Clinical trial results:
Determination of the efficacious and safe dose of ivabradine in paediatric patients with dilated cardiomyopathy and symptomatic chronic heart failure aged from 6 months to less than 18 years.
A randomised, double-blind, multicentre, placebo controlled, phase II/III dose-finding study with a PK/PD characterisation and a 1 year efficacy/safety evaluation.

Summary

EudraCT number	2011-001292-39
Trial protocol	FI GB BE SE DE PT IT HU BG DK ES
Global end of trial date	26 February 2014

Results information

Result version number	v1 (current)
This version publication date	15 February 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CL2-16257-090

Additional study identifiers

ISRCTN number	ISRCTN60567801
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S.)
Sponsor organisation address	50, rue Carnot, Suresnes Cedex, France, 92284
Public contact	TIP (Therapeutic Innovation Pole), Institut de Recherches Internationales Servier, +33 1.55.72.43.66, clinicaltrials@servier.com
Scientific contact	TIP (Therapeutic Innovation Pole), Institut de Recherches Internationales Servier, +33 1.55.72.43.66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000628-PIP01-09
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	26 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2014
Global end of trial reached?	Yes
Global end of trial date	26 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the optimal dose of ivabradine to reach the target heart rate reduction (HRR) of 20% without inducing a bradycardia (i.e. HR should be greater than a predefined HR threshold by age subset) and/or signs or symptoms related to bradycardia,
-To assess the pharmacokinetic (PK) parameters of ivabradine and its active metabolite S 18982 after repeated oral administrations,
-To assess the PKPD relationship of ivabradine and its active metabolite S 18982 using heart rate as evaluation criterion.

Protection of trial subjects:

Treatment could be prematurely and definitively discontinued by the investigator for any of the following reasons:
-Unwillingness of the investigator/patient/parents to continue with the study.
Study drug not tolerated: a premature treatment discontinuation could be decided in case of any suspected adverse reaction which caused permanent discomfort to the patient and led to interruption of his/her usual activities, or in case of a suspected adverse reaction which was considered (by the investigator) as a safety issue.
-Study drug no longer appropriate: the study drug would be considered as no longer appropriate in case of prolonged loss of sinus rhythm (e.g. permanent atrial fibrillation) or in case of pacemaker implantation.
-Study drug considered as contraindicated

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 1

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Romania: 6
Worldwide total number of subjects	116
EEA total number of subjects	84

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)	28
Children (2-11 years)	69
Adolescents (12-17 years)	19
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients to be included were male or female, aged from 6 months to less than 18 years old, with DCM, with a CHF Class II to IV (NYHA or Ross classification), left ventricular ejection fraction (LVEF) ≤45% documented by echocardiography, receiving their usual treatment for CHF at the optimal dose, in sinus rhythm.

Pre-assignment

Screening details:

With a planned maximum duration of 7 days. Eligible patients were randomised by IRS, with a stratification by age in order to obtain the balance of treatment groups within each age subset. These latter were based on age subsets defined for dose titration

Pre-assignment period milestones

Number of subjects started	116
Number of subjects completed	116

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivabradine

Arm description:

Patients taking Ivabradine

Arm type	Experimental
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

The study treatment (double-blind ivabradine or placebo) was taken orally twice daily (either oral liquid paediatric formulation or matching placebo, or adult tablets or matching placebo tablet for patients ≥40 kg (and able to swallow tablets, older than 6 years), in the morning and in the evening during meals at 12-hour intervals. The galenic form to be taken (oral solution or tablets) was defined once at D0 and did not change throughout the study.
A maximum of five doses of ivabradine or matching placebo was to be potentially tested in each patient: the doses were adapted every 2 weeks, through a maximum of 4 dose levels, according to the titration rules taking into account the age, the weight, the achievement or not of the HRR target (reduction of at least 20% of baseline HR) and the occurrence or not of bradycardia

Arm title	Placebo

Arm description:

Patients taking placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

The study treatment (double-blind ivabradine or placebo) was taken orally twice daily (either oral solution paediatric formulation or matching placebo, or adult tablets or matching placebo tablet for patients ≥40 kg (and able to swallow tablets, older than 6 years), in the morning and in the evening during meals at 12-hour intervals. The galenic form to be taken (oral solution or tablets) was defined once at D0 and did not change throughout the study.
A maximum of five doses of ivabradine or matching placebo was to be potentially tested in each patient: the doses were adapted every 2 weeks, through a maximum of 4 dose levels, according to the titration rules taking into account the age, the weight, the achievement or not of the HRR target (reduction of at least 20% of baseline HR) and the occurrence or not of bradycardia (HR lower than the predefined HR threshold by age subset) and/or signs or symptoms related to bradycardia.

Number of subjects in period 1	Ivabradine	Placebo
Started	74	42
Completed	61	28
Not completed	13	14
Adverse event, serious fatal	-	4
Non medical reason	-	1
Adverse event, non-fatal	10	9
Protocol deviation	2	-
Other protocol withdrawal criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ivabradine
Reporting group description:	
Patients taking Ivabradine	
Reporting group title	Placebo
Reporting group description:	
Patients taking placebo	

Reporting group values	Ivabradine	Placebo	Total
Number of subjects	74	42	116
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	18	10	28
Children (2-11 years)	43	26	69
Adolescents (12-17 years)	13	6	19
Gender categorical Units: Subjects			
Female	35	17	52
Male	39	25	64

End points

End points reporting groups

Reporting group title	Ivabradine
Reporting group description:	
Patients taking Ivabradine	
Reporting group title	Placebo
Reporting group description:	
Patients taking placebo	
Subject analysis set title	Randomised Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all patients to whom a therapeutic unit was randomly assigned using IRS.	

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients having received at least one dose of study drug.	
Subject analysis set title	Pharmacokinetic Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Consisted of 70 patients in the ivabradine group.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients of the Randomised Set having received at least one dose of study drug, and with at least two evaluations of resting HR: one at baseline, and one post-baseline.	

Subject analysis set title	Per Protocol Set Titration
Subject analysis set type	Per protocol
Subject analysis set description:	
patients of the FAS with one evaluation at baseline, and one evaluation at the end of titration period and having the studied disease, a protocol required background therapy before treatment period, a complete titration period, a correct and sufficient exposure to study drug during the titration period and no major issue in allocation of study drug during the titration period.	

Primary: Target Heart Rate achievement

End point title	Target Heart Rate achievement
End point description:	
the results represent the number of patients who have reached the target Heart Rate.	
End point type	Primary
End point timeframe:	
D0-End of titration	

End point values	Ivabradine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[1]	31[2]		
Units: number of patients	46	5		

Notes:

[1] - Per Protocol Set

[2] - Per Protocol Set

Statistical analyses

Statistical analysis title	Estimation of treatment effect
Comparison groups	Ivabradine v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Odds ratio (OR)
Point estimate	14.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.79
upper limit	46.77

Notes:

[3] - Estimation of the odds ratio of the target HRR achievement between treatment groups in order to assess the treatment effect

Adverse events

Adverse events information

Timeframe for reporting adverse events:

D0-M12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Ivabradine
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Ivabradine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 73 (28.77%)	17 / 42 (40.48%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Heart transplant			
subjects affected / exposed	1 / 73 (1.37%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Unintentional medical device removal			

subjects affected / exposed	2 / 73 (2.74%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 73 (1.37%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Cardiovascular evaluation			
subjects affected / exposed	4 / 73 (5.48%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate decreased			

subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 73 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 73 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus test positive			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcus test positive			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 73 (1.37%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy failure			

subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 73 (1.37%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 73 (1.37%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	1 / 73 (1.37%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 73 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial flutter			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			

subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Post-traumatic headache			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decorticate posture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Abdominal lymphadenopathy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 73 (1.37%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Ischaemic hepatitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 73 (2.74%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	2 / 73 (2.74%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 73 (1.37%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoiditis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 73 (0.00%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoviral upper respiratory infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 73 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ivabradine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 73 (86.30%)	37 / 42 (88.10%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	6 / 73 (8.22%)	7 / 42 (16.67%)	
occurrences (all)	7	7	
Cardiovascular evaluation			
subjects affected / exposed	5 / 73 (6.85%)	4 / 42 (9.52%)	
occurrences (all)	7	4	
Heart rate decreased			
subjects affected / exposed	5 / 73 (6.85%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	5 / 73 (6.85%)	3 / 42 (7.14%)	
occurrences (all)	10	5	
Accidental overdose			
subjects affected / exposed	3 / 73 (4.11%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 73 (8.22%)	3 / 42 (7.14%)	
occurrences (all)	8	4	
Fatigue			
subjects affected / exposed	0 / 73 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	5 / 73 (6.85%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 73 (8.22%)	6 / 42 (14.29%)	
occurrences (all)	6	7	
Vomiting			
subjects affected / exposed	6 / 73 (8.22%)	5 / 42 (11.90%)	
occurrences (all)	7	6	
Constipation			
subjects affected / exposed	5 / 73 (6.85%)	5 / 42 (11.90%)	
occurrences (all)	5	6	
Abdominal pain			
subjects affected / exposed	4 / 73 (5.48%)	3 / 42 (7.14%)	
occurrences (all)	4	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 73 (5.48%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	16 / 73 (21.92%)	7 / 42 (16.67%)	
occurrences (all)	23	8	
Upper respiratory tract infection			
subjects affected / exposed	9 / 73 (12.33%)	9 / 42 (21.43%)	
occurrences (all)	17	18	
Bronchitis			
subjects affected / exposed	10 / 73 (13.70%)	3 / 42 (7.14%)	
occurrences (all)	13	4	
Gastroenteritis			
subjects affected / exposed	9 / 73 (12.33%)	4 / 42 (9.52%)	
occurrences (all)	10	6	
Viral infection			
subjects affected / exposed	7 / 73 (9.59%)	3 / 42 (7.14%)	
occurrences (all)	11	5	
Gastroenteritis viral			
subjects affected / exposed	5 / 73 (6.85%)	3 / 42 (7.14%)	
occurrences (all)	5	4	
Respiratory tract infection			
subjects affected / exposed	4 / 73 (5.48%)	3 / 42 (7.14%)	
occurrences (all)	4	6	
Rhinitis			
subjects affected / exposed	6 / 73 (8.22%)	1 / 42 (2.38%)	
occurrences (all)	7	2	
Influenza			
subjects affected / exposed	4 / 73 (5.48%)	2 / 42 (4.76%)	
occurrences (all)	5	3	
Respiratory tract infection viral			
subjects affected / exposed	3 / 73 (4.11%)	3 / 42 (7.14%)	
occurrences (all)	6	3	
Pharyngitis			
subjects affected / exposed	5 / 73 (6.85%)	0 / 42 (0.00%)	
occurrences (all)	10	0	
Otitis media			
subjects affected / exposed	4 / 73 (5.48%)	1 / 42 (2.38%)	
occurrences (all)	7	1	
Laryngitis			

subjects affected / exposed	4 / 73 (5.48%)	0 / 42 (0.00%)	
occurrences (all)	4	0	
Pneumonia			
subjects affected / exposed	2 / 73 (2.74%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Tonsillitis			
subjects affected / exposed	2 / 73 (2.74%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Ear infection			
subjects affected / exposed	5 / 73 (6.85%)	0 / 42 (0.00%)	
occurrences (all)	8	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 73 (2.74%)	4 / 42 (9.52%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2011	The objective of this amendment was to comply with local requirements of the French Medicine Agency (AFSSAPS) renamed recently as Agence Nationale de Sécurité du Médicament et des produits de la Santé (ANSM) for the implementation of the CL2-16257-090 clinical trial in France. The following modifications were proposed: The addition in the non-selection criteria list that contraception was required in girls with childbearing potential and sexually active. The addition as a withdrawal criterion for the girls that were unwillingness to use a contraceptive method with a childbearing potential and sexually active. The reporting of the occurrence of any visual adverse event. In case of visual adverse event occurrence, the investigator had to schedule a visit with an ophthalmologist to characterize the symptoms and have an advice for management. The parents and legal representative information and consent/assent forms were amended.
14 February 2012	The objective of this amendment was to comply with the need for clarification, the requirements and the recommendations of the Regulatory Authorities, Ethics Committees and International Scientific Board for the implementation of the CL2-16257-090 clinical trial internationally.
22 May 2012	was applicable to all centres in Germany. The objective of this amendment was to comply with the need for clarification, the requirements and the recommendations of the Berlin Ethics Committee (EC) for the implementation of the CL2-16257-090 study in Germany. At the time of the review of the initial protocol by the Berlin EC the first international amendment No. 2 had been issued (the amendment No. 1 was applicable only for France). The current local amendment took into consideration the changes made by the Amendment No. 2
07 September 2012	was applicable in all countries. It concerned mainly: The update information on concomitant treatments to be used with precaution during the study: potassium-depleting diuretics should be used with precaution according to the modification of the Summary of Product Characteristics, The update of the list of adverse events for which specific information was requested and already collected. The parents and legal representative information and consent/assent forms were also amended with the addition of the new undesirable effect (abnormal ECG heart tracing). This amendment did not require any changes to the patient assent forms.
22 November 2012	was applicable to all centres in all countries. It concerned administrative changes.

23 May 2013	Was applicable in all countries. The objectives were : - to defer the planned study completion date and to update the number of patients to be recruited by age-subset - to update the protocol in accordance with the DSMB recommendations concerning patients with QTcB>450 ms.

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.

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report

Notes: