



Clinical trial results:

Safety of oral chronic administration of ivabradine modified release formulation compared to ivabradine immediate release formulation in patients with chronic heart failure and left ventricular systolic dysfunction. A 6 to 12-month randomised double blind parallel groups multicentre study.

Summary

EudraCT number	2012-001689-13
Trial protocol	CZ HU DE LV LT EE ES BG IT
Global end of trial date	15 May 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	CL3-16257-098
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, 33 155.72.43.66, clinicaltrials@servier.com
Scientific contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, 33 155.72.43.66, clinicaltrials@servier.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	15 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2014
Global end of trial reached?	Yes
Global end of trial date	15 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the safety profiles of the ivabradine modified release (MR) formulation and ivabradine immediate release (IR) formulation over a 6-month period in patients with symptomatic chronic heart failure (CHF), LVEF \leq 35% and under stable cardiovascular condition and treatment.

Protection of trial subjects:

Study treatment could be prematurely and definitively discontinued by the investigator for the following reasons:

IMP not tolerated (occurrence of a suspected adverse reaction which causes discomfort to the patient, leads to interruption of usual activities) or is considered by the investigator as a safety issue (e.g. significant symptoms of low HR or HR < 50bpm on the lower doses of IMP treatment)

IMP no longer appropriate (e.g. permanent atrial fibrillation).

IMP considered as contraindicated (e.g. pregnancy, sick sinus syndrome or concomitant administration of a strong cytochrome P450 3A4 inhibitor).

Unwillingness of the patient to continue with the study.

The occurrence of a serious adverse event did not automatically lead to definitive discontinuation of the IMP. Depending on the clinical status and the medical needs, the IMP could be temporarily stopped and restarted according to investigator's opinion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Bulgaria: 117
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Estonia: 33
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Hungary: 127
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Latvia: 37
Country: Number of subjects enrolled	Lithuania: 36
Country: Number of subjects enrolled	Argentina: 40
Country: Number of subjects enrolled	Brazil: 36

Country: Number of subjects enrolled	Malaysia: 13
Country: Number of subjects enrolled	Philippines: 12
Country: Number of subjects enrolled	Russian Federation: 117
Country: Number of subjects enrolled	Ukraine: 104
Country: Number of subjects enrolled	Vietnam: 30
Worldwide total number of subjects	791
EEA total number of subjects	439

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)	499
From 65 to 84 years	287
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Women or men.

Age ≥ 18 years (or having reached majority if the legal age of majority was over 18 years).

Symptomatic CHF, NYHA class II, III or IV for at least 6 weeks prior to selection and (LVEF) $\leq 35\%$, LVEF $\leq 35\%$, normal sinus rhythm and HR ≥ 75 bpm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivabradine MR

Arm description:

6-month treatment period in the SS.

Arm type	Experimental
Investigational medicinal product name	Ivabradine MR
Investigational medicinal product code	S16257
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

During the randomised double-blind treatment period, patients received the study treatment (either ivabradine MR or IR and a placebo capsule or tablet), which were taken orally twice daily, at 12-hour intervals in the morning (one capsule and one tablet) and the evening (one tablet) during meals.

The IMP starting dose was ivabradine MR 15 mg o.d. / IR 5 mg bid or matching placebo at D0. At the subsequent follow-up visits, the IMP was either maintained at the current dose, or increased in dose or reduced in dose or discontinued, depending on the patient's ECG resting HR and tolerability

Arm title	Ivabradine IR
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Arm description:

6-month treatment period in the SS

Arm type	Active comparator
Investigational medicinal product name	Ivabradine IR
Investigational medicinal product code	S16257
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the randomised double-blind treatment period, patients received the study treatment (either ivabradine MR or IR and a placebo capsule or tablet), which were taken orally twice daily, at 12-hour intervals in the morning (one capsule and one tablet) and the evening (one tablet) during meals.

The IMP starting dose was ivabradine MR 15 mg o.d. / IR 5 mg bid or matching placebo at D0. At the subsequent follow-up visits, the IMP was either maintained at the current dose, or increased in dose or reduced in dose or discontinued, depending on the patient's ECG resting HR and tolerability.

Number of subjects in period 1	Ivabradine MR	Ivabradine IR
Started	393	398
Completed	349	359
Not completed	44	39
non-medical reason	16	10
Adverse event, non-fatal	20	23
Lost to follow-up	-	1
Protocol deviation	8	5

Baseline characteristics

Reporting groups

Reporting group title	Ivabradine MR
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Reporting group description:

6-month treatment period in the SS.

Reporting group title	Ivabradine IR
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Reporting group description:

6-month treatment period in the SS

Reporting group values	Ivabradine MR	Ivabradine IR	Total
Number of subjects	393	398	791
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	244	255	499
From 65-84 years	147	140	287
85 years and over	2	3	5
Age continuous			
Units: years			
arithmetic mean	60.9	60.1	
standard deviation	± 11.5	± 11.2	-
Gender categorical			
Units: Subjects			
Female	101	102	203
Male	292	296	588

End points

End points reporting groups

Reporting group title	Ivabradine MR
Reporting group description: 6-month treatment period in the SS.	
Reporting group title	Ivabradine IR
Reporting group description: 6-month treatment period in the SS	

Primary: Emergent adverse events

End point title	Emergent adverse events ^[1]
End point description: The primary objective was the safety assessment over the first 6 months	
End point type	Primary
End point timeframe: the first 6 months	

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: Emergent adverse events have been analysed using descriptive statistics:

The safety assessment showed that MR and IR ivabradine formulations were very similar in terms of frequency of emergent adverse events as well as AE profile, showing a high consistency with the existing SmPC of ivabradine.

End point values	Ivabradine MR	Ivabradine IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	398		
Units: Number of affected patients	181	192		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study

Adverse event reporting additional description:

The first 6-month treatment period (main analysis) was followed by a blinded extension treatment period of a second 6-months for early recruited eligible patients in each group.

In the following reporting groups, patients in the Ivabradine MR 12-month group were also in the Ivabradine MR first 6-month group (same thing for Ivabradine IR groups)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16
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Reporting groups

Reporting group title	Ivabradine MR first 6 months
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Reporting group description: -

Reporting group title	Ivabradine IR first 6 months
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Reporting group description: -

Reporting group title	Ivabradine MR 12 months
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Reporting group description: -

Reporting group title	Ivabradine IR 12 months
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Reporting group description: -

Serious adverse events	Ivabradine MR first 6 months	Ivabradine IR first 6 months	Ivabradine MR 12 months
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 393 (12.21%)	64 / 398 (16.08%)	26 / 130 (20.00%)
number of deaths (all causes)	3	9	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 393 (0.25%)	2 / 398 (0.50%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 393 (0.51%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			

subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal cancer metastatic			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 393 (0.51%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	2 / 393 (0.51%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac rehabilitation therapy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			

subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve replacement			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Percutaneous coronary intervention			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 393 (0.00%)	5 / 398 (1.26%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 5	0 / 0
Chest pain			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device complication			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			

subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	2 / 393 (0.51%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asphyxia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aspiration			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 393 (0.51%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 393 (0.76%)	3 / 398 (0.75%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	3 / 3	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular evaluation			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriogram coronary			

subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep study			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 393 (0.51%)	1 / 398 (0.25%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wound dehiscence			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			

subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural myocardial infarction			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 393 (1.53%)	5 / 398 (1.26%)	4 / 130 (3.08%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	6 / 393 (1.53%)	5 / 398 (1.26%)	4 / 130 (3.08%)
occurrences causally related to treatment / all	1 / 6	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure chronic			
subjects affected / exposed	3 / 393 (0.76%)	6 / 398 (1.51%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	2 / 393 (0.51%)	4 / 398 (1.01%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 393 (0.25%)	3 / 398 (0.75%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			

subjects affected / exposed	2 / 393 (0.51%)	2 / 398 (0.50%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	2 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 393 (0.00%)	2 / 398 (0.50%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Accelerated idioventricular rhythm			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			

subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular dissociation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracardiac thrombus			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			

subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodal rhythm			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular extrasystoles			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			

subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 393 (0.25%)	5 / 398 (1.26%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 393 (0.51%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia macrocytic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinopathy			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photopsia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy hypertensive			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal degeneration			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Anal fissure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis mesenteric vessel			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polyps			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic congestion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 393 (0.51%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 393 (0.00%)	2 / 398 (0.50%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Haemarthrosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 393 (0.00%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Douglas' abscess			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis chronic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyoderma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 393 (0.25%)	2 / 398 (0.50%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 393 (0.25%)	1 / 398 (0.25%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 393 (0.00%)	1 / 398 (0.25%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	1 / 393 (0.25%)	0 / 398 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ivabradine IR 12 months		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 129 (22.48%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal cancer			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to bone			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Oesophageal cancer metastatic subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoral artery occlusion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Iliac artery occlusion			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery aneurysm			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac rehabilitation therapy			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystectomy			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee arthroplasty			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mitral valve replacement			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Percutaneous coronary intervention			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rehabilitation therapy			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chest pain			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical device complication			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden cardiac death			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic respiratory failure			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asphyxia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspiration			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular evaluation			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriogram coronary			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep study			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal wound dehiscence			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural myocardial infarction			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac failure chronic			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block second degree			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Accelerated idioventricular rhythm			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute left ventricular failure			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial thrombosis			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular dissociation			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracardiac thrombus			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nodal rhythm			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sick sinus syndrome			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular extrasystoles			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinson's disease			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic retinopathy			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Photopsia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinopathy hypertensive			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal degeneration			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis mesenteric vessel			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric polyps			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic congestion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal failure acute			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bronchopneumonia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Douglas' abscess			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative abscess			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis chronic			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyoderma			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 129 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Ivabradine MR first 6 months	Ivabradine IR first 6 months	Ivabradine MR 12 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 393 (46.06%)	192 / 398 (48.24%)	70 / 130 (53.85%)
Investigations			
Heart rate decreased			
subjects affected / exposed	7 / 393 (1.78%)	7 / 398 (1.76%)	5 / 130 (3.85%)
occurrences (all)	7	7	5

Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	7 / 393 (1.78%) 7	6 / 398 (1.51%) 6	5 / 130 (3.85%) 5
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	16 / 393 (4.07%) 16	11 / 398 (2.76%) 11	11 / 130 (8.46%) 11
Cardiac disorders Ventricular extrasystoles subjects affected / exposed occurrences (all)	9 / 393 (2.29%) 12	10 / 398 (2.51%) 10	6 / 130 (4.62%) 9
Atrial fibrillation subjects affected / exposed occurrences (all)	9 / 393 (2.29%) 9	6 / 398 (1.51%) 6	6 / 130 (4.62%) 6
Bradycardia subjects affected / exposed occurrences (all)	13 / 393 (3.31%) 13	8 / 398 (2.01%) 8	4 / 130 (3.08%) 4
Cardiac failure subjects affected / exposed occurrences (all)	12 / 393 (3.05%) 12	7 / 398 (1.76%) 8	4 / 130 (3.08%) 4
Eye disorders Photopsia subjects affected / exposed occurrences (all)	14 / 393 (3.56%) 14	18 / 398 (4.52%) 19	3 / 130 (2.31%) 3
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	5 / 393 (1.27%) 5	2 / 398 (0.50%) 2	4 / 130 (3.08%) 4

Non-serious adverse events	Ivabradine IR 12 months		
Total subjects affected by non-serious adverse events subjects affected / exposed	72 / 129 (55.81%)		
Investigations Heart rate decreased subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	3 / 129 (2.33%) 3		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	9 / 129 (6.98%) 9		
Cardiac disorders Ventricular extrasystoles subjects affected / exposed occurrences (all) Atrial fibrillation subjects affected / exposed occurrences (all) Bradycardia subjects affected / exposed occurrences (all) Cardiac failure subjects affected / exposed occurrences (all)	3 / 129 (2.33%) 3 0 / 129 (0.00%) 0 5 / 129 (3.88%) 5 1 / 129 (0.78%) 2		
Eye disorders Photopsia subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 5		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2012	Amendment No. 1 was applicable in Argentina. The objective of this amendment was to comply with the requirement of the Medicine Agency of Argentina- ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) for the implementation of the clinical trial in Argentina. A pregnancy test at the beginning of the study and at every patient visit for women with childbearing potential was added.
29 April 2013	Amendment No. 2 concerned all investigational sites in all countries. The main changes were: - To comply with the European Medicine Agency scientific advice (issued on the 17 January 2013): Given the importance of clinical data on the ivabradine IR and MR formulations switch, the number of patients evaluated in the setting of 3-month switch period was increased from 60 to 120 in each treatment group. Patient's background treatment (in particular beta-blockers) at the time of formulation switch was collected. - Documentation of events of special interest for ivabradine (bradycardia, ECG prolonged QT interval, eye disorders, rhythm and conduction disorders, increase in blood pressure in hypertensive patients, immune disorders) was detailed, in order to harmonise the study protocol with the latest proposed version of the EU-Risk Management Plan (RMP) of ivabradine hydrochloride (issued on the 22 January 2013). - The amendment also included diverse adaptations to improve the study patient's follow-up by the investigators and spelling corrections.
26 June 2013	Amendment No. 3 was applicable in Poland. The objective was to comply with the local regulatory requirement. A pregnancy test at the beginning of the study and at every patient visit for women with childbearing potential was added. This amendment was approved by the Polish Competent Authority and Ethic Committees. Finally, due to dynamic recruitment in other participation countries, there was no Polish centre opened for participation in this study.
22 January 2014	Amendment No. 4 was applicable in Ukraine for which, according to the local regulation, a substantial protocol amendment was required in case of any change in total study population. The objective was to notify to the local Competent Authorities the recruitment progressed ahead of schedule. This was due to unexpectedly slow completion of the target of 120 patients for Holter assessment. Thus, the final study population achieved 791 patients included.

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:

