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

Summary

EudraCT number	2012-003487-48
Trial protocol	ES HU CZ IT FR
Global end of trial date	03 April 2017

Results information

Result version number	v1 (current)
This version publication date	11 April 2018
First version publication date	11 April 2018
Summary attachment (see zip file)	Synopsis (CSR _ F373280 CA 201_aCSR_synopsis Final Version_15NOV2017.pdf)

Trial information

Trial identification

Sponsor protocol code	F373280CA201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherche Pierre Fabre
Sponsor organisation address	3 Avenue Hubert Curien, Toulouse, France, 31035
Public contact	CTI Desk, Clinical Trial Information Desk Pierre Fabre Medicament, contact_essais_cliniques@pierre-fabre.com
Scientific contact	Karim KEDDAD, INSTITUT DE RECHERCHE PIERRE FABRE - Centre de R&D Pierre Fabre, 0033 (0)5 34 50 61 69, karim.keddad@pierre-fabre.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2017
Global end of trial reached?	Yes
Global end of trial date	03 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary:
Efficacy of F373280 on the maintenance of sinus rhythm after direct electrical cardioversion in patients with persistent atrial fibrillation and chronic heart failure

Protection of trial subjects:

The study was conducted in compliance with GCP, the current version of the Declaration of Helsinki, and all relevant SOPs in application within Pierre Fabre R&D.

Background therapy:

F373280 (a mono ester of pantothenic alcohol and DHA) is a novel pro-drug of DHA (molecular formula: C31H49NO5) that exerts antiarrhythmic properties by interacting with electrical and structural remodelling of the atria. According to data obtained in anaesthetised pigs, rats and canine models and the animal studies described in the Investigator's brochure (IB – F373280, 2013), the non clinical pharmacokinetic profile of F373280 is not associated with specific concerns regarding the proposed clinical phase IIa study.
After single administration of different test doses (0.5 g, 1 g, 2 g, 4 g, 8 g and 16 g) of F373280 to six independent cohorts of 8 subjects (6 of whom received F373280 and 2 received placebo), no difference between F373280 and placebo was reported regarding vital signs (heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]), biological parameters (platelets and fibrinogen) and coagulation parameters (bleeding time, prothrombin time/international normalised ratio [INR], activated partial thromboplastin time [aPTT], thrombin clotting time [TCT]). No serious adverse events (SAEs) occurred during the study.
After single oral administration (0.5 g to 16 g) of F373280 in 36 young healthy male subjects (six per dose level) no circulating F373280 plasma levels were detected, confirming that F373280 is a prodrug.

Evidence for comparator:

This is a placebo-controlled study in 2 parallel groups.

Actual start date of recruitment	20 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Italy: 39
Worldwide total number of subjects	135
EEA total number of subjects	135

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	54
From 65 to 84 years	80
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

157 patients have been screened and signed an informed consent form. After a 1 to 4 week run-in period without study treatment, 135 patients have been randomized to receive either 1g/day of F373280 or placebo per os, for 24 weeks.
1 patient did not receive the study treatment.

Pre-assignment

Screening details:

Were included in the study, patients with persistent AF between 7 days and 6 months duration for whom electrical cardioversion is warranted and with history of first documented persistent AF, ischemic or non ischemic heart failure and NYHA class I or II chronic heart failure at selection and at inclusion.

Pre-assignment period milestones

Number of subjects started	135
Number of subjects completed	

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	F373280

Arm description: -

Arm type	Experimental
Investigational medicinal product name	F373280
Investigational medicinal product code	F373280
Other name	Panthenyl Ester of DHA
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

One capsule dosed at 1g each evening with dinner.

Arm title	Placebo

Arm description: -

Arm type	Experimental
Investigational medicinal product name	F373280
Investigational medicinal product code	F373280
Other name	Panthenyl Ester of DHA
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral, one capsule of 1g each evening with dinner

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral, one capsule each evening with dinner

Number of subjects in period 1	F373280	Placebo
Started	68	67
Completed	34	30
Not completed	34	37
Efficacy concerns	13	11
Safety Concerns	5	8
Other reason	16	18

Baseline characteristics

Reporting groups	
Reporting group title	F373280
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	F373280	Placebo	Total
Number of subjects	68	67	135
Age categorical Units: Subjects			

Age continuous Units: years			
median	67.0	67.0	
full range (min-max)	37 to 85	26 to 84	-
Gender categorical Units: Subjects			
Female	16	16	32
Male	52	51	103

Subject analysis sets	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

• Safety Set, composed of all randomised patients who received at least one dose of the study treatment;

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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

Subject analysis set title	Per Protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

PP set consisted of all FAS patients without any major protocol deviation or other bias for primery criteria analysis

Reporting group values	Safety set	Full Analysis Set (FAS)	Per Protocol set
Number of subjects	134	101	95
Age categorical Units: Subjects			

Age continuous Units: years			
median	67.0	65	65.0
full range (min-max)	26 to 85	26 to 85	26 to 85

Gender categorical Units: Subjects			
Female	31	23	23
Male	103	78	72

End points

End points reporting groups

Reporting group title	F373280
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
• Safety Set, composed of all randomised patients who received at least one dose of the study treatment;	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
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	
Subject analysis set title	Per Protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
PP set consisted of all FAS patients without any major protocol deviation or other bias for primery criteria analysis	

Primary: Patients with Recurrence of AF or AF emergence (FAS)

End point title	Patients with Recurrence of AF or AF emergence (FAS)[1]
End point description:	
End point type	Primary
End point timeframe:	
24 weeks	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Due to premature termination of the study only descriptive statistical analysis were performed and this being an abbreviated report, no statistical analysis is detailed.	

End point values	F373280	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	49		
Units: Number of patients	36	31		

Attachments (see zip file)	F373280 Time to 1st recurrence AF or Atrial flutter - survival

Statistical analyses

No statistical analyses for this end point

Primary: Time to First Recurrence of AF or AF emergence (FAS)

End point title	Time to First Recurrence of AF or AF emergence (FAS)[2]

End point description:

End point type	Primary

End point timeframe:

24 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to premature termination of the study only descriptive statistical analysis were performed and this being an abbreviated report, no statistical analysis is detailed.

End point values	F373280	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	49		
Units: Days				
median (confidence interval 95%)	11.0 (6.0 to 45.0)	16.0 (6.0 to 141.0)		

Attachments (see zip file)	Time to 1st recurrence of AF/Atrial flutter emerge/F373280

Statistical analyses

No statistical analyses for this end point

Primary: Patients with Recurrence of AF or AF emergence (PP)

End point title	Patients with Recurrence of AF or AF emergence (PP)[3]

End point description:

End point type	Primary

End point timeframe:

24 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to premature termination of the study only descriptive statistical analysis were performed and this being an abbreviated report, no statistical analysis is detailed.

End point values	F373280	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Number (%) of patients	34	30		

Statistical analyses

No statistical analyses for this end point

Primary: Time to First Recurrence of AF or AF emergence (PP)

End point title	Time to First Recurrence of AF or AF emergence (PP)[4]

End point description:

End point type	Primary

End point timeframe:

24 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to premature termination of the study only descriptive statistical analysis were performed and this being an abbreviated report, no statistical analysis is detailed.

End point values	F373280	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Days				
median (confidence interval 95%)	13.0 (6.0 to 45.0)	15.5 (6.0 to 141.0)		

Attachments (see zip file)	Time to 1st recurrence of AF/Atrial flutter emerge/F373280

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	F373280
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	F373280	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 67 (7.46%)	1 / 67 (1.49%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer perforation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Edema			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Peritonitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	F373280	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 67 (64.18%)	43 / 67 (64.18%)	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 67 (2.99%)	1 / 67 (1.49%)	
occurrences (all)	2	1	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	24 / 67 (35.82%)	20 / 67 (29.85%)	
occurrences (all)	33	24	
Cardiac disorders			

Intracardiac thrombus subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1	5 / 67 (7.46%) 5	
Cardiac failure subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1	4 / 67 (5.97%) 4	
Nervous system disorders Sciatica subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	2 / 67 (2.99%) 2	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2	0 / 67 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2	1 / 67 (1.49%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	2 / 67 (2.99%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2013	Protocol: contraception method, GP letter (Italy)
23 October 2013	Adjustment of criteria to improve the feasibility of the study, change of SAEs report recipient
22 October 2014	Planned end of study postponed to April 2016; • Clarifications regarding the management of VKA treatment; • Precision regarding the primary efficacy criterion; • Deletion of Visit 5 and Visit 8; • Changes in TTEM transmission frequency; • Previous history of a first documented persistent AF 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); • Non-inclusion criteria of the protocol adapted; • Informed consent form updated following the modifications done to version 8 of the protocol
28 September 2016	• Planned study period: January 2013 – April 2017; • Number of patients: maximum135; • IDMC to review safety data twice during the study (after randomisation of the first 30 patients and after termination of study participation of the first 80 patients)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination: small number of patients

Notes: