical Procedure and Parameters*

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns will be reported in the

e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent AF.

8.4.6. Coagulation parameters

Coagulation assessment will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

The recommendations for the controls of INR are the following [25, 26]:

1) During the pre-cardioversion period, if the anticoagulation by VKA has to be initiated, the treatment must be initiated at least 3 weeks prior to cardioversion then the INR will be monitored as follow:

- The adjustment of the dosage of VKA should be performed stepwise by controlling INR 2 to 3 times a week until stabilization within the target range (2 - 3) on 2 successive tests.
- When the INR is within the target range (2 - 3) on 2 successive tests, the dose of VKA should be maintained. Then the controls of INR will be progressively spaced within a few weeks.
- When INR is stabilized, at least one test should be performed each week.
- In all cases, an INR control must be performed within 24 h before ECV.

2) During the pre-cardioversion period, if the anticoagulation by VKA was already initiated, the INR will be monitored as follow:

- One INR per week up to ECV
- An INR control must be performed within 24 h before ECV

3) After cardioversion : one INR every 4 weeks

4) Throughout the duration of the study if INR > 3 the advocated actions are:

- No transesophageal echocardiography before cardioversion
- For asymptomatic patients:
 - $3 < \text{INR} < 4$: no omission of VKA (dose adjustment if required), no vitamin K
 - $4 \leq \text{INR} < 6$: omit one dose of VKA, no vitamin K
 - $6 \leq \text{INR} < 10$: interrupt VKA, vitamin K 2 mg orally
 - $\text{INR} \geq 10$: interrupt VKA, vitamin K 5 mg orally

For $\text{INR} \geq 6$, an adverse event has to be reported (asymptomatic overdose).

Anti-coagulation by VKA should be given at least 3 weeks before ECV and continued for the whole study duration.

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9.

The quantity of blood samples collected at each time for coagulation parameters will be 2 ml.

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.

8.5. CONCOMITANT TREATMENTS

Concomitant treatments will be evaluated at each study visit.

Requirements related to patient's concomitant treatments started before selection visit and continued throughout the trial, or started during the trial, can be found in section 7.

8.6. COMPLIANCE

The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.

At each visit (except at visit 4), the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week - 4 to Week -1):

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If the patient accepts to participate in the study, he/she will sign the informed consent form and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and AF characteristics
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria:

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory. The Central Reading Laboratory will send his/her assessment regarding the confirmation of persistent AF within 2 working days to the Investigator.

- The patient will enter the selection and pre-cardioversion periods in which anticoagulant (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) in the range of 2 to 3 before ECV.

At the end of the visit, the Investigator will contact the IVRS/IWRS to confirm the patient selection (which will automatically order the treatment delivery) and organise the appointment for the next visit.

The patient will receive from the investigational centre the participant card to be kept for all the duration of the study.

Visit 2 - Inclusion Visit (Day 1):

If the patient's behaviour during the selection period and/or the result of complementary examinations, particularly the confirmation of the presence of persistent AF by the Central Reading Laboratory during this period and the laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 2 for the first 12-week period.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.4.6) in order to fulfil the ECV conditions (refer to paragraph 3).

At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period (one case of treatment).

Visit 3 (Week 4: D28 -2/+7 days) cardioversion:

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, RBC concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be performed 4 weeks after randomization in patients with AF. ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge.

Patients who will not revert to sinus rhythm or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 8-week period (two cases of treatment).

Visit 4 (Week 5: D35 -2/+7 days):

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of AE
- Concomitant treatments (authorised, disallowed)
- Bodyweight (bodyweight measured at V3 to be used)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to perform one transmission per week from this visit (initial call to perform with the patient) to the visit 9 (week 24 – end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.

Visit 6* (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) :

*see amendment PA05 dated 22OCT2014

Patient will be assessed for the following criteria:

- Adverse events

- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV due to occurrence of VKA intolerance, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using the TTEM device through one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

In addition, at visit 6:

- the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period.
- an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.

At the end of each visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next treatment period: one case at visit 6 and two cases at visit 7.

Visit 9* - End-of-Study Visit (Week 24: D168 ± 7 days):

*see amendment PA05 dated 22OCT2014

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight

- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT), Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.

The total volume of blood collected should be about 90 ml for the study duration (30 ml for the total volume of haematology and biochemistry, 2 ml for each blood samples for coagulations parameters and 4 ml for each blood samples of DHA).

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An AE is any adverse change from the patient's baseline condition, i.e. any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

AE includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

10.1.3. Reporting of Adverse Events

The records of AE in the e-CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A SAE includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect

Other events such as cancer and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure
- preparation for routine health assessment/procedure (e.g. routine colonoscopy)
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required)
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by FAX at the following number:

+ 33 1 49 10 80 90

In case of non-inclusion, the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial, an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose and associated adverse event if any, are reported only on the Adverse Event page of the e-CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must also be transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the Sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and must be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is withdrawn from the study.

The Investigator must report to the Sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The Investigator must immediately notify the Sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the Investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the Sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING

PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An e-CRF will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files that will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and should include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF. Training sessions will be held by the subcontractor for all participants using this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRFs (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. Follow-up Visits

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of primary end point measures, the safety data. The IDMC will thereafter recommend to the Sponsor whether to continue, modify, or stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on the e-CRFs.

The e-CRFs used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate the coding.

12.4. DATA STORAGE

Computer data files as well as their modifications will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e. data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by PFB or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence or atrial flutter emergence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients

per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 3 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety.
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol

deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence of AF or atrial flutter emergence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes in the first week following V3

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes in the first week following V3

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAEs
- With at least three TEAEs
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.

Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:

- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity
- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TEAE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patients).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

SAE will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

CNALV (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and HR in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. Individual Patient Changes

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) minus number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days ± 7days)

13.11. INTERIM ANALYSIS AND DATA MONITORING

No analyses of efficacy data are planned for IDMC that ensures that the overall probability of type I error is controlled. No Type I error and sample size adjustments are necessary. Any recommendations of the IDMC to alter study conduct will be based on safety, so IDMC monitoring of the study will not affect the statistical operating characteristics of the final analysis.

The IDMC will review, two times during the study period (after the first 30 subjects will have been randomized and when the first 80 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor Pierre Fabre Médicament, has an insurance policy intended to guarantee against possible damage resulting from the research. The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Médicament are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities.

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not.

- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents.
- Authorises direct access to source documents for monitoring, audits and inspections.
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. Early Study Termination Decided by the Competent Authorities

The Competent Authorities may suspend or prohibit a study if they consider that either the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both its representatives (Study Manager, CRA...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at Pierre Fabre Médicament and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed in writing with the Study Manager, the Investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the Sponsor's responsibility.

Upon data analysis completion, a final report including a review of the objectives and methods, a presentation and a discussion of the results is drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the Investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow the use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The Investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) Investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all Investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1]. **F373280 INVESTIGATOR'S BROCHURE**, version October 2013
- [2]. NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3]. NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57;870-879
- [4]. MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5]. GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6]. CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7]. KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8]. BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9]. **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10]. **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11]. TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedarone for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12]. LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13]. **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14]. **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15]. **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16]. SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.
- [17]. LEGRAND P., SCHMITT B., MOUROT J., CATHELINE D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.

The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human.

Lipids, 2010, 45, 11-19.

- [18]. HARRIS WS, VON SCHACKY C.
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19]. ABSTRACT: P5161.
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M, DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20]. **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21]. **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22]. **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23]. ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108
- [24]. JOHN J.V. McMURRAY, STAMATIS ADAMOPOULOS, STEFAN D. ANKER, ANGELO AURICCHIO, MICHAEL BÖHM, KENNETH DICKSTEIN, VOLKMAR FALK, GERASIMOS FILIPPATOS, CÂNDIDA FONSECA, MIGUEL ANGEL GOMEZ-SANCHEZ, TINY JAARSMA, LARS KØBER, **GREGORY Y.H. LIP, ALDO PIETRO MAGGIONI, ALEXANDER PARKHOMENKO, BURKERT**

M. PIESKE, BOGDAN A. POPESCU, PER K. RØNNEVIK, FRANS H. RUTTEN, JUERG SCHWITTER, PETAR SEFEROVIC, JANINA STEPINSKA, PEDRO T. TRINDADE, ADRIAAN A. VOORS, FAIEZ ZANNAD, ANDREAS ZEIHNER
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012
European Heart Journal (2012) 33, 1787–1847

- [25]. AGENCE NATIONALE DE SECURITE DU MEDICAMENT ET DES PRODUITS DE SANTE (ANSM).
Bon usage des médicaments antivitamine K (AVK)
Actualisation – Juillet 2012
- [26]. GILLES PERNOD, ANNE GODIER, CLAIRE GOZALO, BENJAMIN TREMEY, PIERRE SIE
French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding)
Thrombosis Research 126 (2010) e167–e174

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity,

integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be

enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY
TO PIERRE FABRE CORPORATE VIGILANCES DIVISION

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION BY E-MAIL WITHIN 24H TO HQ.pharmacovigilance@pierre-fabre.com OR BY FAX WITHIN 24H – Fax N°: 33 (0) 1.49.10.80.90

Transmission date (ddmmyyyy) Country :
SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ **SUBJECT CHARACTERISTICS**

Gender	<input type="checkbox"/> 1=M, 2=F	Height	<input type="text"/> <input type="text"/> <input type="text"/> cm	Birth date	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Weight	<input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg
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➤ **DESCRIPTION OF THE EVENT**

The serious adverse event resulted in : <input type="checkbox"/> Death (whatever may be the cause) <input type="checkbox"/> Hospitalisation (*) or extension thereof <input type="checkbox"/> Life threatening <input type="checkbox"/> Invalidity or disability	<input type="checkbox"/> Congenital abnormality or abnormal pregnancy outcome <input type="checkbox"/> Cancer <input type="checkbox"/> Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts) Other fact to be notified : <input type="checkbox"/> Pregnancy exposure
Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :	
AE onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Seriousness onset date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)	
Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) :	
(*) Except hospitalisations with durations and goals planned in the protocol	

➤ **THE SAE IN RELATION TO THE TRIAL**

TREATMENT NUMBER <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
• Time of occurrence of SAE <input type="checkbox"/> During the selection or run-in period <input type="checkbox"/> During the administration phase of the study treatment <input type="checkbox"/> After the administration phase of the study treatment	
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> (ddmmyyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If yes, or if this is an open study, drug(s) administered :	
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :	

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ MEASURES TAKEN FOLLOWING THE SAE

• Study treatment

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readadministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• The event led to :

- ☐ Prescription of corrective or symptomatic treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Discontinuation of concomitant treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Others, specify :

➤ OUTCOME

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)

Study drug: Related to study protocol:

☐ Not Suspected ☐ Suspected ☐ Not Suspected ☐ Suspected

Comments:

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(⊞)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(⊞) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		<ul style="list-style-type: none"> • < 1 500/mm³ whatever the baseline value
WBC (if missing value for neutrophils)		<ul style="list-style-type: none"> • < 3 000/mm³ whatever the baseline value
PLATELETS		<ul style="list-style-type: none"> • < 100 000/mm³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

Title of the 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.

An international, multicentric, randomised, double-blind, placebo controlled study.

Dear patient,

You are currently or you have been taking part of the above-named research study evaluating the effect of F373280 on the maintenance of normal cardiac rhythm after direct electrical cardioversion in patients with persistent Atrial Fibrillation and cardiac failure.

The purpose of this letter it is to provide you with new information about the study.

In fact, as it was explained to you at the beginning of your participation in the trial, it was planned to involve in the study 152 male or female patients suffering from persistent Atrial Fibrillation, aged more than 18 years, in several countries.

However, since May 2013, only 88% of needed patients have been involved in the study. Therefore, due to very slow recruitment over more than 3 years, the Sponsor, Pierre Fabre Médicament, has decided to stop prematurely the recruitment of patients. There will be a maximum of 135 patients involved in this trial.

This decision is not related to any new safety information linked to the product. Ongoing patients may therefore, continue being involved in the study, receiving treatment; and, analyses of all collected data are maintained.

All the other information that were given to you previously remain unchanged

CONTACT FOR FURTHER INFORMATION

If you feel that you would need more information or should there be anything that is not clear, don't hesitate to ask your investigator (doctor in charge of the study):

Dr. _ _ _ _ _ Telephone number : _ _ _ _ _

We thank you for your participation in this study.

***16.1.1.11. Protocol amendment n° PA07
Local (Italy) and substantial dated on 06 December
2016 linked to Protocol and appendices
(version 9: 06 December 2016)***

F 373280 CA 2 01

CLINICAL STUDY PROTOCOL

Efficacy and safety study of F373280 for maintenance of sinus rhythm after electrical cardioversion in patients with persistent Atrial Fibrillation and Chronic Heart Failure.

International, multicentric, randomised, double-blind, placebo controlled study

F373280 / Soft Capsules / 1g

Pierre Fabre Study Code:

F 373280 CA 2 01

EudraCT Number:

2012 – 003487 - 48

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Version 9 – 06DEC2016

The information contained in this document is confidential and is the property of the Sponsor, Pierre Fabre Médicament. This information is given for the needs of the study and must not be disclosed without prior written consent of the Sponsor Pierre Fabre Médicament. Persons to whom this information is given for the needs of the study must be informed that it is confidential and must not be disclosed.

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For Centralised Reading of Holter ECG and TTEM and equipment supply:

Biomedical System

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E-mail: sjacobs@biomedsys.com

For intra erythrocyte DHA dosage:

Agrocampus Ouest

Laboratoire de Biochimie
65 rue de Saint Brieuc – CS 84215
35042 RENNES Cedex - FRANCE
Phone: +33 2 23 48 55 49 - Fax: +33 2 23 48 55 50
E-mail: daniel.catheline@agrocampus-ouest.fr

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Theradis Pharma

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06800 CAGNES-SUR-MER – FRANCE
Phone: +33 (0)4 97 02 07 07 - Fax: +33 (0)4 97 10 08 78
E-mail: chantal.raffy@theradis.pharma.com

Protocol F 373280 CA 2 01
APPROVAL FORM
Protocol Version 9 – 06DEC2016

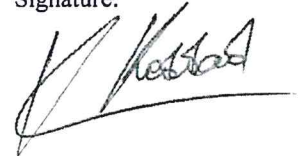
Sponsor's Representative:

Head of Medical Unit:
Karim KEDDAD, MD, PhD

Date:

06/Dec./2016

Signature:



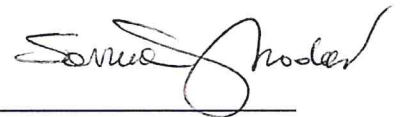
Study Coordinating Investigator:

Savina NODARI, MD

Date:

13/Dec/2016


Signature:



<p>Protocol F 373280 CA 2 01</p> <p>COUNTRY COORDINATING INVESTIGATOR</p> <p>SIGNATURE FORM</p> <p>Protocol Version 9 – 06DEC2016</p>

Country:ITALY.....

Country Coordinating Investigator:

"Name"	Date:	Signature:
SARINA NODARI	13 / Dec / 2016	

Protocol F 373280 CA 2 01
INVESTIGATOR SIGNATURE FORM
Protocol Version 9 – 06DEC2016

By my signature below, I, Dr / Pr " SAVINA VONDERA", hereby confirm that I agree:

- to conduct the trial described in the protocol F 373280 CA 2 01, dated 06DEC2016 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor Pierre Fabre Médicament and given approval / favourable* opinion by the Ethics Committee;
- to document the delegation of significant study-related tasks and to notify the Sponsor of changes in site personnel involved in the study;
- to comply with the procedure for data recording and reporting;
- to allow monitoring, auditing and inspection;
- to retain the trial-related essential documents until the Sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this trial.

I have been informed that certain regulatory authorities require the Sponsor Pierre Fabre Médicament to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial relationships with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- to supply the Sponsor with any information regarding ownership interest and financial relationships with the Sponsor (including those of my spouse and dependent children);
- to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study;
- that the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

* To be adapted

Date:

13 / Dec / 2016

Signature:



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SYNOPSIS

Name of Sponsor:	<i>Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre (IRPF)</i>	
Name of Finished Product:	Not applicable	
Name of Active Substance:	F373280 (Panthenyl-Ester of DHA)	
Title of the 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. <i>International, multicentric, randomised, double-blind, placebo controlled study</i>	
Abbreviated Title:	Not applicable	
Study Coordinating Investigator:	Pr Savina NODARI	
Study Centres:	International, multicentric	
Publication / Rationale:	<p>F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after electrical cardioversion in persistent atrial fibrillation (AF) patients with chronic heart failure.</p> <p>The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing.[1]</p> <p>Moreover, the effectiveness of PolyUnsaturated Fatty Acid (PUFA) has been proven in the following conditions:</p> <ul style="list-style-type: none"> - prevention of AF recurrence in patients with persistent AF, in co-administration with amiodarone (add on therapy) [2] - Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5] <p>Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent atrial fibrillation and chronic heart failure.</p> <p>This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after electrical cardioversion (ECV) in patients with persistent atrial fibrillation and chronic heart failure.</p>	
Planned Study Period:	January 2013 – April 2017	Clinical Phase: IIa
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure <p>Secondary:</p> <ul style="list-style-type: none"> - Efficacy of F373280 on the efficiency of direct electrical cardioversion - Effect of F373280 on echocardiographic parameters - Safety and tolerability of F373280 	
Methodology:	<ul style="list-style-type: none"> - International, multicentre, randomised, double-blind, placebo-controlled - Selection period - Start of treatment 4 weeks before ECV <ul style="list-style-type: none"> • Condition to ECV: <ul style="list-style-type: none"> - Ideally INR 2-3 (vitamin K antagonist should be given at least 3 weeks before ECV) - No spontaneous cardioversion before ECV - Follow-up 20 weeks after visit 3 (ECV visit) <ul style="list-style-type: none"> • Condition: successful ECV or spontaneous CV - Cardiac monitoring: 	

	<ul style="list-style-type: none"> • 7-days continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients with sinus rhythm • TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms. <p>- Treatment duration: 24 weeks</p>
Study Schedule:	<p>7 visits will be scheduled:</p> <ul style="list-style-type: none"> - V1/ W-4 to W-1: selection visit (7 to 28 days before the inclusion visit) - V2/ D1: Inclusion visit (start of study treatment) - V3/ W4 (D28 -2/+7 days): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter device) - V4/ W5 (D35 -2/+7 days): follow-up visit (removing of the Holter device and installation of the TTEM) - V6/ W12* (D84 ± 7 days): follow-up visit <p>*see amendment PA05 dated 22OCT2014</p> <ul style="list-style-type: none"> - V7/ W16 (D112 ± 7 days): follow-up visit - V9/ W24* (D168 ± 7 days): final study visit <p>*see amendment PA05 dated 22OCT2014</p>
Number of Patients:	Maximum 135 patients
Diagnosis and Criteria for Inclusion:	<p>Inclusion Criteria:</p> <p><i>Demographic Characteristics and Other Baseline Characteristics:</i></p> <ol style="list-style-type: none"> 1. Men or women aged more than 18 years (inclusive) 2. Patients with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted 3. Previous history of first documented episode of persistent AF. 4. Previous history of ischemic or non ischemic heart failure 5. NYHA class I or II chronic heart failure at selection and at inclusion 6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ or for patients with a LVEF $> 45\%$: <ul style="list-style-type: none"> • 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 7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers 8. Left atrial area ≤ 40 cm² at selection and at inclusion 9. Patients treated or having to be treated by vitamin K antagonist 10. For female patient of child-bearing potential: <ul style="list-style-type: none"> • In all the countries except Italy: <ul style="list-style-type: none"> - Use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator, for at least 2 months before the selection in the study, and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment - Documented as surgically sterilized • In Italy only: <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or - Use of double barrier contraception method (use of effective medical contraception

	<p>method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or</p> <ul style="list-style-type: none"> - Documented as surgically sterilized <p>11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion</p> <p>12. For male with a child-bearing potential partner (In Italy only):</p> <ul style="list-style-type: none"> - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or - Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study. <p><i>Ethical / legal considerations:</i></p> <p>13. Having signed his/her written informed consent,</p> <p>14. Affiliated to a social security system, or is beneficiary (if applicable in the national regulation)</p> <p>Non-Inclusion Criteria:</p> <p><i>Criteria related to pathologies:</i></p> <ol style="list-style-type: none"> 1. No previous history of first documented episode of persistent AF 2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months 3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV) 4. NYHA class III or IV heart failure at selection or at inclusion 5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease 6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection 7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 ml/min) at selection 8. Bradycardia (HR \leq 50 bpm) 9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection 10. Cardiac surgery within 3 months before selection or planned during the study duration <p><i>Criteria related to treatments:</i></p> <ol style="list-style-type: none"> 11. Previously ineffective pharmacological or electrical cardioversion 12. Concomitant treatment with ranolazine or any antiarrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, betablockers, calcium-blockers 13. Concomitant treatment with oral amiodarone or dronedarone from selection 14. Concomitant treatment with intravenous amiodarone from selection 15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months 16. Treatment with any Polyunsaturated Fatty Acid (PUFA) within the last 3 months 17. Dietary supplement with ω 3 or ω 6 according to investigator's judgement 18. Having undergone any form of ablation therapy for AF 19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible
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	<p>antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel</p> <p><i>Other criteria:</i></p> <ol style="list-style-type: none"> 20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion 21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection 22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself/herself to its constraints 23. Patient family member or work associate (secretary, nurse, technician,...) of the Investigator 24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship 25. Breastfeeding female patient
Exclusion criteria before V3:	<p>Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study.</p> <p>However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study.</p> <p>If necessary, for meeting these INR conditions, the ECV (and following visits) could be postponed by 7 days.</p>
Test Product:	F373280 Soft Capsules
Dose:	Arm with 1g of F373280
Mode of Administration:	Oral, one capsule each evening with dinner.
Duration of Treatment:	24 weeks of treatment exposure with F373280 (25 weeks if ECV postponed by 1 week)
Reference Therapy	Placebo soft capsules Placebo will be administered in the same conditions as the tested product.
Mode of Administration:	Oral, one capsule each evening with dinner
Evaluation Criteria:	<p>Efficacy evaluation variables:</p> <p><u>Primary evaluation variable:</u></p> <ul style="list-style-type: none"> - Time to first Atrial Fibrillation 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). <p>Handling of AF recurrences or atrial flutter emergences: 7-day continuous 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 will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24).</p> <p>For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5). Moreover, during this TTEM period, if patient experiences any AF or atrial flutter symptoms, it should be recorded and documented using the TTEM.</p> <p>All ECG (Holter and TTEM) will be evaluated by a Central Reading Laboratory.</p> <p><u>Secondary evaluation variables:</u></p> <p>During the 7-day continuous ECG monitoring,</p>

	<ul style="list-style-type: none"> Numbers of AF episodes Duration of AF episodes <p><u>Clinical parameters:</u></p> <p>During the whole study:</p> <ul style="list-style-type: none"> Number of recurrence of symptomatic AF episodes EHRA score Hospitalization for cardiovascular events Hospitalization for thromboembolic stroke All causes of hospitalization <p><u>Cardioversion:</u></p> <ul style="list-style-type: none"> Assessment of spontaneous cardioversion Assessment of successful cardioversion Shocks distribution (1, 2 or 3 shocks) Number of patients needing an other cardioversion after the initial ECV <p><u>Other:</u></p> <ul style="list-style-type: none"> Evolution of echocardiographic parameters (at V4, V6 and V9) (Left atrial diameter (mm), Left atrial area (cm²), Left atrial volume (ml), Left atrial volume/BSA (ml/m²), Left ventricular ejection fraction (%), Left ventricular end diastolic volume/BSA (ml/m²), Left ventricular end systolic volume/BSA(ml/m²), 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 DHA (<i>For this assessment samples will be centralized</i>). <p>Safety criteria:</p> <ul style="list-style-type: none"> Adverse events (observed and / or spontaneously reported) Vital signs (Blood pressure (supine and standing), heart rate) Physical examination (body weight, body surface area) Standard 12-lead ECG: heart rate (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns (ECG not centralized) Haematology: haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, reticulocytes, platelets Biochemistry: sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatin phosphokinase (CPK) fibrinogen (<i>local laboratory</i>) Coagulation parameters: Activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), INR (<i>local laboratory</i>), Prothrombine Time (PT). <p>Concomitant treatments</p> <p>Compliance</p>
Statistical Methods:	<p>Sample Size:</p> <p>Assuming an AF recurrence or atrial flutter emergence rate under placebo of 85%, a power of 80%, an alpha risk of 5% and a rate of not assessable patients of 15%, 76 randomised patients per group will be necessary, using a log-rank test of survival curves, a difference between groups of 20%.</p> <p>Primary Efficacy Analysis</p>

	<p>The primary analysis, performed on the Full Analysis Set (FAS: all randomised patients with at least one dose of treatment and with a successful cardioversion observed at visit 3), will be a survival analysis using the Kaplan Meier method and Cox regression model.</p> <p>Secondary Analyses</p> <p>All secondary efficacy criteria will be described and compared using appropriate tests on the FAS.</p> <p>Safety Analyses</p> <p>Descriptive statistics will be performed on the Safety Set (all randomised patients with at least one dose of treatment).</p>
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STUDY FLOW-CHART

F373280 CA 201

	V1	V2	V3	V4		V6	V7		V9
Weeks	W-4 to W-1	D1	W4 (28 -2D/+7 D)	W5 (35 -2D/+7 D)		W12 (84+/-7D)	W16 (112+/-7D)		W24 (168+/-7D)
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR					X			X	(2)
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Haematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment number allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration									
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	(4)			(5)					
TTEM (6)									

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)

(2) In case of VKA introduction: INR 2 to 3 times a week until stabilization, then weekly until the ECV, then every 4 weeks after ECV

(3) In patients with AF

(4) 24-hour Holter ECG

(5) 7-day Holter ECG

(6) TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms.

TTEM once a week even in case of AF recurrence or atrial flutter emergence for at least 10 minutes.

LIST OF ABBREVIATIONS

aPTT	: Activated partial thromboplastin time
AE	: Adverse event
AF	: Atrial fibrillation
ALA	: Alpha-linoleic acid
ALT	: Alanine aminotransferase
AST	: Aspartate aminotransferase
AUC	: Area under the plasma concentration versus time curve
AUC _{inf}	: Total area under the curve extrapolated to infinity
βHCG	: beta human chorionic gonadotrophin
BLQ	: Below the limit of quantification
BMI	: Body mass index
BP	: Blood pressure
BSA	: Body Surface Area
CEP	: Protocol evaluation committee
CHMP	: Committee for medicinal products for human use
C _{max}	: Maximum concentration
C _{min}	: Minimum concentration
CNALV	: Clinically noteworthy abnormal laboratory value
CPK	: Creatin phosphokinase
CPP	: Comité de protection des personnes
CRA	: Clinical research associate
CRT	: Cardiac resynchronization therapy
CSC	: “Clinically Significant Change”, i.e., Predefined potentially clinically significant change leading to a potentially clinically significant value (vital signs)
CV	: Coefficient of variation
DBP	: Diastolic blood pressure
DHA	: Docosahexaenoic acid
EC	: Ethics committee
ECG	: Electrocardiogram
ECHO –TE	: Transesophageal echocardiograph
ECV	: Electrical cardioversion
EHRA	: European heart rhythm association
EPA	: Eicosapentaenoic acid
e-CRF	: Electronic case report form
FAS	: Full analysis set
Fe	: Fraction of the administered drug excreted in urine
GCP	: Good clinical practice
GFR	: Glomerular Filtration Rate
HBs	: Hepatitis B antigen
HCV	: Hepatitis C virus
HDL	: High density lipoprotein

HF	:	Heart failure
HIV	:	Human immunodeficiency virus
HR	:	Heart rate
ICH	:	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	:	Independent data monitoring committee
INR	:	International normalized ratio
IRPF	:	Institut de Recherche Pierre Fabre
IVRS	:	Interactive voice response system
LAA	:	Left atrial area
LC/MS-MS	:	Liquid chromatography with tandem mass spectrometry
LDL	:	Low density lipoprotein
LOQ	:	Limit of quantification
LVEF	:	Left ventricular ejection fraction
MedDRA	:	Medical dictionary for regulatory activities
MR	:	Mineralocorticoid receptor
MR perfusion	:	Magnetic Resonance perfusion
MTD	:	Maximum tolerated dose
N	:	Number of determinations or replicates
NOAEL	:	No observed adverse effect level
NYHA	:	New York heart association
od	:	Once a day
PC	:	“Predefined Change”, i.e., Predefined potentially clinically significant change (lab or vital signs)
PCA	:	PC leading to an out-of-range value (lab values)
<i>PFB</i>	:	<i>Pierre Fabre Biométrie</i>
PSC	:	Potentially Clinically Significant Change
PSCV	:	Potentially Clinically Significant Value
PUFA	:	PolyUnsaturated fatty acid
p.o.	:	Per os
PP	:	Per protocol data set
QTcB	:	QT interval using Bazett’s correction formula
QTcF	:	QT interval using Fridericia’s correction formula
RBC	:	Red blood cells
SAE	:	Serious adverse event
SBP	:	Systolic blood pressure
SD	:	Standard deviation
T _{1/2}	:	Terminal half-life
T ₀	:	Time of drug administration
T _{max}	:	Time to reach the maximal concentration
TCT	:	Thrombin clotting time
TEAEs	:	Treatment emergent adverse events
TTEM	:	TransTelephonic ECG monitoring
VKA	:	Vitamin K Antagonist
WBC	:	White blood cells
WHO-DRUG	:	World health organization drug reference list

1. INTRODUCTION AND STUDY RATIONALE

1.1. TARGET PATHOLOGY AND THERAPY

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial electric activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disorder, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality [7].

In 2009, Decision Resources estimated that there were 7.8 million diagnosed prevalent cases of AF in US, Europe and Japan. This age-related pathology should increase to 9.4 million cases in 2019.

Except for the conventional class I and class III anti-arrhythmic agents, the Polyunsaturated Fatty Acids (PUFAs) constitute one emerging antiarrhythmic therapy. These compounds potently address the AF substrate by directly targeting both the electrical and the structural remodelling of the deficient atria. The n-3 PUFAs, essential for human, are alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, PUFAs specifically modulate ionic channels by fastening their inactivating mode which renders these compounds selective for pathological situations (such as AF) without any major effect in normal conditions. PUFAs are “open $K_{v1.5}$ channel blockers” leading to a lengthening of atrial action potential duration and are “persistent $Na_{v1.5}$ channel blockers” leading to hyperpolarization of diastolic resting potential. Second, PUFAs influence structural remodelling through their anti-inflammatory effects as they directly compete with arachidonic acid in the production of inflammatory eicosanoids. In summary, PUFAs share unique, well-tolerated antiarrhythmic potential by interacting with the electrical and structural remodelling during sustained AF. In animal studies, it was recently demonstrated that DHA is particularly effective in pathologic conditions such as ischemia and/or AF.

The potential anti-arrhythmic effects of a PUFA were previously developed in AF: nicotinyl ester of DHA (pro-drug based on DHA delivery) was assessed in a two-week ventricular tachypaced

canine model. Dogs were subjected to 4 weeks of medication prior to undergoing an electrophysiology study, and received either placebo or nicotiny ester of DHA. Dogs were tachypaced at 240 beats per min for the final two weeks of the treatment plan. The results showed that the tested PUFA reduced the duration of AF induced by burst pacing, and the incidence of sustained AF, compared to dogs treated with the placebo [1].

In clinical practice, Nodari and coll [2] assessed n-3 PUFAs in the prevention of AF recurrences after electrical cardioversion (ECV). All included patients were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. The 199 patients were assigned either to placebo or n-3 PUFAs 2 g/d and then underwent direct ECV 4 weeks later. The primary end point was the maintenance of sinus rhythm at 1 year after cardioversion. At the 1-year follow up, the maintenance of sinus rhythm was significantly higher in the n-3 PUFAs treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; $p = 0.0001$). The study concludes that in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Previously, during the World Congress of Cardiology in 2006, an abstract reported the effectiveness of PUFAs on top of traditional treatment (amiodarone, beta blockers, renin-angiotensin-aldosterone system inhibitor) in the prevention of AF relapses in patients having undergone ECV. In the PUFA group, AF relapses were significantly lower than in the placebo group at 1 month (3.3% vs 10%; $p = 0.043$), at 3 months (10% vs 25%; $p = 0.004$) and at 6 months (13.3% vs 40%; $p < 0.0001$) [19].

In contrast, in the general AF population (paroxysmic atrial fibrillation and persistent atrial fibrillation), PUFAs failed to prove their efficacy [7] because of the absence of cardiac remodelling or because of a short pre-treatment duration before ECV (1 week) [8]. The effects of PUFAs were only observed in patients with persistent AF on add on therapy and after a sufficient pre-treatment before ECV. Persistent AF is commonly associated to heart failure. Previous studies performed in heart failure population demonstrated the benefit of PUFAs on the improvement of functional ventricular parameters and morbi-mortality, and on the reduction of hospitalisation [3, 4, 5].

Nodari and coll [3] performed a trial in patients with chronic heart failure (NYHA I to III and LVEF < 45%). After a treatment of 133 patients with PUFAs ($n=67$) or placebo ($n=66$) at a dosage

of 5 g/day for 1 month, then 2 g/day for 11 months, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to:

- LVEF (increased by 10.4% and decreased by 5.0%, respectively)
- peak VO_2 (increased by 6.2% and decreased by 4.5%, respectively)
- exercise duration (increased by 7.5% and decreased by 4.8%, respectively)
- mean New York Heart Association functional class (decreased from 1.88 ± 0.33 to 1.61 ± 0.49 and increased from 1.83 ± 0.38 to 2.14 ± 0.65 , respectively).

The hospitalization rates for patients with HF were 6% in the n-3 PUFAs and 30% in the placebo group ($p < 0.0002$).

Moertl and coll [4] performed a dose-ranging study in patients with a more severe chronic heart failure (NYHA III and IV and $\text{LVEF} < 35\%$). It was a double-blind, randomised, controlled pilot trial in 43 patients treated with PUFAs or placebo for 3 months (1 g/d n3-PUFA ($n = 14$), 4 g/d n3-PUFA ($n = 13$), or placebo ($n = 16$)). After treatment, left ventricular ejection fraction increased in a dose-dependent manner ($p = 0.01$ for linear trend) in the 4 g/d (baseline vs 3 months [mean \pm SD]: $24\% \pm 7\%$ vs $29\% \pm 8\%$, $p = 0.005$) and 1 g/d treatment groups ($24\% \pm 8\%$ vs $27\% \pm 8\%$, $p = 0.02$).

No changes in any investigated parameters were noted with placebo.

Taking into account these studies performed with PUFAs, it seems that the best target for DHA is persistent AF in patients with heart failure. The aim of this proof of concept study is to assess in stand alone therapy (without association of other anti-arrhythmic treatments), the effect of F373280 in patients with persistent AF and heart failure in the maintenance of sinus rhythm after ECV.

1.2. INFORMATION ON THE TEST PRODUCT

F373280 or panthenyl ester of DHA is the mono-ester of panthotenic alcohol and DHA, selected to be developed for the management of AF.

F373280 is a prodrug of DHA.

A brief summary of F373280 known characteristics is presented in this section. For further details, please refer to the F373280 *Investigator's Brochure*. [1]

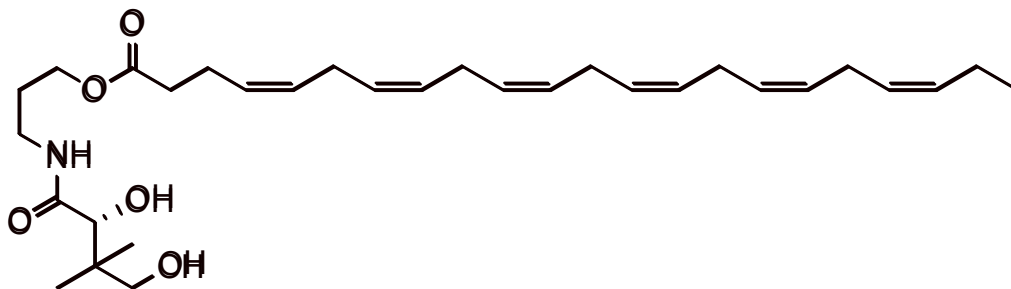
1.2.1. Chemical and pharmaceutical characteristics

1.2.1.1. Nomenclature and structure

Chemical name (IUPAC):

(4Z,7Z,10Z,13Z,16Z,19Z)-3-((R)-2,4-dihydroxy-3,3-dimethylbutanamido) propyl docosa-4,7,10,13,16,19-hexaenoate

Structural formula:



Laboratory code: F373280

Molecular formula: C₃₁H₄₉NO₅

Molecular mass: 515.7

1.2.1.2. Physical and chemical general properties

Appearance: Clear oily viscous liquid

Solubilities:

- Water: Practically insoluble
- Alcohol: Very soluble
- Trimethylpentane: Slightly soluble

1.2.2. Non-clinical Data

Non-clinical data are exhaustively detailed in the Investigator's brochure [1]. A brief summary is provided below.

1.2.2.1. Pharmacological profile

F373280 (mono-ester of panthotenic alcohol and DHA) is a novel pro-drug of DHA which exerts antiarrhythmic properties by interacting with the electrical and structural remodelling of the atria.

Experimental investigations were conducted in HEK293 cell line transfected with human Kv1.5 channel using the whole cell patch clamp technique to evaluate whether F373280 could block the sustained component of $I_{Kv1.5}$. F373280 concentration-dependently reduced Kv1.5 channel activity with an IC_{50} value of 13.7 μ M.

The effects of F373280 on atrial effective refractory period were investigated in anesthetized pig using a conventional pacing protocol through epicardial electrodes placed on the left atrium. F373280 administered as a bolus and an infusion (10 mg/kg) significantly increased atrial effective refractory period (23.8 ± 2.2 ms versus -7.3 ± 11.5 ms in the presence of vehicle, $p < 0.05$). In addition, F373280 was devoid of significant effect on the hemodynamic and the electrocardiogram (ECG) intervals.

Proof of the pharmacological concept was performed with a different DHA derivative named: Nicotinyl ester of DHA (pro-drug based on DHA delivery). Ventricular tachypacing-induced congestive heart failure provides a clinically-relevant animal model of AF associated with structural remodelling, as is often seen clinically. It has been shown that sustained oral PUFA administration suppresses congestive heart failure-induced AF-promotion and fibrosis in the ventricular tachypacing canine model. Nicotinyl ester of DHA was tested in this model, at 1 g/day and 5 g/day, during 4 weeks, to prevent congestive heart failure-related atrial structural remodelling and AF promotion in dogs. Nicotinyl ester of DHA dose dependently reduced heart failure-induced increases in AF duration (989 ± 111 sec, $n=5$ in the presence of placebo versus 637 ± 196 sec, $n=5$ in the presence of 1 g/kg/d Nicotinyl ester of DHA and 79 ± 51 sec, $n=5$, in the presence of 5 g/kg/d Nicotinyl ester of DHA). The protective effect of Nicotinyl ester of DHA was associated with a marked increase of plasma level of DHA and important incorporation of DHA in the left atrial tissue. Because F373280 similarly to Nicotinyl ester of DHA increases plasma level of DHA, it could be estimated that the compound may exert a similar protective effect [1].

1.2.2.2. *Safety pharmacology*

A battery of safety pharmacology studies was performed to evaluate the effects of F373280 on the central nervous, cardiovascular and respiratory systems. Data of these studies are exhaustively detailed in the Investigator's brochure [1].

No particular alerts were evidenced with F373280.

1.2.2.3. *Toxicology profile*

Concerning the toxicological data, 4-week and 26-week repeat-dose studies in rat and dog were performed. Compared to the high administered doses of F373280 (500 to 2000 mg/kg/day), low circulating concentrations of F373280 were measured.

During these toxicity studies, no toxicity was observed in rat after 4 and 26 weeks of dosing and in dog after 4 weeks of dosing. A NOAEL of 2000 mg/kg/day was established in these repeat toxicity studies.

During the 26-week toxicity study in dogs, the NOAEL was set at 1000 mg/kg/day based on changes observed on red blood cell parameters.

Based on toxicological profiles, F373280 is considered to support the proposed clinical trial.

1.2.2.4. *Pharmacokinetic data*

According to animal studies described in the Investigator's brochure [1], the non-clinical pharmacokinetic profile of F373280 is not associated with particular alerts concerning the proposed clinical phase IIa study.

1.2.3. Clinical data

Part A: Single dose

Six consecutive single ascending doses were tested (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) on 6 independent cohorts of 8 subjects (6 verum + 2 placebo). 49 subjects were treated and 48 completed the study.

No Serious Adverse Events (SAE) occurred in the course of the study.

Regarding the reported Treatment Emergent Adverse Events (TEAEs) that were judged by the Investigator as having a causal relationship with the study drug administration in the absence of

an alternative explanation, 3 TEAEs were observed in the placebo group (palpitation, dizziness in standing position, symptomatic orthostatic hypotension without loss of consciousness) and 4 in the group of F373280 at the dosage of 16 g (meteorism, liquid stool, symptomatic orthostatic hypotension and dizziness in standing position). None of these adverse events (AE) were reported in the groups of F373280 at the dosages of 0.5 g, 1 g, 2 g, 4 g and 8 g.

After a single administration of the different tested doses no difference between the tested product and placebo has been reported, regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters (related to coagulation: platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/INR, activated partial thromboplastin time, thrombin clotting time). Variations of these parameters were within the physiological ranges.

After single oral administration of F373280 from 0.5 g to 16 g in 36 young healthy male subjects (6 per dose level), the following was observed:

- **F373280:** Whatever the tested dose there is no circulating F373280 in plasma: only few, sparse and non consecutive samples with quantifiable level of F373280 close to LOQ were observed. This confirms that F373280 is a prodrug.
- **Panthenol:** C_{max} and AUC increased with the administered dose between 0.5 and 16 g. Panthenol concentrations were rapidly cleared from plasma with a mean terminal half-life around 2 hours.
- **DHA:** after 0.5 and 1 g, low increased in DHA plasma concentrations compared to the baseline levels led to a high inter-individual variability of the corresponding Pharmacokinetics parameters. Plasma exposure in DHA increased with the administered dose between 2 and 16 g with no departure from proportionality (baseline corrected parameters).

Part B: Multiple doses

Three consecutive repeated ascending doses (1, 2 and 4 g) were tested on 3 independent cohorts of 12 subjects (9 verum + 3 placebo, double blind). 36 subjects completed the study. Each treatment was administered over a period of 28 days. Pharmacokinetic parameters were assessed over a period of 14 days.

Among the TEAE judged by the investigator as suspected to F373280, 5/9 TEAEs were classified according the System Organ Class in vascular system disorder with orthostatic hypotension (2 in the 1 g group, 1 in the 2 g group and 2 in the 4 g group) and 4/9 were classified in nervous system disorder with 3 dizziness (2 in the 2 g group and 1 in the 4 g group) and 1 migraine (in the 1 g group). These TEAEs have already been reported with PUFAs and are commonly observed in phase I studies.

After a repeated administration of the different tested doses, no difference between the tested products and placebo was reported regarding vital signs (heart rate, systolic blood pressure and diastolic blood pressure), biological parameters. The assessment of coagulation parameters and platelet function after administration of repeated dose of F373280 did not report any bleeding issue. The reported changes in coagulation parameters and platelet function were within physiological ranges.

After a 14-day repeated oral administration of F373280 from 1 g to 4 g, the following was observed:

- ✓ **Panthenol:** C_{max} and AUC increased with the administered dose between 1 and 4 g. No accumulation of panthenol in plasma was observed.
- ✓ **DHA:** Plasma exposure increased with dose. A 2-fold accumulation in total plasma exposure of DHA was observed after 14 days of administration, whatever the administered dose.

1.3. STUDY RATIONALE

F373280 is a new therapy based on DHA delivery (pro-drug) developed for the maintenance of sinus rhythm after ECV in persistent AF patients with chronic heart failure.

The results of a pharmacological study performed in animals evidenced that DHA reduces the duration of AF induced by burst pacing [1].

Moreover, the effectiveness of PUFAs has been proven in the following conditions:

- Prevention of AF recurrence in patients with persistent AF in co-administration with amiodarone (add on therapy) [2],
- Improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

Taking into account these studies, it seems that DHA might be of therapeutic interest in the treatment of patients with both persistent AF and chronic heart failure.

This phase IIa study is designed to assess the efficacy and the safety of the investigational product (F373280) for maintenance of sinus rhythm after ECV in patients with persistent AF and chronic heart failure.

1.4. OVERALL RISK AND BENEFIT ASSESSMENT

F373280 is a new pro-drug of DHA.

DHA is a well-known long chain PUFAs with a long-term clinical experience in cardiovascular diseases. DHA is contained in several medicinal products such as Omacor®, (1 g of Omacor contains about 320 mg of DHA acid) marketed by Laboratoires Pierre Fabre for hypertriglyceridemia and as an adjuvant treatment for secondary prevention after myocardial infarction. According to the summary product characteristics of Omacor® [9]:

- The frequencies of adverse reactions are ranked according to the following: common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$), not known (cannot be estimated from the available data).

- The reported adverse events are:

- Infection and infestations:
Uncommon: gastroenteritis
- Immune system disorders:
Uncommon: hypersensitivity
- Metabolism and nutrition disorders:
Rare: hyperglycaemia
- Nervous system disorders:
Uncommon: dizziness, dysgeusia
Rare: headache
- Vascular disorders:
Very rare: hypotension
- Respiratory thoracic and mediastinal disorders:

Very rare: nasal dryness

- Gastrointestinal disorders:

Common: dyspepsia, nausea

Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper

Rare: gastrointestinal pain

Very rare: lower gastrointestinal haemorrhage

- Hepatobiliary disorders:

Rare: hepatic disorders

- Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

- General disorders and administration site conditions:

Rare: malaise sensation

- Investigations:

Very rare: white blood count increased, blood lactate dehydrogenase increased

Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Panthenol is a well-known substance with a long-term experience in medical, nutraceutic and cosmetic uses. According to the summary product characteristics of a product such as Bépanthene® (tablet indicated in alopecia) which contains panthenol (100 mg), adverse event observed are rare cases of urticaria and erythema [10]. Panthenol is metabolised in panthotenic acid, i.e. B5 vitamin.

Concerning toxicological studies performed results can support the administration of F373280 in the proposed clinical phase II study without particular alert [1].

Any safety warning was reported during a phase I study performed with F373280 administered to 84 healthy volunteers in single dose in a range between 500 mg and 16 g or in repeated dose during 28 days in a range between 1 g and 4 g. Adverse events reported and related to study treatment were minor to moderate. The adverse events were palpitations, orthostatic hypotension, dizziness, meteorism and liquid stool. Most were reported in both groups (placebo and F373280) without a dose relationship. The assessment of coagulation parameters and platelet function after

administration of repeated dose of F373280 did not report any bleeding concern: the reported changes in coagulation parameters and platelet function were within physiological ranges.

Moreover, DHA has been associated with anticoagulant products in AF studies [2, 8]. The range of PUFAs doses tested was between 2 g to 3 g (640 mg to 960 mg of DHA) and the range of study durations between 6 to 12 months. This association did not report a significant side effect of bleeding.

DHA has already been used in HF patients in several studies without safety concern [3, 4, 5]. The range of PUFAs doses tested was between 1 g to 5 g (1 g of the tested PUFAs contains about 320 mg of DHA acid) and the range of study durations was between 3 months to 3.9 years.

Thus, inclusion of patients with no specific antiarrhythmic treatment is acceptable. They will receive an anticoagulant treatment to prevent the thrombo-embolic complications of AF (particularly stroke) and the adequate treatments to control the heart rate and heart failure.

In conclusion, the overall available data allow in safe conditions the treatment of patients with persistent AF and chronic heart failure with F373280 in safe conditions.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to assess:

- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

3. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial is conducted according to Good Clinical Practices (CPMP/ICH/135/95), the National regulations and the Declaration of Helsinki and its subsequent amendments (see Appendix 17.1). This protocol and the informed consent form will be submitted for approval to independent local or national Institutional Review Boards/Ethics Committees before the study set up, according to national regulation.

All the protocol amendments or critical events liable to increase the risks incurred by the patients or to compromise the validity of the study or patients' rights will be submitted to the coordinator and to the Ethics Committees.

After being informed orally and in writing of all potential risks and constraints of the trial, as well as their freedom to withdraw their participation at any time, patients will then sign a consent form. A time of reflection will be given to the patients, before giving a written consent and starting the study procedures.

The use of a placebo is in accordance with EMA Addendum to the guideline on antiarrhythmics on AF and atrial flutter (EMA/CHMP/EWP/213056/2010) [21] and is acceptable because the included patients will remain under the standard treatment of AF and chronic heart failure. Except antiarrhythmics, they will receive anticoagulant (vitamin K antagonist, VKA), rate control treatment, chronic heart failure treatment. During the study, in case of AF recurrence or atrial flutter emergence that would require cardioversion or the introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance, patients will be withdrawn and the tested product stopped. These patients will be considered as treatment failure.

In this study, patients will be carefully screened, particularly for their cardiac condition, with ECG, 24-hour holter monitor and echocardiographic data, and their biologic and coagulation condition.

The study will be addressed only to patients requiring an ECV due to their persistent AF, in the following conditions:

- ECV in patients not presenting a contra-indication
- Anticoagulation with vitamin K antagonist (VKA) for at least 3 weeks before ECV
- ECV will be performed in patients with AF and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last

tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Patients who do not revert to sinus rhythm or present an early AF relapse or an early atrial flutter emergence within the observation period after ECV will be withdrawn and the tested product stopped.

During the whole study, patients will remain under medical control: visits in cardiology units will be performed throughout the study period. This follow up will include clinical signs, ECG, biological and coagulation parameters. Moreover, patient's cardiac rhythm will be monitored once a week between visits using Trans Telephonic ECG Monitoring (TTEM) reviewed by a Central Reading Laboratory.

Patients may withdraw from the study at any time without having to give a reason and can expect to receive regular conventional therapy.

4. STUDY DESIGN

4.1. OVERALL DESCRIPTION

This phase IIa trial will be conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, trial in 135 patients suffering from persistent AF and chronic heart failure.

After a 1 to 4-week of run-in period without study treatment, patients will be randomised into one of the following treatment groups: F373280 1g or placebo for 24 weeks.

Seven visits are planned for the study:

- Visit 1 (V1): W-4 to W-1: Selection visit (7 to 28 days before the Inclusion Visit)
- Visit 2 (V2): D1: Inclusion visit (start of study treatment)
- Visit 3 (V3): W4 (D28-2/+7D): cardioversion visit (outpatient or hospitalization according to clinical practice of the centre) (installation of the Holter ECG device)

- Visit 4 (V4): W5 (D35 -2/+7D): follow-up visit (removing of Holter ECG device and installation of the TTEM)
- Visit 6* (V6): W12 (D84 \pm 7D): follow-up visit
*see amendment PA05 dated 22OCT2014
- Visit 7 (V7): W16 (D112 \pm 7D) : follow-up visit
- Visit 9* (V9): W24 (D168 \pm 7D): final study visit
*see amendment PA05 dated 22OCT2014

4.2. DISCUSSION OF THE STUDY DESIGN

4.2.1. Choice of the Study Population

The target indication of F373280 will be the maintenance of sinus rhythm after cardioversion of patients with persistent AF and chronic heart failure. In the present proof of concept study, the evaluation will focus on patients within this indication. This target population is justified by:

- The proved efficacy of PUFAs in patients with persistent AF with or without heart failure in co-administration with amiodarone (add on therapy) [2]
- The proved efficacy of PUFAs on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5]

The study aim is to investigate the product effect in patients with:

- Previous history of persistent AF with duration of the current episode from 7 days to 6 months.
- A systolic heart failure defined by a reduced left ventricular ejection fraction ($\geq 30\%$ and $\leq 45\%$) 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 [23, 24].

According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would be effective to prevent recurrence of AF after cardioversion in patients with moderately abnormal LVEF.

- A Left Atrial Area (LAA) not severely abnormal (no greater than 40 cm² as defined in the report from the American Society of Echocardiography's Guideline) [23]. According to a sub-group analysis performed in patients with persistent AF associated to heart failure (Nodari S. personal data), PUFAs would not be effective to prevent recurrence of AF after cardioversion of patients with severely abnormal LAA.

For the successful rate of ECV, patients should have a stable medical treatment of heart failure and should not have any myocardial infarction or unstable angina or unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection.

4.2.2. Choice of the Study Design

As the target indication would be the prevention of AF recurrence after ECV, the study design meets the requirements of EMA guideline on antiarrhythmics in AF (EMA/CHMP/EWP/213056/2010) [21].

As F373280 aims to be a safe treatment for the prevention of AF recurrence, it will not be tested as an add-on therapy during the study. To avoid any interaction with the tested product, antiarrhythmics class I and III will be forbidden during the study.

The study design is defined in order to avoid methodological bias. A double blind study is appropriate to assess the efficacy and safety of the use of F373280 to prevent recurrence of AF episodes. Moreover, this study design is similar to the design of almost all trials that have assessed intervention for rhythm control [2, 8, 11, 12].

According to the target indication, only patients with persistent AF and requiring an ECV will be included in order to assess the time to first documented recurrence of AF (or emergence of atrial flutter) since cardioversion.

To confirm the persistent nature of AF, a 24-hour holter monitoring will be performed during the selection visit.

Eligible participants will enter a selection phase in which anticoagulant treatment (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) of 2 to 3 before ECV. According to guidelines for the management of AF [6], VKA should be given at least 3 weeks before cardioversion because of risk of thrombo-embolism due to post-cardioversion.

Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur [22]. In addition, as shown in Nodari's study [2], the duration of pre-treatment with PUFAs before cardioversion appears to be a contributing factor in success. Therefore, before starting follow up for the assessment of AF recurrence, treatment with F373280 should be started 28 days before ECV.

Detection of AF recurrence will be performed using systematic (scheduled) ECG recording, thus allowing detection of asymptomatic (about 50% of episodes) as well as symptomatic AF episodes. According to previous studies, most of AF recurrences occurred during the first days after cardioversion [11, 15]. So that, the heart rhythm will be closely monitored during the first week after successful cardioversion using an ambulatory continuous 7-day holter ECG recording in order to increase sensibility to detect asymptomatic AF episodes. Thereafter, to improve patient compliance, this follow up will be continued using an easier device to carry and to use, i.e. a TTEM.

Finally, during the study, patients will be scheduled for a clinical visit every 4 weeks or 8 weeks (with an additional visit 7 days after visit 3 (ECV visit)) in order to ensure a close medical monitoring and to assess efficacy and safety parameters.

4.2.3. Choice of the Dose

According to a previous study in patients with AF [2], the tested PUFA product (Omacor®) at the dose of 2 g (i.e. 640 mg of DHA acid) was effective in the prevention of AF after cardioversion. Moreover, PUFAs at dosage of 1 g and 2 g were also effective on the improvement of ventricular functional parameters, morbi-mortality and duration of hospitalisation in patients with heart failure [3, 4, 5].

From the F373280 phase I study, after a 14-day repeated administration of F373280 (1 g/day), observed plasma concentrations of DHA measured before treatment (C_{min}) were similar to that of an effective dose of Omacor® at 2 g/day (60 to 95 mg/ml and 60 to 90 mg/ml, respectively) (phase I study of F373280 and [16]). With regard to the rhythm of administration, mean peak/trough

fluctuation (baseline corrected) was around 0.3. This value supports a once-daily administration allowing a 24-hour plasma exposure in DHA. Therefore, a 1 g daily dose of F373280 is considered to be appropriate for this proof of concept study.

4.2.4. Choice of the Sample Size

See chapter 13.

5. STUDY POPULATION

Each patient fulfilling all the inclusion criteria and none of the non inclusion criteria will be eligible.

5.1. INCLUSION CRITERIA

Demographic Characteristics and Other Baseline Characteristics:

1. Men or women aged more than 18 years (inclusive)
2. Patient with current episode of persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted
3. Previous history of first documented episode of persistent AF
4. Previous history of ischemic or non ischemic heart failure
5. NYHA class I or II chronic heart failure at selection and at inclusion
6. Left ventricular systolic dysfunction defined at selection and at inclusion by a reduced left ventricular ejection fraction (LVEF) $\geq 30\%$ and $\leq 45\%$ 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
7. On appropriate, stable medical treatments for heart failure, including a diuretic and/or angiotensin-converting enzyme, and/or angiotensin-receptor blocker and/or mineralocorticoid receptor (MR) antagonists, and/or betablockers

8. Left atrial area $\leq 40 \text{ cm}^2$ at selection and at inclusion
9. Patient treated or having to be treated by vitamin K antagonist
10. For female patient of child-bearing potential:
 - **In all the countries except Italy:**
 - Use of an effective method of contraception (hormonal contraception or intra-uterine device) assessed by the investigator for at least 2 months before the selection in the study and agreement to go on using it during the whole duration of the study and up to 1 month after the last dose of the study treatment or
 - Documented as surgically sterilized
 - **In Italy only:**
 - Absolute abstention from sexual intercourse during the whole duration of the study and for a month after the end of the study or
 - Use of double barrier contraception method (use of effective medical contraception method) from at least 2 months before the start of the study to the entire duration of the study and for a month after the end of the study or
 - Documented as surgically sterilized
11. For female patient of child-bearing potential: negative urine pregnancy test at inclusion
12. For male with a child-bearing potential partner (**In Italy only**):
 - Absolute abstention from sexual intercourse during the whole duration of the study and for 3 months after the end of the study or
 - Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 3 months after the end of the study.

Ethical /legal considerations:

13. Having signed his/her written informed consent,

14. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation)

5.2. NON INCLUSION CRITERIA

Criteria related to pathologies:

1. No previous history of first documented episode of persistent Atrial Fibrillation
2. More than two successful cardioversions (electrical or pharmacological) in the last 6 months,
3. Secondary Atrial Fibrillation due to alcohol or severe valvular heart disease (grade III to IV),
4. NYHA class III or IV heart failure at selection or at inclusion
5. Thyroid disease uncontrolled by treatment: TSH \pm T4L \pm T3L to be checked in case of treatment for thyroid disease
6. Myocardial infarction or unstable angina or presence of unstable ischemic coronaropathy assessed by coronarography or cardiac stress test (Echo stress, exercise stress test, nuclear or MR perfusion evaluation methods) within 6 months before selection
7. Severe chronic kidney disease (creatinine \geq 25 mg/L or estimated glomerular filtration rate $<$ 30 ml/min) at selection
8. Bradycardia (HR \leq 50 bpm)
9. Hyperkalemia or hypokalemia (according to the standards of local laboratories) at selection
10. Cardiac surgery within 3 months before selection or planned during the study duration

Criteria related to treatments:

11. Previously ineffective pharmacological or electrical cardioversion
12. Concomitant treatment with ranolazine or any anti-arrhythmic drug (within 7 days prior to selection), except amiodarone, dronedarone and stable dose of digoxin, beta-blockers, calcium-blockers.
13. Concomitant treatment with oral amiodarone or dronedarone from selection
14. Concomitant treatment with intravenous amiodarone from selection
15. Patient requiring a cardiac resynchronization therapy (CRT) or having undergone CRT implantation within the last 6 months

16. Treatment with any Polyunsaturated Fatty Acid within the last 3 months
17. Dietary supplement with $\omega 3$ or $\omega 6$ according to investigator's judgment
18. Having undergone any form of ablation therapy for AF
19. Patient treated with oral anticoagulant treatment other than vitamin K antagonist: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or treated with irreversible antiplatelet agents P2Y12 inhibitors such as ticlopidine, clopidogrel or prasugrel

Others criteria:

20. Patient liable not to comply with protocol instructions and/or with treatment, in the investigator's opinion,
21. Patient having taken part in a clinical trial in the preceding 2 months or taking part in a trial at the time of selection,
22. Patient linguistically or mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing to patient himself / herself to its constraints,
23. Patient family member or work associate (secretary, nurse, technician...) of the Investigator,
24. Patient having forfeited his / her freedom by administrative or legal award or being under guardianship,
25. Breastfeeding female patient.

5.3. NUMBER OF PATIENTS

Maximum 135 patients (taking into account 15% of non-evaluable patients).

5.4. RECRUITMENT MODALITIES

Patients will be recruited within the medical consultation of each centre involved in the study. If necessary and when authorized by local and national regulation, some specific supports or tools will be used to improve the recruitment (announcement, mailing to general practitioners, leaflet, website including ClinicalTrials.gov, CRO...).

Before implementation, the documents will be submitted to and approved by the Ethics Committee.

5.5. PATIENT IDENTIFICATION

Patient's code will contain 7 digits: the 2 first digits corresponding to the country number, the following 2 digits corresponding to the centre number and the last 3 digits corresponding to the patient's chronological order once having signed the written informed consent.

5.6. WITHDRAWAL CRITERIA

Reasons for a patient's premature withdrawal from the study may be the following:

- Patient's decision. A patient who wishes to withdraw from the study for any reason may do so at any time but must inform the investigator. In all cases, the Investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
 - have the patient's decision written on the consent form
 - obtain the reason(s) for withdrawal and report it/them in the case report form
 - evaluate the patient's clinical condition
 - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.
- Investigator's decision in the patient's interest, particularly if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient. The monitor will be informed by phone or fax and a letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.
- Erroneous inclusion according to the study protocol. The decision to maintain or not the patient in the study will be taken jointly by the investigator and the sponsor. Erroneous inclusions will not be paid to the investigator.
- Patients who could not be treated with VKA for at least 3 weeks before ECV or who will experience a VKA intolerance during the study.
- Patients without dyskalemia who will not have INR values ≥ 2 on the 3 last tests performed before ECV should not have an ECV and will be excluded from the study. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal

echocardiography) performed on the same day (before ECV) and the patient can continue the study.

- Patients who will not revert to sinus rhythm (i.e. unsuccessful ECV) or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be considered to have finished follow-up.
- Occurrence of AF recurrence or atrial flutter emergence that would require, at the investigator's judgement, a cardioversion or an introduction of an anti-arrhythmic because of intolerable and/or uncomfortable clinical symptoms for instance.

5.7. REPLACEMENT OF PATIENTS

Withdrawn patients will not be replaced.

5.8. POST-STUDY EXCLUSION PERIOD

Patients will not be allowed to participate in another clinical trial during 3 months following the study termination.

5.9. STUDY CARD AND LETTER FOR GENERAL PRACTITIONER(S)

The patient will receive from the Investigating Centre at Visit 1 - Selection Visit:

- a personal card to be kept all along the study duration and providing the following information: patient's name, sponsor's name, study code, EUDRACT number, start date and expected end date of the study, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number in case of emergency (French and English languages): 33 (0)5 63 35 25 83. For Italy, this card will be in Italian only, without any English mention.
- in Italy, a letter to be given to his/her general practitioner. This letter intends to inform the general practitioner(s) (and any other doctors who take care of the patient) that the patient participates to the clinical study. It describes the study treatment and includes some information on the forbidden treatment during the study.

6. STUDY TREATMENT

The Clinical Pharmacy Department of the Institut de Recherche Pierre Fabre (IRPF) will supply the investigational centres with the treatment necessary for the conduct of the trial.

6.1. SOURCE, PRESENTATION AND COMPOSITION OF INVESTIGATIONAL PRODUCT

F373280 and placebo will be prepared in Soft Capsules similar presentation.

- **F373280**

Formulation of F373280, 1 g, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: Panthenyl ester of DHA, gelatine, glycerol, titanium, dioxide, purified water.

- **Placebo**

Formulation of placebo matching tested product, Soft Capsules: oral administration, oblong size 20, off-white, Soft Capsules containing: paraffin liquid, fish flavour, gelatine, glycerol, titanium, dioxide, purified water.

Placebo and F373280 capsules will be packaged in opaque blisters.

6.2. PACKAGING AND LABELLING

The treatment units will be packed and labelled by the Clinical Pharmacy Department of the IRPF according to European Directive and local requirements.

6.2.1. Packaging

Each treatment unit will be composed of 3 cases for a 12-week treatment period.

Two 12-week treatment units will contain 3 cases, each case of 4-week treatment containing: 10 blister packs of four 1 g F373280 soft capsules or 1 g placebo soft capsules each.

6.2.2. Labelling

Investigational Products will be labelled according to the following rules:

Labelling should comply with the local requirements for Investigational Medicinal Products.

On the treatment units and cases, the labels will bear the following indications:

- a) name and address of the sponsor
- b) protocol number
- c) packaging batch number
- d) treatment number
- e) storage conditions
- f) expiry date
- g) pharmaceutical dose form
- h) route of administration
- i) quantity of dosage units
- j) direction for use
- k) legal statements:

-“for clinical trial only”, “keep out of the reach and the sight of children”, “please return to your doctor any unused product”, respect the prescribed dose”

On the treatment unit, another label will be affixed with the mention of the Investigator’s name and patient’s code (completed by the Investigator).

In addition, on each case will be mentioned the case number and a detachable label will bear the following indications:

- Protocol number
- Packaging batch number
- Expiry date
- Case number
- Treatment number

On the blister pack, the label will mention the protocol number, the packaging batch number, the case number and the treatment number.

6.3. DISTRIBUTION TO CENTRE AND STORAGE

The Clinical Pharmacy Department of the IRPF will supply the Investigational Centre with the treatment units along the study according to the need, upon request triggered by the patient’s selection.

As soon as the Pharmacist or the Investigator receives the trial medication, he/she will check the contents and immediately acknowledges the receipt in the IVRS/IWRS. The copy of the acknowledgement will be kept in the Investigator's or the Pharmacist's file. The same procedure will be applied to all further supplies during the course of the trial.

At the time of the delivery to the Centre, the following information will be provided:

- Details of storage conditions that should be respected
- And, upon request and for the 1st delivery only, a letter of release for the Investigational Medicinal Product from the Sponsor's Qualified Person

The CRA will ensure during the monitoring visits that trial medications have been received in good conditions and the acknowledgment of receipt has been performed adequately.

Treatment units should remain intact until dispensation to the patients. They should be kept at temperature below 30°C in an appropriate lockable room only accessible to the person authorised to dispense them, under the responsibility of the Pharmacist or the Investigator.

In the case of undue delay in study execution, the Pharmacist or the Investigator should ensure that the expiry date has not been exceeded.

6.4. ALLOCATION OF TREATMENTS AND DISPENSATION TO PATIENT

A randomisation list will be established by the Clinical Pharmacy Department of the IRPF. This list will be computer-generated with internal software. The randomisation methodology is validated by the Biometry Department before generation.

Treatments F373280 or placebo will be balanced in a 1:1 ratio.

As the treatment units are prepared for 12-week treatment periods, the Investigator will have to allocate a treatment number at inclusion visit (V2) and another one at visit 6.

For each patient, the treatment number given at visit 6 will not be the same that the one given at inclusion visit (V2).

The treatment numbers will be given through the IVRS/IWRS.

At selection visit (V1), practically, once patient's eligibility is confirmed:

- The Investigator:
 - Contacts the IVRS/IWRS

- Answers the questions related to the patient
- The IVRS/IWRS company:
 - Confirms this information by fax/email to the Investigator
 - Fills the “Request for Delivery of Investigational Product” form and sends it by email and/or fax to the Clinical Pharmacy Department of the *IRPF*.
- The Clinical Pharmacy Department of the *IRPF* sends the corresponding treatment unit to the Investigator within 5 days from reception of the email request form.

At inclusion visit (V2), the treatment number to be allocated for the first 12-week period to the patient is given by the IVRS/IWRS.

At visit 6, the Investigator will contact again the IVRS/IWRS to obtain the treatment number for the last 12-week period of treatment.

The Investigator will dispense to the patient the 4-week treatment cases (one or two according to the visit) which label indicates the treatment number and the administration period.

6.5. DRUG ADMINISTRATION

6.5.1. Duration of Treatment

For a patient completing the study, the theoretical study treatment exposure to F373280 or placebo will be 24 weeks.

If the ECV is postponed by 1 week to allow INR stabilization, the treatment duration will be 25 weeks.

6.5.2. Dose Schedule

One soft capsule of 1g of F373280 or placebo to be taken each day during 24 weeks.

6.5.3. Route and Conditions of Administration

The soft capsules are to be taken orally. One soft capsule is to be taken each evening with the dinner during 24 weeks.

6.6. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT

The Investigator should maintain accurate written records of drug received, dispensed, returned and any remaining treatment units, on the drug accountability form. These records should be made available for Clinical Research Associate (CRA) monitoring. The packaging of the medication should remain intact until just before the dispensation.

At each visit, the Investigator will record the number of soft capsules returned by each patient using the appropriate page of the e-CRF.

At the end of the study, all used and unused treatments including packaging should be noted, and return is organised by the CRA to the Clinical Pharmacy Department of the IRPF for destruction. A copy of the drug accountability form should be provided by the Investigator to the CRA.

6.7. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the Sponsor), the Investigator will immediately be informed by the Sponsor.

The Investigator in collaboration with the Sponsor's representatives (Study Manager, CRA) must urgently:

- Stop the delivery of the concerned investigational products to the patients.
- Inform the concerned patients that they must immediately stop taking these investigational products and bring them back.

The Study Manager/CRA organises the return of the recalled products to the Clinical Pharmacy Department of the IRPF according to the Sponsor's procedures.

7. CONCOMITANT TREATMENTS

Any existing concomitant treatment (at selection visit), any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the electronic Case Report Forms (e-CRF). All treatments should be evaluated by the Investigator at patient's selection, and treatment prolongation or stop during the study should be considered.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the e-CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration of treatment.

7.1. VITAMIN K ANTAGONIST TREATMENT

VKA should be given for at least 3 weeks before ECV and continued for the whole study duration. However, VKA should be stopped in case of occurrence of VKA intolerance during the study and the patient should be withdrawn from the study. The VKA used will be left to the decision of each Investigator according to his/her local practice.

7.2. PROHIBITED TREATMENTS

- Class I and class III antiarrhythmic treatments:

- Class I:
 - Class IA: Disopyramide, Procainamide, Quinidine
 - Class IB: Lidocaine, Mexiletine
 - Class IC: Flecainide, Propafenone
- Class III: Dofetilide, Ibutilide, Sotalol, Amiodarone, Dronedarone.

- Ranolazine

- Any PUFA

- Any oral anticoagulant treatment other than VKA: new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or irreversible antiplatelet agents P2Y₁₂ inhibitors such as ticlopidine, clopidogrel or prasugrel

- Dietary supplement with Omega 3 or Omega 6

Prohibited treatments at selection must not be prescribed for the duration of the study except in case of occurrence of an adverse event or AF episode that requires a corrective treatment in the interest of the patient's health.

7.3. AUTHORISED TREATMENTS

Other treatments will be authorised during the study duration.

However, if medication other than study drugs is administered at any time from the start of the study, details must be recorded in the e-CRF. During the study, patients must be asked whether they have been on a course of prescribed drug treatment or have taken any OTC or herbal drugs since the visit.

8. EVALUATION CRITERIA

8.1. PRIMARY EFFICACY CRITERION

8.1.1. Time to the first Atrial Fibrillation Recurrence or Atrial Flutter Emergence

8.1.1.1. *Definition*

Time to first AF recurrence or atrial flutter emergence is defined by the time to first episode of AF or atrial flutter (symptomatic or not) lasting for at least 10 minutes.

8.1.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of ECV visit (visit 3) to the final study visit (visit 9).

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed after visit 3 (from week 5).

8.1.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will be carried out from visit 3 to visit 4 using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) fixed after ECV visit.

Following holter monitoring, the heart rhythm will be documented using Trans Telephonic ECG Monitoring (TTEM).

- Trans Telephonic ECG Monitoring:

The ECG follow up will be documented using the TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). The patient will be requested to contact the Central Reading Laboratory for transmission of each stored TTEM.

Moreover, if patient experiences AF or atrial flutter symptoms during this TTEM period, it should be documented using the TTEM.

In case of AF recurrence or atrial flutter emergence and provided that the patient does not require a cardioversion or an introduction of an anti-arrhythmic at Investigator's judgement, the patient could be maintained in the study with the treatment in order to assess a spontaneous cardioversion. For that purpose the patient will continue to transmit a TTEM once a week.

- Process of centralisation of ECG (Holter and TTEM)

ECG (Holter and TTEM) will be centralized by the Central Reading Laboratory. The ECG will be validated by a trained technician, then analysed by a cardiologist. The cardiologist interpretation will be emailed to the site (or per fax on request of the site). The investigator will be asked to review and sign these documents.

The Holter and TTEM process will be fully described in separate documents.

8.2. SECONDARY EFFICACY CRITERIA

8.2.1. Numbers of AF episodes in the first week following visit 3 (ECV visit)

8.2.1.1. Definition

Number of AF episodes will consist in the assessment of AF episodes with duration at least 10 minutes (N_{Sup10}) and of less than 10 minutes (N_{Inf10}), respectively.

8.2.1.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the study visit 4.

8.2.1.3. *Evaluation Methods*

- 7-day holter monitor:

The heart rhythm monitoring will start using a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) after ECV visit from visit 3 to visit 4.

8.2.2. Duration of AF episodes in the first week following visit 3 (ECV visit)

8.2.2.1. *Definition*

Duration of AF episodes will consist in the sum of duration of each AF episode.

8.2.2.2. *Schedule*

The heart rhythm follow up will be performed from the end of successful ECV visit (visit 3) to the follow up study visit (visit 4).

8.2.2.3. *Evaluation Methods*

Duration of AF episodes will be assessed using the 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording.

8.2.3. Clinical parameters evaluation

8.2.3.1. *EHRA score assessment*

8.2.3.1.1. *Definition*

AF related symptoms will be evaluated by the EHRA (European Heart Rhythm Association) score [20]. The following items “during presumed arrhythmia episodes” are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’
- EHRA II - ‘Mild symptoms’; normal daily activity not affected
- EHRA III - ‘Severe symptoms’; normal daily activity affected
- EHRA IV - ‘Disabling symptoms’; normal daily activity discontinued

This classification relates exclusively to the patient-reported symptoms.

In addition to this score, the frequency will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily.

8.2.3.1.2. *Schedule*

EHRA evaluation will be performed in case of evocative symptoms of arrhythmia.

8.2.3.1.3. *Evaluation Methods*

EHRA evaluation will be collected by Central Reading Laboratory during TTEM period.

8.2.3.2. *Time to first AF recurrence less than 10 minutes*

Time to first AF recurrence less than 10 minutes will be assessed during TTEM period.

8.2.3.3. *Recurrence of symptomatic AF*

Recurrence of symptomatic AF will be assessed during TTEM period.

The number of recurrences of symptomatic AF consists of the number of AF recurrences associated with a symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) and confirmed by an ECG.

The time to first symptomatic AF recurrence is defined by the time to first episode of symptomatic AF.

8.2.3.4. *Number and duration of hospitalizations*

- Number and duration of hospitalizations for cardiovascular events
 - Hospitalization for AF treatment

- Hospitalization for worsening of heart failure
- Hospitalization for myocardial infarction
- All cause of hospitalization
- Number and duration of hospitalizations for thromboembolic stroke

8.2.4. Cardioversion assessment

- Assessment of spontaneous cardioversion before visit 3
- Assessment of successful cardioversion at visit 3 (i.e. return to sinus rhythm)
- Shocks distribution (1, 2 or 3 shocks)
- Number of patients needing another cardioversion after initial ECV

8.2.5. Evolution of echocardiographic parameters

8.2.5.1. Definition

The following echocardiographic parameters will be assessed: Left atrial diameter (mm), LAA (cm²), Left atrial volume (ml), Left atrial volume/BSA (ml/m²), LVEF (%), Left ventricular end diastolic volume/BSA (ml/m²), Left ventricular end systolic volume/BSA (ml/m²), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (ml), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (ml).

8.2.5.2. Schedule

Measurements will be performed at visit 1 and visit 2 to check the eligibility of the patient.

Measurements performed at visit 4, visit 6 and visit 9 are done to follow the echocardiographic evolution of the patients in sinus rhythm.

8.2.5.3. Evaluation method

The echography evaluations will be carried out according to the recommendations for chamber quantification drawn up by the American Society of Echocardiography and the European

Association of Echocardiography [23]. So, the recommended method for volume measurements is to use the biplane method of discs (modified Simpson's rule) from 2-D measurement.

8.3. BIOMARKER ASSESSMENT: RED BLOOD CELL CONCENTRATIONS OF DHA

8.3.1. Definition

Because of the limited human tissue accessibility for biopsy, red blood cell DHA contents is a marker of tissue DHA concentration [13], [14].

8.3.2. Blood samples

8.3.2.1. Collection schedule

Blood samples will be collected to determine the red blood cells (RBC) concentrations of DHA.

Blood samples will be performed at visit 2 before treatment, visit 3, visit 6 and visit 9.

Actual sampling times will be individually reported in the e-CRFs.

8.3.2.2. Technical handling

Two blood samples (2 x 4 ml) will be collected in EDTA tubes. They will be homogenized slowly by inverting the tube without shaking, stored between +2°C/+8°C in a fridge (no freezing will be allowed) and sent to Analytical Centre in refrigerated conditions (between +2°C and +8°C). Analysis will be performed within 2 weeks following reception at the Analytical Centre.

8.3.3. DHA concentration measurement

Analytical determination of RBC concentrations of DHA will be carried out by the Analytical Centre.

Lipids will be extracted from red blood cells samples with a mixture of hexane/isopropanol after acidification [17]. Total lipid extracts will be saponified and methylated. The fatty acid methyl esters (FAME) will be extracted and analyzed by Gas Chromatography.

Identification of FAME will be based on retention times obtained for FAME prepared from fatty acid standards. The area under peaks will be determined using ChemStation Software (Agilent)

and results will be expressed as % of total fatty acids. DHA concentration will be calculated using the internal standard and expressed as µg/g for red blood cells samples. Thus, omega-3 index will be assessed. The omega-3 index represents the content of EPA plus DHA in red blood cells (expressed as a percent of total fatty acids). It is a biomarker considered as a new marker of risk for death from coronary disease [18].

Results of this analytical determination will be kept confidential by the dosing centre until the end of the study, and will be provided only at the end of the study (after database lock) in a separate file.

8.4. SAFETY ASSESSMENT

8.4.1. Adverse Events

At selection, any concomitant disease will be reported on the e-CRF. At each further visit, the occurrence of AEs since the last visit will be based on the patient's spontaneous reporting, the Investigator's non-leading questioning and his/her clinical evaluation. All AEs will be reported on the e-CRF (see section 10).

8.4.2. Laboratory Investigations

8.4.2.1. Schedule

Laboratory investigations will be performed at visit 1 (before treatment) and visit 9 (end of treatment) or End of Treatment visit.

At visit 3 and 6, only a standard haematologic dosage will be performed.

Furthermore the kalemia will be checked before electrical cardioversion at visit 3.

The total volume of blood samples taken for haematology and biochemistry analysis should not exceed 30 ml.

8.4.2.2. Technical Procedures and Parameters

The following tests will be performed:

Haematology: *haematocrit, haemoglobin, RBC count, white blood cells (WBC) count, WBC differential counts (% and/or absolute), reticulocytes, platelets.*

Biochemistry: *sodium, potassium, bicarbonate, chloride, alkaline phosphatase, gamma GT, albumin, total bilirubin, conjugated bilirubin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, total cholesterol, cholesterol (HDL, LDL), triglycerides, creatine phosphokinase (CPK), fibrinogen.*

Blood samples will be taken in the morning in fasting conditions.

The estimation of GFR at selection relies on the measurement of serum creatinine and the Cockcroft- Gault formula:

Cockcroft-Gault formula

- with serum creatinine expressed as mg/L:

in men:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})]$$

in women:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / (7.2 \times \text{serum creatinine in mg/L})] \times 0.85$$

- with serum creatinine expressed as $\mu\text{mol/l}$:

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight} / \text{serum creatinine in } \mu\text{mol/l}] \times k, \text{ where } k = 1.23 \text{ for men, } 1.04 \text{ for women.}$$

(weight in kg, age in years)

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.

8.4.3. Global Physical Examination

A global physical examination including the measurement of body weight will be carried out on each body system at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9.

The Body surface area (BSA) will be calculated at the same visits using Mostellers' formula:

$$BSA = [(Weight \times Height)/3600]^{1/2}$$

(Weight in kg, height in cm)

The physical examination will be globally evaluated as "normal/abnormal". Further target inspection will be undertaken for any abnormal finding.

8.4.4. Vital Signs

Vital signs will consist in blood pressure and heart rate at rest.

8.4.4.1. *Schedule*

Vital signs will be measured at each visit.

8.4.4.2. *Technical Procedure and Parameters*

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), expressed in mmHg, will be measured after at least 5 minutes in supine position and after 2 minutes in standing position.

The heart rate (HR), expressed in beats per minute (bpm), will be measured by auscultation by counting the beats for at least 30 seconds, after at least 5 minutes in supine position and after 2 minutes in standing position.

Bodyweight will be measured with patient in underwear and with the same balance at each visit.

8.4.5. Electrocardiogram (ECG)

8.4.5.1. *Schedule*

An ECG will be recorded after at least 10 minutes of rest at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9 using a usual standardised 12-lead cardiograph.

8.4.5.2. *Technical Procedure and Parameters*

- Electrocardiogram:

The global interpretation from manual reading (normality, clinical relevance) and HR (bpm), PR (ms), QRS (ms), QT (ms), QTcB (ms), QTcF (ms), repolarisation patterns will be reported in the

e-CRF. Each print-out will include the patient's code, date, time, technician's initials and investigator's signature.

In case of thermic paper ECG print out, a photocopy will be made by the centre to ensure safe filing.

- 24 hour-Holter - ECG

An ambulatory continuous 24-hour ECG (5-leads/2 or 3 channels) will be recorded at selection visit using a holter ECG, in order to confirm persistent AF.

8.4.6. Coagulation parameters

Coagulation assessment will be evaluated by the following parameters:

- Prothrombin Time/INR (PT/INR)
- Activated Partial Thromboplastin Time (aPTT)
- Thrombin Clotting Time (TCT)

The recommendations for the controls of INR are the following [25, 26]:

1) During the pre-cardioversion period, if the anticoagulation by VKA has to be initiated, the treatment must be initiated at least 3 weeks prior to cardioversion then the INR will be monitored as follow:

- The adjustment of the dosage of VKA should be performed stepwise by controlling INR 2 to 3 times a week until stabilization within the target range (2 - 3) on 2 successive tests.
- When the INR is within the target range (2 - 3) on 2 successive tests, the dose of VKA should be maintained. Then the controls of INR will be progressively spaced within a few weeks.
- When INR is stabilized, at least one test should be performed each week.
- In all cases, an INR control must be performed within 24 h before ECV.

2) During the pre-cardioversion period, if the anticoagulation by VKA was already initiated, the INR will be monitored as follow:

- One INR per week up to ECV
- An INR control must be performed within 24 h before ECV

3) After cardioversion : one INR every 4 weeks

4) Throughout the duration of the study if INR > 3 the advocated actions are:

- No transesophageal echocardiography before cardioversion
- For asymptomatic patients:
 - $3 < \text{INR} < 4$: no omission of VKA (dose adjustment if required), no vitamin K
 - $4 \leq \text{INR} < 6$: omit one dose of VKA, no vitamin K
 - $6 \leq \text{INR} < 10$: interrupt VKA, vitamin K 2 mg orally
 - $\text{INR} \geq 10$: interrupt VKA, vitamin K 5 mg orally

For $\text{INR} \geq 6$, an adverse event has to be reported (asymptomatic overdose).

Anti-coagulation by VKA should be given at least 3 weeks before ECV and continued for the whole study duration.

aPTT and TCT will be performed at visit 1, visit 2, visit 3, visit 6, visit 7, and visit 9.

The quantity of blood samples collected at each time for coagulation parameters will be 2 ml.

Additional tests may be done at the Investigator's discretion, in the patient's interest. In case of any abnormal and/or clinically significant results, the Investigator should order laboratory control tests.

8.5. CONCOMITANT TREATMENTS

Concomitant treatments will be evaluated at each study visit.

Requirements related to patient's concomitant treatments started before selection visit and continued throughout the trial, or started during the trial, can be found in section 7.

8.6. COMPLIANCE

The patient will be reminded at each visit to bring back at the following visit any used or unused remaining soft capsule, blister and case.

At each visit (except at visit 4), the Investigator will record the number of supplied and remaining soft capsules in the e-CRF.

9. STUDY PROCEDURES

Visit 1 - Selection Visit (Week - 4 to Week -1):

The patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form (see section 14.3). If the patient accepts to participate in the study, he/she will sign the informed consent form and will keep a copy.

The patient will be assessed for the following:

- Demographic characteristics (gender, age, height, body surface area)
- Personal and medico-surgical history
- Habits (Tobacco, alcohol consumption, dietary habits including fish consumption...)
- Cardiovascular diseases, mainly detailed history of Heart Failure and AF characteristics
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Concomitant diseases, adverse signs or symptoms (able to be used for treatment emergent AE determination)
- Concomitant treatments (authorised, disallowed)
- Global physical examination/bodyweight
- Vital signs
- Biology: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Biology assessment of renal function: creatinine or estimated glomerular filtration rate

If the results of the above assessments are compatible with the selection criteria:

- A 24-hour continuous ECG ambulatory recording (Holter ECG) device will be installed on the patient to monitor the patient heart rhythm. The patient will be requested to bring back the device after the termination of 24 hours recording. The recording will be transmitted from the Investigational site to the Central Reading Laboratory. The Central Reading Laboratory will send his/her assessment regarding the confirmation of persistent AF within 2 working days to the Investigator.

- The patient will enter the selection and pre-cardioversion periods in which anticoagulant (VKA) will be adjusted to achieve ideally an International Normalized Ratio (INR) in the range of 2 to 3 before ECV.

At the end of the visit, the Investigator will contact the IVRS/IWRS to confirm the patient selection (which will automatically order the treatment delivery) and organise the appointment for the next visit.

The patient will receive from the investigational centre the participant card to be kept for all the duration of the study.

Visit 2 - Inclusion Visit (Day 1):

If the patient's behaviour during the selection period and/or the result of complementary examinations, particularly the confirmation of the presence of persistent AF by the Central Reading Laboratory during this period and the laboratory tests, are compatible with the inclusion criteria, the patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: red blood cell concentrations of DHA and coagulation parameters Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination/bodyweight
- Vital signs
- Echocardiography using a two-dimensional echocardiography
- 12-lead ECG
- Urine pregnancy test for women of child bearing potential

If the results of the above assessments are compatible with the inclusion criteria, the patient will be included and the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 2 for the first 12-week period.

Between this Inclusion visit and the next visit (V3), the INR will be closely monitored (refer to paragraph 8.4.6) in order to fulfil the ECV conditions (refer to paragraph 3).

At the end of the visit, the Investigator will organise the appointment for the next visit and will give the treatment for the next 4-week period (one case of treatment).

Visit 3 (Week 4: D28 -2/+7 days) cardioversion:

Patient will be assessed for the following criteria:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Haematology, RBC concentrations of DHA, Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT)
- Global Physical examination /bodyweight
- Vital signs
- 12-lead ECG
- Electrocardioversion (ECV): ECV has to be performed 4 weeks after randomization in patients with AF. ECV will be performed in the morning, with the patient in the fasting state and without dyskalemia. An INR value control must be performed within 24h before ECV. INR values ≥ 2 on the 3 last tests performed before ECV are required. However, if only 2 INR values are ≥ 2 among those 3 last tests, an ECV can be performed if the presence of atrial thrombosis can be excluded with an ECHO-TE (transesophageal echocardiography) performed on the same day (before ECV) and the patient can continue the study. Anesthesia will be induced and patients will be cardioverted with administration of a synchronized, biphasic current. The initial shock will be set at 100 J if the body weight is less than 70 kg and at 150 J for higher body weights. Successful cardioversion will be defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, will be administered. Failure of ECV is defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients will be monitored on telemetry for at least 6 hours before discharge.

Patients who will not revert to sinus rhythm or with early AF relapse or early atrial flutter emergence within the observation period after ECV will be withdrawn from the study and will be considered to have finished their follow-up.

At the end of the visit, a 7-day continuous ECG (5-leads/2 or 3 channels) ambulatory recording (holter ECG) will be installed on the patient in order to monitor the patient heart rhythm after ECV.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

At the end of the visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next 8-week period (two cases of treatment).

Visit 4 (Week 5: D35 -2/+7 days):

After removal of the continuous ECG ambulatory device, the patient will be assessed for the following criteria:

- Assessment of AE
- Concomitant treatments (authorised, disallowed)
- Bodyweight (bodyweight measured at V3 to be used)
- Vitals Signs
- Echocardiography using a two-dimensional echocardiography

At the end of the visit, the patient will be given the TTEM device for cardiac monitoring. The patient will be clearly instructed on the frequency and modalities of transmission. The patient will be requested to perform one transmission per week from this visit (initial call to perform with the patient) to the visit 9 (week 24 – end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.

Visit 6* (Week 12: D84 ± 7 days) - Visit 7 (Week 16: D112 ± 7 days) :

*see amendment PA05 dated 22OCT2014

Patient will be assessed for the following criteria:

- Adverse events

- Concomitant treatments (authorised, disallowed)
- Laboratory examination: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT). However, in case of discontinuation of anticoagulation after ECV due to occurrence of VKA intolerance, the monitoring of INR, aPTT and TCT should be stopped.
- Global Physical examination/bodyweight
- Vital signs
- 12-lead ECG
- The cardiac monitoring will be continued using the TTEM device through one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24, end of study). Moreover, in case of AF or atrial flutter symptoms, additional transmissions may be performed.

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused capsules for each 4-week treatment period.

In addition, at visit 6:

- the investigator will contact the IVRS/IWRS to obtain the treatment unit number to be dispensed at visit 6 for the last 12-week period.
- an echocardiography will be performed, an haematology examination will be done and the RBC concentration of DHA will be measured.

At the end of each visit, the Investigator will organise the appointment for the next visit and give the treatment to be taken during the next treatment period: one case at visit 6 and two cases at visit 7.

Visit 9* - End-of-Study Visit (Week 24: D168 ± 7 days):

*see amendment PA05 dated 22OCT2014

Patient will be assessed for the following:

- Adverse events
- Concomitant treatments (authorised, disallowed)
- Global Physical examination/bodyweight

- Vital signs
- 12-lead ECG
- Laboratory examination: haematology, biochemistry, assessment of coagulation parameters: Prothrombin Time/INR (PT/INR), Activated Partial Thromboplastin Time (aPTT), Thrombin Clotting Time (TCT), Red blood cell concentration of DHA.
- Urine pregnancy test for women of childbearing potential
- Echocardiography using a two-dimensional echocardiography

The Investigator will collect all unused cases, blisters and soft capsules, and will count the unused soft capsules.

The total volume of blood collected should be about 90 ml for the study duration (30 ml for the total volume of haematology and biochemistry, 2 ml for each blood samples for coagulations parameters and 4 ml for each blood samples of DHA).

10. ADVERSE EVENTS: DEFINITION AND REPORTING

10.1. ADVERSE EVENTS

10.1.1. Definition of Adverse Events

An AE is any adverse change from the patient's baseline condition, i.e. any subjective signs and symptoms or change in a concomitant disease present at the Selection Visit considered or not related to the treatment.

AE includes intercurrent signs, symptoms, illnesses and significant deviations from baseline for vital signs and laboratory values which may occur during the course of the clinical study.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the laboratory normal ranges and that are clinically significant. The frequency of such checks should be defined by the Investigator according to the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and *Pierre Fabre Médicament* notified.

10.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

10.1.3. Reporting of Adverse Events

The records of AE in the e-CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

10.2. SERIOUS ADVERSE EVENTS (SAE)

10.2.1. Definition

A SAE includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires the patient's hospitalisation or prolongation of current hospitalisation *
- Is a congenital anomaly or birth defect

Other events such as cancer and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the Investigator considers significant enough or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE (see section 10.3).

Any pregnancy occurring during/after exposure to the study drug(s) should be reported on the SAE notification form (see section 10.4).

* any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below:

- planned (as per protocol) medical/surgical procedure
- preparation for routine health assessment/procedure (e.g. routine colonoscopy)
- planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required)
- administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances)

will not be reported as a SAE.

10.2.2. Reporting of SAE

All Serious Adverse Events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, and occurring once the informed consent form has been signed, must be reported by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Sponsor of this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") with all the available information about the event (see appendix 17.2), to the Sponsor's Corporate Vigilances e-mail dedicated box:

HQ.pharmacovigilance@pierre-fabre.com

In case it is not possible to send the report by e-mail it can be sent by FAX at the following number:

+ 33 1 49 10 80 90

In case of non-inclusion, the reporting period ends when the non-inclusion is documented.

10.2.3. Follow-up of SAE

The Investigator must draw-up a specific clinical report and use the "Notification of serious adverse event" form ("follow-up") (see appendix 17.2) and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

10.2.4. SAE Occurring After the Study

Any SAE occurring during 30 days following the end of the study for the patient should be notified to the Sponsor.

Must also be notified to the Sponsor any event occurring at any time after the end of the study for the patient which may be related to the study treatment in the Investigator's opinion.

10.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

For the purpose of this trial, an overdose will be defined as any dose exceeding the planned prescribed dose of the study drug or the administration of any dose of an associated product that is considered both excessive and medically important.

In the absence of seriousness criteria, the overdose and associated adverse event if any, are reported only on the Adverse Event page of the e-CRF. **If the definition** of seriousness criteria **is met**, the SAE notification form must also be transmitted to the Sponsor.

10.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the Sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug and must be withdrawn immediately from the study.

If pregnancy is suspected while the patient is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner and the patient is withdrawn from the study.

The Investigator must report to the Sponsor any pregnancy which occurs during or after the patient has been exposed to the study drug and until 30 days after the last study drug administration. The Investigator must immediately notify the Sponsor using the SAE notification form and also report the pregnancy on the AE page of the e-CRF.

Women who become pregnant after exposure to the study drug must be followed by the Investigator until the completion/termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the Sponsor (baby's healthy status).

10.5. SPONSOR'S RESPONSIBILITIES FOR SAFETY REPORTING

PURPOSES

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements.

11. DATA COLLECTION AND STUDY MONITORING

11.1. DATA COLLECTION

11.1.1. Case Report Form

An e-CRF will be used to record all patient data required by the protocol except the central ECG (Holter ECG, TTEM) and DHA data which will be transferred from vendors to the subcontractor as electronic data files that will be loaded into the study database.

The e-CRF should be fully validated, compliant with ICH-GCP requirements and European regulations and should include a traceability system for data corrections and deletions (audit trail).

Prior to the start of the study, the Investigator will complete a "*Delegation of significant study-related duties*" form. The signature and initials of all personal in charge of e-CRF completion should be recorded on this form. Each person involved in e-CRF completion, review, correction and / or validation will be trained and will have an individual login and access code to the e-CRF. Training sessions will be held by the subcontractor for all participants using this tool. An e-CRF user manual will be available for investigators and CRAs.

All the information included into the e-CRF will be recorded from source documents onto the e-CRF by an authorised person.

The Investigator is responsible for the management and accuracy of the information on the e-CRF. At each monitoring visit, the e-CRF(s) should be at the CRA's disposition for review and validation.

At the end of the study, a CD-ROM containing the pdf version of all e-CRFs (including audit-trail) will be sent by the subcontractor to the Sponsor and to the investigational sites for archiving. The subcontractor must store all study data for at least 15 years after the end of the study and ensure their legibility and accessibility during all the storage period.

11.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data.

Source documents along with all other trial-related documents (copies of all "informed consent" forms, e-CRFs CD-ROM, drug inventories and any correspondence related to the study) must be kept in the investigator's file throughout the study, and then, must be stored in the study centre's archives for a period of at least 15 years or as per local legal requirements, whatever is the longest.

For further details see section 15.2.

11.2. STUDY MONITORING

11.2.1. Monitoring visits

On-site visits will be carried out by a representative of the Sponsor's staff (Study Manager or CRA) prior to study initiation and at regular intervals (every 4 to 6 weeks) throughout the study. Additional visits and communication by telephone fax or meeting may be performed if necessary. Any site visit performed by the Sponsor's representatives will be recorded in the Investigator's study file.

11.2.1.1. Site Preselection Visit

Before selecting a centre for the study, a visit will be carried out by the CRA and/or the Study Manager to ensure that the Investigator has the necessary capacities (availability, patient's recruitment, environment), technical means and staff to carry out the study.

11.2.1.2. Initiation Visit

Before the start of the study at all investigational sites, an initiation visit will be carried out by the CRA to check at the latest that:

- The Investigator:
 - has received the technical protocol, administrative and financial agreement signed by all parties
 - has received the written statement of the Ethics Committee approval and the list of its members and their functions
- The original dated and signed *curriculum vitae* of the investigator(s) has been collected
- Laboratory normal ranges have been collected
- All study materials are available on the study site
- All participants agree with the monitoring procedures and know the study procedures
- All participants are aware of a possible audit or inspection

The CRA has also to provide training on the study protocol requirements and study specific procedures.

11.2.1.3. Follow-up Visits

Throughout the study, regular follow-up visits will be carried out by the CRA to check compliance with GCP, patient's informed consents, strict application of the protocol, conformity of the data entered on the e-CRF with the source documents and ensure its correct completion, adverse events reporting, proper retention, storage and management of the study medication, as well as the source and other trial-related documents.

11.2.1.4. Closing Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the e-CRFs CD-ROM with pdf files are correctly stored
- Control the accountability of intact and used treatment units and return them to the Clinical Pharmacy Department of the *IRPF* for destruction
- Obtain the last data clarifications and/or solutions if any
- Collect the patient's consent forms in sealed envelopes (except in case of specific country requirements),
- Make an on-site review of all study documentation and complete it if necessary
- And finally, remind the Investigator of his regulatory obligations, study document archiving process and duration.

11.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Sponsor representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Sponsor representatives keep professional confidentiality with regards to the patient data.

11.3. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to assess at intervals the progress of the clinical trial, the compliance with the inclusion criteria, the quality of follow up, the quality of primary end point measures, the safety data. The IDMC will thereafter recommend to the Sponsor whether to continue, modify, or stop the study.

The IDMC operating procedures will be described in an independent document.

12. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerised database by the Data Management Department of the subcontractor and under the supervision of the Data Manager of Pierre Fabre Biometry (PFB) according to the following procedures.

12.1. DATA ENTRY

All required data will be collected by the Investigator or authorised designee (duly identified into the delegation task list) on the e-CRFs.

The e-CRFs used for this study will be developed and maintained by the Data Management Department of the subcontractor and approved by the Sponsor.

Electronic data (Holter ECG, TTEM and DHA) will be transferred by the 3rd party vendor according to the specifications given by the Data Manager of the subcontractor. These data will be captured and handled in accordance with the European GCP ICH E6 guideline.

12.2. DATA CLEANING

The subcontractor will define in the Data Validation Plan for reviewing and querying data, descriptions of both manual and electronic edit checks. Upon Sponsor approval, the subcontractor will program the checks.

The subcontractor will review the data over the course of the study, working with the Sponsor to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the e-CRF.

12.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded by the subcontractor using the MedDRA dictionary (latest version in use).

Concomitant medication will be coded by the subcontractor using the WHO-DRUG dictionary (latest version in use).

The Sponsor Clinical Development Physician will validate the coding.

12.4. DATA STORAGE

Computer data files as well as their modifications will be archived by the subcontractor and kept available upon request of the Sponsor.

12.5. DATABASE LOCK

The validated database will be locked by the subcontractor upon request of the Data Manager of PFB following the completion of all steps required, i.e. data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation committee.

Then, the subcontractor will transfer the locked database in SAS format to the Data Manager of PFB who assume storage on the PFB secured server.

13. STATISTICAL ANALYSIS

After the database lock and the randomisation code release, the statistical analysis will be performed by PFB or under the supervision of the statistician of PFB using SAS[®] software, according to the Statistical Analysis Plan approved by the Validation Committee.

13.1. GENERAL CONSIDERATIONS

The main objective of the study is to assess the efficacy of F373280 versus placebo on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded within a descriptive perspective.

The statistical significance level of the various two sided tests of all analyses will be 5 %.

13.2. SAMPLE SIZE

Assuming an AF recurrence or atrial flutter emergence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients

per group is required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level.

According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients will have to be randomised per group.

Due to the premature stop of the recruitment 135 patients were finally randomised.

13.3. PROTOCOL DEVIATIONS

Prior to the database lock and the randomisation code release, the Validation Committee members will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see section 13.4).

A listing of all protocol deviations will be provided for all randomised patients, including the type (major/minor) of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set defined in section 13.4.

13.4. DATA SETS ANALYSED

The following 3 data sets will be analysed (as defined by the Validation Committee):

- The Safety Set composed of all randomised patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety.
- The 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. This data set will be used to perform analyses of Efficacy.
- The Per Protocol Set (PP) which is the subset of the Full Analysis Set composed of all patients with a primary efficacy criteria available and without any major protocol

deviation or other source of bias for primary criteria analyses. This data set will be used to perform the supportive analysis of the primary efficacy criterion.

13.5. HANDLING OF DROPOUTS AND MISSING DATA

13.5.1. Dropouts

The number of patients who withdraw from the study after their randomisation will be provided by treatment group for all treated patients (Safety Set). All withdrawn patients will be further described regarding their time to dropout and reasons for withdrawal.

13.5.2. Repositioning of Visits

No repositioning of visits will be done.

13.5.3. Missing Data

Missing values will not be substituted by estimated values, but considered as missing in statistical analysis.

13.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, patient's background, medical and surgical history, demographic data and disease characteristics will be described by treatment group on the Safety Set.

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values.
- Qualitative parameters will be described by treatment group and overall using frequencies.

Concomitant diseases, as well as medical and surgical histories will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

If more than 10% of patients are excluded from the FAS and PP set, the description of patients by treatment group at selection and inclusion will be repeated on the FAS and PP set for all parameters.

No statistical test of comparability of treatment groups at baseline will be performed.

13.7. EFFICACY ANALYSIS

13.7.1. Primary Criterion

13.7.1.1. Primary Analysis

The primary criteria, time to first recurrence of AF or atrial flutter emergence, will be analysed using the Kaplan Meier method and compared with the Log rank test. Hazard ratios and 95% confidence intervals will be estimated with the Cox regression model.

The primary analysis will be performed on the FAS.

13.7.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

13.7.1.3. Additional Analysis

To take into consideration the sample size reduction, the **predictive probability of success** with the expected sample size based on observed data, the **predictive power** and the **conditional power** will be provided to support the statistical decision.

13.7.2. Secondary Criteria

All secondary analyses will be performed on the FAS. If more than 10% of patients are excluded from the PP set, the secondary analyses will be repeated on the PP set.

13.7.2.1. Numbers of Atrial Fibrillation Episodes in the first week following V3

Both the numbers of AF episodes (symptomatic or not) lasting for at least 10 minutes and with duration less than 10 minutes (N_{Sup10} and N_{Inf10}) will be described by treatment group and compared by the chi-square test (or CMH test adjusted for centre) or Fisher's exact Test.

13.7.2.2. Duration of Atrial Fibrillation Episodes in the first week following V3

The duration of all AF Episodes will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centres effects) or Wilcoxon test.

13.7.2.3. Time to first AF recurrence less than 10 minutes or symptomatic

The time to the first AF recurrence less than 10 minutes and the time to the first symptomatic AF recurrence will be analysed as the primary analysis.

13.7.2.4. Clinical parameters evaluation

The EHRA score will be described by treatment group and analysed using a chi-squared test (or CMH test adjusted for centre) or Fisher's exact Test.

The frequency of presumed arrhythmia will be described by treatment group.

The number of recurrence of symptomatic AF, of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes), of spontaneous cardioversion, of successful cardioversion (including number of shocks distribution) and the number of patients needing cardioversion after initial ECV will be described by treatment group and compared using a chi-square test or a Fisher Test (if the numbers are relevant).

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using the Student t (or using an ANOVA with treatment and centre effects) or Wilcoxon test.

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to V9 and from V2 to V9.

13.7.2.5. Biomarker analysis: red blood cell concentrations of DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time.

13.8. SAFETY ANALYSIS

The Safety Set will be used to perform all analyses of the safety criteria.

13.8.1. Adverse Events

Any adverse event having been reported during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Adverse events will be classified as:

- Treatment emergent adverse events, *i.e.*, any adverse event which occurs or worsens on study treatment during the randomised period.
- Or non treatment emergent adverse events, *i.e.*, any adverse event which occurs during the run-in period (before V2) or is reported as concomitant disease with the same intensity.

For each study period, any patient with at least one reported adverse event will be classified as a patient:

- With at least one adverse event
- With at least one treatment emergent adverse event
- With one TEAE
- With two TEAEs
- With at least three TEAEs
- With at least one related TEAE
- With an adverse event leading to the study treatment discontinuation (definitive or temporary)
- With an adverse event leading to withdrawal
- With at least one serious adverse event.

Numbers and percentages of patient with at least one reported treatment emergent adverse event will be tabulated by treatment group:

- By system organ class
- By system organ class and preferred term
- By system organ class and preferred term, taking into consideration its most severe intensity

- And by system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

The number and percentage of patient with at least one most common (reported in 1% patients in any group) drug related TEAE ("not excluded or unassessable") will be tabulated by Preferred Term and Treatment group in decreasing order for the treatment group (for all patients).

The number and percentage of patients with at least one reported most common treatment emergent adverse event will also be plotted by treatment group. This graphical representation will highlight the frequencies of the most severe intensities reported by system organ class and preferred term.

SAE will also be described on an individual basis: treatment group, patient's code, sex and age, Investigator's reported term, preferred term, time of onset according to the time of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the Investigator's opinion.

13.8.2. Clinical Laboratory Evaluation

For each laboratory parameter, data will be tabulated by treatment group and assessment time.

The absolute changes post-trial drug administration - baseline (the baseline value being the value measured on the last blood sample collected before the first trial drug administration) will be calculated and tabulated by parameter, treatment group and post-trial drug administration assessment time. Results of retests performed post-trial drug administration will not be analysed and tabulated. They will only be displayed in individual data listings.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 24 value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by

locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendix 17.3).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

CNALV (see in Appendix 17.3) will be identified and described on an individual basis. If relevant, five separate individual data listings by treatment group will be provided:

- CNALV for haemoglobin (including corresponding individual results of erythrocytes and haematocrit)
- CNALV for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- CNALV for platelets (including corresponding individual results of erythrocytes and leucocytes)
- CNALV for liver function parameters (including corresponding individual results of gamma-GT)
- CNALV for serum creatinine

13.8.3. Global Physical Examination

Recorded data of the global physical examination performed will not be tabulated as any abnormal findings post-randomisation should be reported as AEs (if clinically significant).

Physical examination assessments will be provided in the listings of individual data.

13.8.4. Vital Signs, Physical Findings and Other Observations Related to Safety

13.8.4.1. Vital Sign Measurements Over Time

For each parameter (systolic blood pressure, diastolic blood pressure and HR in supine and standing positions), descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.2. Body weight

Descriptive statistics over time of values and changes from baseline will be tabulated by treatment group and assessment time.

13.8.4.3. Individual Patient Changes

The number and percentage of patient with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (see Table 1 in Appendix 17.3).

According to the pharmacological drug profile mentioned previously in this Protocol, the changes from baseline to the maximum and/or minimum post-baseline value could be categorized and tabulated by treatment group with frequencies and decreasing cumulative percentages.

If there is a signal of a drug effect toward one direction rather than the other, additionally shift tables of variations from baseline to the maximum or minimum post-baseline value could be also provided (see Table 2 to 4 in Appendix 17.3).

An individual data listing of patients with symptomatic or asymptomatic orthostatic hypotension will be provided by treatment group (see Table 5 in Appendix 17.3).

13.8.5. ECG

Frequencies on the clinical interpretation (normal, abnormal CS or NCS) will be presented by treatment group and assessment time. Individual tabulated data for ECG abnormalities will be also displayed.

13.8.6. Coagulation parameters

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration will be produced.

13.9. CONCOMITANT TREATMENTS

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

13.10. COMPLIANCE

The percentage of compliance will be described by treatment group using the quantity

$$Compliance(\%) = \frac{Estimated_actual_consumption}{Theoretical_consumption} \times 100$$

with: Estimated actual consumption = number of tablets provided at the start of study (Visit 2) minus number of tablets returned at the end of study (Visit 9)

Theoretical consumption = number of days of treatment intake planned between the start and the end of study (168 days \pm 7days)

13.11. INTERIM ANALYSIS AND DATA MONITORING

No analyses of efficacy data are planned for IDMC that ensures that the overall probability of type I error is controlled. No Type I error and sample size adjustments are necessary. Any recommendations of the IDMC to alter study conduct will be based on safety, so IDMC monitoring of the study will not affect the statistical operating characteristics of the final analysis.

The IDMC will review, two times during the study period (after the first 30 subjects will have been randomized and when the first 80 subjects will have terminated their study participation), safety data results across treatment groups and judges whether the overall safety and feasibility (not futility) of the trial remain acceptable.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee whose procedures and operations meet the GCP and National Legal Requirements.

Depending on National Regulations, the application is submitted to the Ethics Committee by the Sponsor (or representative) or by the Investigator.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required (depending on National Regulations) is carried out by the Sponsor.

The screening of patients does not start before the approval of the Ethics Committee has been obtained and the study authorised by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

14.3. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patients before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure starts.

This information and consent procedure is under the Investigator's responsibility.

The information and consent document are made in triplicate: the original copy is kept by the Investigator, one copy is given to the patient and the last copy is kept by the Clinical Quality Assurance Unit of the Sponsor in a sealed envelope at the end of study (except in case of specific country requirement).

Specific areas of the Sponsor's copy are not triplicated to avoid the reading of the patient's surname (except the first 3 letters), first name, address and signature.

If any information becomes available during the trial that may be relevant to the patient's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the patient to confirm agreement to continue participating.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility in accordance with the French law, "Loi Informatique et Libertés" (January 6, 1978, and subsequent amendments) and with the European Directive 95/46/CE.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the Sponsor Pierre Fabre Médicament, has an insurance policy intended to guarantee against possible damage resulting from the research. The studies and/or experiments performed on behalf of the Sponsor Pierre Fabre Médicament are specifically and expressly guaranteed.

It is advisable to underline that non compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities.

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigator:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, a CD Rom containing a pdf copy of e-CRF, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file.
- Retains all documents relating to the screening (consent and investigation results) of all patients included in the trial or not.

- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on e-CRFs with those from source documents.
- Authorises direct access to source documents for monitoring, audits and inspections.
- The trial-related documents must be retained as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the last visit of the last patient undergoing the trial.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety
- New information that could jeopardise the patient's safety
- Stopping of the development ...

15.3.2.2. Early Study Termination Decided by the Competent Authorities

The Competent Authorities may suspend or prohibit a study if they consider that either the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor is responsible for making sure that both its representatives (Study Manager, CRA...) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organised internally at Pierre Fabre Médicament and at the investigational site where the e-CRFs are matched against source documents.

All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department.

Oral information about the audit results are given to the Investigator.

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion, to verify the conduct of the study and quality of the data. The Investigator must provide to the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol and related documentation, e-CRF, Investigator's Brochure) contain confidential information.

Except if agreed in writing with the Study Manager, the Investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. CLINICAL STUDY REPORT

Data analysis and clinical study report writing are under the Sponsor's responsibility.

Upon data analysis completion, a final report including a review of the objectives and methods, a presentation and a discussion of the results is drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95).

The report is a clinical and statistical integrated report. It must be signed by the Sponsor's representative(s) and the Coordinating Investigator.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, the global results of the Research are communicated to the Investigator. According to the Local Regulation, the patient can ask the Investigator for the results.

15.9. STUDY RESULTS PUBLICATION

The information and data collected during the conduct of this clinical study are considered confidential and are used by the Sponsor in connection with the development of the study drug. This information may be disclosed if deemed necessary by the Sponsor.

To allow the use of the information derived from this clinical study and to insure compliance with Current Regulations, the Investigator must provide the Sponsor with complete test results and all data collected during the study.

Only the Sponsor may make study information available to physicians and to Regulatory Agencies, except as required by Current Regulations.

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor.

In the event the Sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The Investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the Sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) Investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the Sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

The authors list is agreed by all Investigators prior to publication. The names of the authors are provided according to their participation in the design of the protocol as well as their recruitment of eligible and analysable patients.

16. REFERENCES

- [1]. **F373280 INVESTIGATOR'S BROCHURE**, version October 2013
- [2]. NODARI S., TRIGGIONAI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
n-3 Polyunsaturated Fatty Acids in the prevention of atrial Fibrillation Recurrences after electrical cardioversion. A prospective, Randomised study
Circulation, 2011; 124:1100-1106
- [3]. NODARI S., TRIGGIANI M., CAMPIA U., MANERBA A., MILESI G., CESANA M.B., GHEORGHIADE M., DEI CAS L.
Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy
J. Am. Coll. Cardiol. 2011;57;870-879
- [4]. MOERTL D., HAMMER A., STEINER S., HUTULEAC R., VONBANK K., BERGER R.
Dose-dependant effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non ischemic origin: A double-blind, placebo-controlled, 3-arm study
American Heart Journal 2011; 161:915.e1-915.e9 - volume 161, number 5
- [5]. GISSI-HF INVESTIGATORS
Effects of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GSSI-HF Trial): a randomised, double-blind, placebo-controlled trial
The lancet on line - August 2008
- [6]. CAMM A.J., KIRCHHOF P., LIP G.Y., SCHOTTEN U., SABELIEVA I., ERNST S., VAN GELDER I.C., AL-ATTAR N., HINDRICKS G., PRENDERGAST B., HEIDBUCHEL H., ALFIERI O., ANGELINI A., ATAR D., COLONNA P., DE CATERINA R., DE SUTTER J., GOETTE A., GORENEK B., HELDAL M., HOHLOSER S.H., KOLH P., LE HEUZEY J.Y., PONIKOWSKI P., RUTTEN F.H.
Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Eur Heart J. 2010 Oct;31(19):2369-429
- [7]. KOWEY PR, REIFFEL JA, ELLENBOGEN KA, NACCARELLI GV, PRATT CM.
Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomised controlled trial.
JAMA. 2010;304:2363–2372.

- [8]. BIANCONI L., CALO L., MENNUNI M., SANTINI L., MOROSETTI P., AZZOLINI P., BARBATO G., BISCIONE F., ROMANO P., SANTINI M.
N-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomised, double-blind, multicentre study
Europace (2011) 13, 174-181
- [9]. **OMACOR®** SUMMARY PRODUCT CHARACTERISTICS (SPC) dated 17/02/2012
- [10]. **BEPANTHENE®** SUMMARY PRODUCT CHARACTERISTICS (SPC)
- [11]. TOUBOUL P, BRUGADA J, CAPUCCI A, CRIJNS HJ, EDVARDSSON N, HOHNLOSER SH.
Dronedarone for prevention of atrial fibrillation: a dose-ranging study.
Eur Heart J 2003;24(16):1481-7.
- [12]. LE HEUZEY JY AND ALL.
A Short-Term, Randomised, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study.
J Cardiovasc Electrophysiol.
- [13]. **METCALF G.R., JAMES J.M., GIBSON A.R., EDWARDS J., STUBBERFIELD J., STUKLIS R., YOUNG D.G., ROBERTS-THOMSON K. & CLELAND G.L.M.L. & OKEN H.**
Effects of fish-oil supplementation on myocardial fatty acids in humans.
Am J Clin Nutr (2007); 85 : 1225.
- [14]. **ARTERBURN M.L. & OKEN H.**
Distribution, interconversion and dose response of n-3 fatty acids in humans.
Am J Clin Nutr (2006);83 : 1469-1473S.
- [15]. **TIELEMAN RG, VAN GELDER IC, CRIJNS HJ, DE KAM PJ, VAN DEN BERG MP, HAAKSMA J, VAN DER WOUDE HJ, AND ALLESSIE MA.**
Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodelling of the atria?
J. Am. Coll. Cardiol. 1998;31;167-173
- [16]. SALM P, TAYLOR PJ, KOSTNER K
Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry.
Biomed Chromatogr 2011 Jun;25(6):652-9.
- [17]. LEGRAND P., SCHMITT B., MOUROT J., CATHELINE D., CHESNEAU G., MIREAUX M., KERHOAS N., WEILL P.

The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese human.

Lipids, 2010, 45, 11-19.

- [18]. HARRIS WS, VON SCHACKY C.
The Omega-3 Index: a new risk factor for death from coronary heart disease?
Prev Med. 2004 Jul; 39(1):212-20
- [19]. ABSTRACT: P5161.
NODARI S, MANERBA A., MADURERI A., BERLINGHIERI N., PULCINI E., FRATTINI S., METRA M, DEI CAS L.
Effects of Polyunsaturated Fatty Acids n-3 (PUFA n-3) in the prophylaxis of atrial fibrillation relapses after external electric cardioversion
World Congress of Cardiology 2006, 2-6 September, Barcelona – Spain
- [20]. **KIRCHHOF P., AURICCHIO A., BAX J., CRIJNS H., CAMM J., DIENER HC., GOETTE A., HINDRICKS G., HOHNLOSER S., KAPPENBERGER L., KUCK KH., LIP HYG., OLSSON B., MEINERTZ T., PRIORI S., RAVENS U., STEINBECK G., SVERHAGE E., TIJSSEN J., VINCENT A., BREITHARDT G.**
Outcome parameters from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.
Europace 2007, 9, 1006-1023
- [21]. **EUROPEAN MEDICINES AGENCY**
Addendum to the guideline on antiarrhythmics on atrial fibrillation and atrial flutter.
EMA/CHMA/EWP/213056/2010
- [22]. **OWEN AJ, PETER-PRZYBOROWSKA BA, HOY AJ, MCLENNAN PL.**
Dietary fish oil dose- and time-response effects on cardiac phospholipid fatty acid composition.
Lipids. 2004;39:955–961
- [23]. ROBERTO M. LANG, MICHELLE BIERIG, RICHARD B. DEVEREUX, FRANK A. FLACHSKAMPF*, ELYSE FOSTER, PATRICIA A. PELLIKKA, MICHAEL H. PICARD, MARY J. ROMAN, JAMES SEWARD, JACK SHANEWISE, SCOTT SOLOMON, KIRK T. SPENCER, MARTIN ST. JOHN SUTTON, WILLIAM STEWART.
Recommendations for chamber quantification
Eur J Echocardiography (2006) 7, 79-108
- [24]. JOHN J.V. McMURRAY, STAMATIS ADAMOPOULOS, STEFAN D. ANKER, ANGELO AURICCHIO, MICHAEL BÖHM, KENNETH DICKSTEIN, VOLKMAR FALK, GERASIMOS FILIPPATOS, CÂNDIDA FONSECA, MIGUEL ANGEL GOMEZ-SANCHEZ, TINY JAARSMA, LARS KØBER, **GREGORY Y.H. LIP, ALDO PIETRO MAGGIONI, ALEXANDER PARKHOMENKO, BURKERT**

M. PIESKE, BOGDAN A. POPESCU, PER K. RØNNEVIK, FRANS H. RUTTEN, JUERG SCHWITTER, PETAR SEFEROVIC, JANINA STEPINSKA, PEDRO T. TRINDADE, ADRIAAN A. VOORS, FAIEZ ZANNAD, ANDREAS ZEIHNER
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012
European Heart Journal (2012) 33, 1787–1847

- [25]. AGENCE NATIONALE DE SECURITE DU MEDICAMENT ET DES PRODUITS DE SANTE (ANSM).
Bon usage des médicaments antivitamin K (AVK)
Actualisation – Juillet 2012
- [26]. GILLES PERNOD, ANNE GODIER, CLAIRE GOZALO, BENJAMIN TREMEY, PIERRE SIE
French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding)
Thrombosis Research 126 (2010) e167–e174

17. APPENDICES

17.1. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity,

integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be

enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

17.2. SAE REPORT FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE) OR PREGNANCY
TO PIERRE FABRE CORPORATE VIGILANCES DIVISION

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION BY E-MAIL WITHIN 24H TO
HQ.pharmacovigilance@pierre-fabre.com OR BY FAX WITHIN 24H – Fax N°: 33 (0) 1.49.10.80.90

Transmission date (ddmm/yyyy) Country :
SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ SUBJECT CHARACTERISTICS

Gender	<input type="checkbox"/> 1=M, 2=F	Height	<input type="text"/> <input type="text"/> <input type="text"/> cm	Birth date	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Weight	<input type="text"/> <input type="text"/> <input type="text"/> · <input type="text"/> kg
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➤ DESCRIPTION OF THE EVENT

The serious adverse event resulted in :

- ☐ Death (whatever may be the cause)
☐ Hospitalisation (*) or extension thereof
☐ Life threatening
☐ Invalidity or disability

- ☐ Congenital abnormality or abnormal pregnancy outcome
☐ Cancer
☐ Other (any other serious clinical or laboratory event according to the investigator or the protocol, overdosage meeting seriousness criteria, suicide attempts)

Other fact to be notified :

- ☐ Pregnancy exposure

Nature of the event (if clinical nature, indicate the diagnosis or the major symptom) :

.....
.....
.....

AE onset date (ddmm/yyyy)

Seriousness onset date (ddmm/yyyy)

Summary description (if clinical cause, significant history, progression of event, available laboratory results, etc...) :

(*) Except hospitalisations with durations and goals planned in the protocol

➤ THE SAE IN RELATION TO THE TRIAL

	TREATMENT NUMBER	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
• Time of occurrence of SAE		
<input type="checkbox"/> During the selection or run-in period		
<input type="checkbox"/> During the administration phase of the study treatment		
<input type="checkbox"/> After the administration phase of the study treatment		
• Date of first study treatment administration	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	(ddmm/yyyy)
• Date of last study treatment administration before the occurrence of SAE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	(ddmm/yyyy)
• Was the blind broken ? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable		
If yes, or if this is an open study, drug(s) administered :		
.....		
Conditions of administration (cycles(s), daily dose(s), route(s) of administration, etc..) :		
.....		

Transmission date (ddmmyyyy) Country :

SAE N° FIRST NOTIFICATION ☐ FOLLOW-UP ☐ N°

➤ CONCOMITANT MEDICATION SINCE TRIAL INITIATION and UP UNTIL THE OCCURRENCE OF THE SAE
(EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

➤ MEASURES TAKEN FOLLOWING THE SAE

• Study treatment

- ☐ No change
- ☐ Dosage modification, specify : Modification Date : __/__/__
- ☐ Temporarily discontinued Readadministration date : __/__/__
- ☐ Withdrawn End date : __/__/__
- ☐ Not applicable

• The event led to :

- ☐ Prescription of corrective or symptomatic treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Discontinuation of concomitant treatments:

Trade name (or INN)	Daily dose	Start date (dd/mm/yy)	Ongoing at occurrence of the event	Stop date (dd/mm/yy)	Route of admin.	Indication
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		
		__/__/__	<input type="checkbox"/>	__/__/__		

- ☐ Others, specify :

➤ OUTCOME

- ☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
- ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown
- In case of death, has an autopsy been conducted ? ☐ Yes ☐ No

➤ INVESTIGATOR CAUSALITY ASSESSMENT (investigator's assessment to be done as soon as possible)

Study drug: Related to study protocol:

☐ Not Suspected ☐ Suspected ☐ Not Suspected ☐ Suspected

Comments:

Enclose in the notification the results of carried out examinations, reports of hospitalisation, etc...

17.3. PREDEFINED LIMITS OF LABORATORY AND VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND VALUES

List of Predefined Potentially Clinically Significant Change For Laboratory Values^(⊞)

PARAMETERS		UNIT	PSC	
			Decrease	Increase
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	μmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	μmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	l	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	μmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(⊞) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Centre, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Definition of Clinically Noteworthy Abnormal Laboratory Values (CNALV)

PARAMETERS		CNALV
HAEMOGLOBIN		<ul style="list-style-type: none"> • Decrease of at least 2g/dl and value < 10 g/dl whatever the baseline value • If missing baseline : value <10g/dl
NEUTROPHILS		<ul style="list-style-type: none"> • < 1 500/mm³ whatever the baseline value
WBC (if missing value for neutrophils)		<ul style="list-style-type: none"> • < 3 000/mm³ whatever the baseline value
PLATELETS		<ul style="list-style-type: none"> • < 100 000/mm³ whatever the baseline value
SERUM CREATININE		<ul style="list-style-type: none"> • Increase of at least 30 % as compared to baseline value and value > 150 µmol/l whatever the baseline value • If missing baseline : value > 150 µmol/l
LIVER FUNCTION TESTS		
	ALAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ALAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	ASAT	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • ASAT > 2 N ♦ If abnormal baseline : <ul style="list-style-type: none"> → if baseline value ≤ 2.5 N : <ul style="list-style-type: none"> • increase of at least 100 % as compared to baseline value → if baseline value > 2.5 N : <ul style="list-style-type: none"> • value > 5 N
and/or	Alkaline phosphatase (AP)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • AP > 1.25 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • AP > 2 N
and/or	Total bilirubin (TB)	<ul style="list-style-type: none"> ♦ If normal baseline : <ul style="list-style-type: none"> • TB > 1.5 N ♦ If abnormal baseline : <ul style="list-style-type: none"> • TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	SBP ≥ 160 mmHg and increase ≥ 20 mmHg SBP ≤ 90 mmHg and decrease ≥ 20 mmHg
DBP	Increase ≥ 10 mmHg Decrease ≥ 10 mmHg	DBP ≥ 100 mmHg and increase ≥ 10 mmHg DBP ≤ 50 mmHg and decrease ≥ 10 mmHg
HR	Increase ≥ 10 bpm Decrease ≥ 10 bpm	HR ≥ 110 bpm and increase ≥ 10 bpm HR ≤ 50 bpm and decrease ≥ 10 bpm

Table 2: Predefined Classes for changes from Baseline to the Maximum (and/ or Minimum) Post-baseline Value

Classes of Change from Baseline to the Maximum Post-baseline Value			Classes of Change from Baseline to the Minimum Post-baseline Value		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
All	All	All	All	All	All
≥ 0	≥ 0	≥ 0	≤ 0	≤ 0	≤ 0
> 0	> 0	> 0	< 0	< 0	< 0
≥ 10	≥ 5	≥ 10	≤ -10	≤ -5	≤ -10
≥ 20	≥ 10	≥ 20	≤ -20	≤ -10	≤ -20
≥ 30	≥ 15	≥ 30	≤ -30	≤ -15	≤ -30
≥ 40	≥ 20		≤ -40	≤ -20	
	≥ 25			≤ -25	
	≥ 30			≤ -30	

Table 3: Classes for Vital Signs Maximum or Minimum Values

Classes for the Maximum Post-baseline Value for each parameter			Classes for the Minimum Post-baseline Value for each parameter		
SBP mmHg	DBP mmHg	HR bpm	SBP mmHg	DBP mmHg	HR bpm
< 120	< 80	≤ 50	≤ 90	≤ 50	≤ 50
$[120 ; 140[$	$[80 ; 90[$	$]50 ; 75[$	$[90 ; 120[$	$[50 ; 80[$	$]50 ; 75[$
$[140 ; 160[$	$[90 ; 100[$	$[75 ; 100[$	$[120 ; 140[$	$[80 ; 90[$	$[75 ; 100[$
≥ 160	≥ 100	≥ 100	≥ 140	≥ 90	≥ 100

Table 4: Classes for Maximum or Minimum of BP in its entirety

Classification of Maximum Values for Blood Pressure (mmHg)	Classification of Minimum Values Blood Pressure (mmHg)
SBP < 140 and DBP < 90	SBP > 90 and DBP > 50
SBP $[140 ; 160[$ and DBP < 100 or DBP $[90 ; 100[$ and SBP < 160	SBP ≤ 90 or DBP ≤ 50
SBP ≥ 160 or DBP ≥ 100	

Table 5: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

* Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.