Clinical trial results:
Safety of oral chronic administration of ivabradine modified release formulation compared to ivabradine immediate release formulation, in patients with stable coronary artery disease. A 6 to 12-month randomised double blind parallel groups multicentre study

Summary

EudraCT number	2012-001668-31
Trial protocol	GB HU DE SK NL ES BG IT
Global end of trial date	14 April 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	CL3-16257-097

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 (I.R.I.S)
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	ITP (Innovation Therapeutic Pole), Institut de Recherches Internationales Servier, 33 155.72.43.66, clinicaltrials@servier.com
Scientific contact	ITP (Innovation Therapeutic 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	14 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2014
Global end of trial reached?	Yes
Global end of trial date	14 April 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

Protection of trial subjects:

Study treatment could be prematurely and definitively discontinued by the investigator for any of the following reasons:
Study drug not tolerated: occurrence of suspected adverse drug reaction that cause discomfort to the patient, led to interruption of usual activities, or was considered by the investigator as a safety issue (e.g. significant symptoms of low HR or HR < 50 bpm on the lowest study treatment doses).
Study drug no longer appropriated (e.g. permanent atrial fibrillation).
Study drug 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.

In case the investigator had no news of a patient, he/she had to make every effort to contact him/her (unless the patient withdrew her/his consent), to obtain the date and the reason for discontinuation, to kindly ask the patient to resume the study procedures or at least come for an end-of-study visit. If all attempts failed, the investigator declared the patient "lost to follow-up". All actions implemented were documented in the corresponding medical file

Background therapy:

Standard guideline recommended

Evidence for comparator: -

Actual start date of recruitment	13 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	Russian Federation: 83
Country: Number of subjects enrolled	Vietnam: 40
Country: Number of subjects enrolled	Korea, Republic of: 72
Country: Number of subjects enrolled	Netherlands: 91
Country: Number of subjects enrolled	Slovakia: 51
Country: Number of subjects enrolled	Spain: 107
Country: Number of subjects enrolled	United Kingdom: 58
Country: Number of subjects enrolled	Bulgaria: 117

Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Hungary: 119
Country: Number of subjects enrolled	Italy: 45
Worldwide total number of subjects	842
EEA total number of subjects	647

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)	479
From 65 to 84 years	360
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Women or men;
- Age ≥ 18 years;
- Documented stable CAD with or without chronic stable angina pectoris;
. In stable condition for at least 1 month before selection with regards to clinical symptoms and cardiovascular treatments
- Normal sinus rhythm;
- Resting heart rate ≥ 60bpm.

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	Investigator, Monitor, Carer, Subject

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	
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 starting dose of ivabradine or matching placebo was MR 15 mg o.d. / IR 5 mg b.i.d. at D0. At the subsequent follow-up visits, the study treatment 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

Arm description:

6-month treatment period in the SS.

Arm type	Active comparator
Investigational medicinal product name	Ivabradine IR
Investigational medicinal product code	
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 starting dose of ivabradine or matching placebo was MR 15 mg o.d. / IR 5 mg b.i.d. at D0. At the subsequent follow-up visits, the study treatment 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	421	421
Completed	351	371
Not completed	70	50
Other protocol withdrawal critéria	-	1
Adverse event	41	36
Lost to follow-up	1	-
Non-medical reason	19	11
Protocol deviation	9	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	842	842	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	479	479	
From 65-84 years	360	360	
85 years and over	3	3	
Gender categorical Units: Subjects			
Female	206	206	
Male	636	636	

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

End point values	Ivabradine MR	Ivabradine IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	421		
Units: Number of affected patients	240	265		

Statistical analyses

No statistical analyses for this end point

Primary: Emergent adverse events in the angina patients subgroup

End point title	Emergent adverse events in the angina patients subgroup[2]
End point description: Safety assessment over the first 6 months of treatment in the Angina patients subgroup.	
End point type	Primary
End point timeframe: the first 6 months of treatment	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Emergent adverse events have been analysed using descriptive statistics

End point values	Ivabradine MR	Ivabradine IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	245		
Units: Number of affected patients	142	150		

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 6 months for early recruited eligible patients in each group.
Therefore,In the following reporting groups, patients in the Ivabradine MR 12-month group were also in the Ivabradine MR 6-month group (same thing for Ivabradine IR groups).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Ivabradine MR first 6-month period
Reporting group description: -	
Reporting group title	Ivabradine IR first 6-month period
Reporting group description: -	
Reporting group title	Ivabradine MR 12 months
Reporting group description: -	
Reporting group title	Ivabradine IR 12 months

Reporting group description: -

Serious adverse events	Ivabradine MR first 6-month period	Ivabradine IR first 6-month period	Ivabradine MR 12 months
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 419 (12.89%)	69 / 421 (16.39%)	25 / 140 (17.86%)
number of deaths (all causes)	3	3	0
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 / 419 (0.24%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma stage II			

subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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 myeloid leukaemia			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Ovarian cancer			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to heart			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer stage 0			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 419 (0.24%)	8 / 421 (1.90%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure inadequately controlled			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cardiac rehabilitation therapy			
subjects affected / exposed	1 / 419 (0.24%)	3 / 421 (0.71%)	0 / 140 (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
Bladder neck operation			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Coronary artery bypass			

subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Cranioplasty			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Gastric bypass			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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 operation			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Percutaneous coronary intervention			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rehabilitation therapy			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Sympathetic nerve destruction			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
chest pain			
subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	2 / 419 (0.48%)	1 / 421 (0.24%)	0 / 140 (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
Sudden death			
subjects affected / exposed	2 / 419 (0.48%)	0 / 421 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Social circumstances			
Impaired driving ability			
subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 419 (0.24%)	2 / 421 (0.48%)	0 / 140 (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
Pulmonary embolism			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Acute pulmonary oedema			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Acute respiratory failure			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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

Dyspnoea exertional			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Epistaxis			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Lung infiltration			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 419 (0.48%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Investigations			

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 419 (0.00%)	2 / 421 (0.48%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigation			
subjects affected / exposed	0 / 419 (0.00%)	2 / 421 (0.48%)	0 / 140 (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
Angiogram			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Arteriogram coronary			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Cardiovascular evaluation			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Oesophagogastroduodenoscopy			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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 / 419 (0.48%)	2 / 421 (0.48%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery restenosis			
subjects affected / exposed	2 / 419 (0.48%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anaemia postoperative			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Clavicle fracture			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Fibula fracture			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Humerus fracture			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Joint dislocation			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Radius fracture			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Bone fissure			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Road traffic accident			

subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Traumatic haematoma			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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			
Angina unstable			
subjects affected / exposed	3 / 419 (0.72%)	5 / 421 (1.19%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 419 (0.72%)	6 / 421 (1.43%)	3 / 140 (2.14%)
occurrences causally related to treatment / all	0 / 3	0 / 6	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	3 / 419 (0.72%)	5 / 421 (1.19%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	4 / 419 (0.95%)	2 / 421 (0.48%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	4 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	3 / 419 (0.72%)	2 / 421 (0.48%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 419 (0.48%)	2 / 421 (0.48%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 419 (0.24%)	2 / 421 (0.48%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 419 (0.24%)	2 / 421 (0.48%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	0 / 140 (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
Acute left ventricular failure			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Cardiac failure acute			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Palpitations			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Sinus arrest			

subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Sinus bradycardia			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Tricuspid valve incompetence			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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 fibrillation			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Intracardiac thrombus			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torsade de pointes			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 419 (0.24%)	3 / 421 (0.71%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 419 (0.24%)	3 / 421 (0.71%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 419 (0.00%)	2 / 421 (0.48%)	0 / 140 (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
Cerebral atrophy			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Cerebral infarction			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Embolic cerebral infarction			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Neuritis			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Polyneuropathy			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Tremor			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Vascular headache			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Blood and lymphatic system disorders			
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Anaemia			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Pancytopenia			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Thrombocytopenia			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Photopsia			
subjects affected / exposed	3 / 419 (0.72%)	2 / 421 (0.48%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			

subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Choroidal detachment			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Choroidal haemorrhage			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Retinal disorder			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Retinopathy hypertensive			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Vitreous detachment			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Gastrointestinal disorders			
Diverticulum intestinal			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Enterocolitis			

subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Nausea			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Vomiting			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Abdominal pain			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Defaecation urgency			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Gastritis erosive			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Gastroduodenitis haemorrhagic			

subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
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			
Cholangitis			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Cholelithiasis			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Dermatitis atopic			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Hyperhidrosis			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Renal and urinary disorders			
Renal artery stenosis			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	0 / 140 (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
Gouty arthritis			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	0 / 140 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Spinal osteoarthritis			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 419 (0.24%)	1 / 421 (0.24%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Bronchopneumonia			

subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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
Respiratory tract infection			
subjects affected / exposed	1 / 419 (0.24%)	0 / 421 (0.00%)	0 / 140 (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
Bacteraemia			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 419 (0.00%)	0 / 421 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 419 (0.00%)	2 / 421 (0.48%)	0 / 140 (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
Hypertriglyceridaemia			
subjects affected / exposed	0 / 419 (0.00%)	1 / 421 (0.24%)	0 / 140 (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

Serious adverse events	Ivabradine IR 12 months		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 130 (22.31%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma stage II			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung cancer metastatic			

subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to heart				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal cancer stage 0				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	4 / 130 (3.08%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood pressure inadequately controlled				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 130 (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 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cardiac rehabilitation therapy			
subjects affected / exposed	2 / 130 (1.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder neck operation			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystectomy			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery bypass			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cranioplasty			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric bypass			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc operation			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Percutaneous coronary intervention			

subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rehabilitation therapy				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sympathetic nerve destruction				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
chest pain				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Impaired driving ability				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute pulmonary oedema			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory failure			
subjects affected / exposed	0 / 130 (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 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigation			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angiogram			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriogram coronary			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiovascular evaluation				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagogastroduodenoscopy				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary artery restenosis				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia postoperative				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clavicle fracture				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Joint dislocation			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone fissure			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	2 / 130 (1.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			

subjects affected / exposed	3 / 130 (2.31%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	0 / 130 (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 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus arrest			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			

subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracardiac thrombus				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Torsade de pointes				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral atrophy				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Embolic cerebral infarction				

subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuritis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular headache			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			

subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Photopsia				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vision blurred				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Glaucoma				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Choroidal detachment				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Choroidal haemorrhage				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal disorder				

subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retinopathy hypertensive				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vitreous detachment				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diverticulum intestinal				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Defaecation urgency				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroduodenitis haemorrhagic				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	0 / 130 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dermatitis atopic				

subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperhidrosis			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal artery stenosis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 130 (1.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gouty arthritis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Spinal osteoarthritis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection bacterial			
subjects affected / exposed	0 / 130 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 130 (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: 5 %

Non-serious adverse events	Ivabradine MR first 6-month period	Ivabradine IR first 6-month period	Ivabradine MR 12 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	240 / 419 (57.28%)	265 / 421 (62.95%)	93 / 140 (66.43%)
Investigations			
Heart rate decreased			
subjects affected / exposed	30 / 419 (7.16%)	21 / 421 (4.99%)	12 / 140 (8.57%)
occurrences (all)	30	22	12
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 419 (5.25%)	33 / 421 (7.84%)	12 / 140 (8.57%)
occurrences (all)	23	34	12
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 419 (1.91%)	19 / 421 (4.51%)	1 / 140 (0.71%)
occurrences (all)	9	19	1
Eye disorders			
Photopsia			
subjects affected / exposed	44 / 419 (10.50%)	29 / 421 (6.89%)	14 / 140 (10.00%)
occurrences (all)	46	32	15
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 419 (3.58%) 15	12 / 421 (2.85%) 12	9 / 140 (6.43%) 9

Non-serious adverse events	Ivabradine IR 12 months		
Total subjects affected by non-serious adverse events subjects affected / exposed	97 / 130 (74.62%)		
Investigations Heart rate decreased subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 7		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	15 / 130 (11.54%) 16		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	9 / 130 (6.92%) 9		
Eye disorders Photopsia subjects affected / exposed occurrences (all)	12 / 130 (9.23%) 14		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 130 (6.15%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2012	Amendment No. 1, dated 29 November 2012, was applicable in Argentina. To comply with local requirements 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. Finally, due to dynamic recruitment in other participating countries together with regulatory timelines, there were no Argentinian centres opened for participation in this study.
29 April 2013	Amendment No. 2, dated 29 April 2013, concerned all investigational sites in all countries. The main changes were: Following the European Medicine Agency scientific advice (issued on the 17th of 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 arm. Patient's background treatment (in particular beta-blockers) at the time of formulation switch was collected. In order to reach the target of 120 patients for PK assessment, the total number of patients planned to be evaluated was increased from 700 up to approximately 850. 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 22nd of January 2013). The amendment also included diverse adaptations to improve the study patient's follow-up by the investigators, spelling corrections.

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 ClinicalStudy Report.

Notes: