



Clinical trial results:

Determination of the efficacious and safe dose of ivabradine in paediatric patients with dilated cardiomyopathy and symptomatic chronic heart failure aged from 6 months to less than 18 years.

A randomised, double-blind, multicentre, placebo controlled, phase II/III dose-finding study with a PK/PD characterisation and a 1 year efficacy/safety evaluation.

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CL2-16257-090 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000628-PIP01-09 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 February 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 February 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the optimal dose of ivabradine to reach the target heart rate reduction (HRR) of 20% without inducing a bradycardia (i.e. HR should be greater than a predefined HR threshold by age subset) and/or signs or symptoms related to bradycardia,

-To assess the pharmacokinetic (PK) parameters of ivabradine and its active metabolite S 18982 after repeated oral administrations,

-To assess the PKPD relationship of ivabradine and its active metabolite S 18982 using heart rate as evaluation criterion.

Protection of trial subjects:

Treatment could be prematurely and definitively discontinued by the investigator for any of the following reasons:

-Unwillingness of the investigator/patient/parents to continue with the study.

Study drug not tolerated: a premature treatment discontinuation could be decided in case of any suspected adverse reaction which caused permanent discomfort to the patient and led to interruption of his/her usual activities, or in case of a suspected adverse reaction which was considered (by the investigator) as a safety issue.

-Study drug no longer appropriate: the study drug would be considered as no longer appropriate in case of prolonged loss of sinus rhythm (e.g. permanent atrial fibrillation) or in case of pacemaker implantation.

-Study drug considered as contraindicated

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 28 |
| Children (2-11 years) | 69 |
| Adolescents (12-17 years) | 19 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 116 |
| Number of subjects completed | 116 |

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ivabradine |

Arm description:

Patients taking Ivabradine

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

Dosage and administration details:

The study treatment (double-blind ivabradine or placebo) was taken orally twice daily (either oral liquid paediatric formulation or matching placebo, or adult tablets or matching placebo tablet for patients ≥ 40 kg (and able to swallow tablets, older than 6 years), in the morning and in the evening during meals at 12-hour intervals. The galenic form to be taken (oral solution or tablets) was defined once at D0 and did not change throughout the study.

A maximum of five doses of ivabradine or matching placebo was to be potentially tested in each patient: the doses were adapted every 2 weeks, through a maximum of 4 dose levels, according to the titration rules taking into account the age, the weight, the achievement or not of the HRR target (reduction of at least 20% of baseline HR) and the occurrence or not of bradycardia

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Patients taking placebo

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Ivabradine |
|-----------------------|------------|

Reporting group description:

Patients taking Ivabradine

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients taking placebo

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

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Ivabradine |
| Reporting group description: Patients taking Ivabradine | |
| Reporting group title | Placebo |
| Reporting group description: Patients taking placebo | |
| Subject analysis set title | Randomised Set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: all patients to whom a therapeutic unit was randomly assigned using IRS. | |
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients having received at least one dose of study drug. | |
| Subject analysis set title | Pharmacokinetic Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Consisted of 70 patients in the ivabradine group. | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients of the Randomised Set having received at least one dose of study drug, and with at least two evaluations of resting HR: one at baseline, and one post-baseline. | |
| Subject analysis set title | Per Protocol Set Titration |
| Subject analysis set type | Per protocol |
| Subject analysis set description: patients of the FAS with one evaluation at baseline, and one evaluation at the end of titration period and having the studied disease, a protocol required background therapy before treatment period, a complete titration period, a correct and sufficient exposure to study drug during the titration period and no major issue in allocation of study drug during the titration period. | |

Primary: Target Heart Rate achievement

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

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

Notes:

[1] - Per Protocol Set

[2] - Per Protocol Set

Statistical analyses

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

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

D0-M12

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Ivabradine |
|-----------------------|------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

| | |
|-------------|--|
| 23 May 2013 | <p>Was applicable in all countries. The objectives were :</p> <ul style="list-style-type: none"> - to defer the planned study completion date and to update the number of patients to be recruited by age-subset - to update the protocol in accordance with the DSMB recommendations concerning patients with QTcB>450 ms. |
|-------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: