I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**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.
Test drug code	**Ivabradine (S 16257-2)**
Indication	**Chronic heart failure**
Development phase	**Phase II/III**
Protocol code	**CL2-16257-090**
Study initiation date	**21 December 2011**
Study completion date	**26 February 2014**
Main coordinator	███████████████████████████
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot, 92284 Suresnes Cedex - France** **Les Laboratoires Servier Representative office** **Paveletskaya sq 2, bld 3, floor 3, 115054 Moscow - Russia** **Laboratorios Servier S.L.** **Avenida De los Madroños 33, 28043 Madrid - Spain** **Servier Research and Development** **Wexham Springs, Framewood Road** **Wexham Slough SL3 6RJ - United Kingdom**
Responsible medical officers	███████████████████████████
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**18 July 2014**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

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2. SYNOPSIS

Name of Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S.), 50 rue Carnot, 92284 Suresnes Cedex - France** **Les Laboratoires Servier Representative office, Paveletskaya sq 2, bld 3, floor 3, 115054 Moscow - Russia** **Laboratorios servier S.L., Avenida De los Madroños 33, 28043 Madrid - Spain** **Servier Research and Development, Wexham Springs, Framewood Road Wexham Slough SL3 6RJ - United Kingdom**	*(For National Authority Use only)*

Test drug
Name of Finished Product:
Corlentor®: all countries of the study except Brazil, Mexico and Russia **Procoralan®**: all countries of the study except Russia **Coraxan®**: Russia.
Name of Active Ingredient:
IVABRADINE – S 16257

Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: 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.

The description of the study protocol given hereafter includes the modifications of the substantial amendments (6 amendments).

Protocol No.: CL2-16257-090
EudraCT No.: 2011-001292-39

International Coordinator:

National Coordinators:

Study centres:
In all, 47 centres located in 16 countries included 116 patients: Belgium (1 centre, 1 patient), Brazil (5 centres, 13 patients), Bulgaria (3 centres, 6 patients), Finland (2 centres, 3 patients), France (4 centres, 16 patients), Germany (6 centres, 11 patients), Hungary (1 centre, 2 patients), Italy (3 centres, 8 patients), Mexico (2 centres, 2 patients), Poland (3 centres, 13 patients), Portugal (3 centres, 9 patients), Romania (2 centres, 6 patients), Russia (4 centres, 17 patients), Spain (5 centres, 5 patients), Sweden (2 centres, 3 patients), United Kingdom (1 centre, 1 patient).

Publication (reference): Not Applicable.

Studied period: - Initiation date: 21 December 2011 (date of first visit first patient) - Completion date: 26 February 2014 (date of last visit last patient)	**Phase of development of the study:** Phase II/ III

Objectives:
The purpose of this study was to determine the efficacious and safe dose of ivabradine in paediatric patients aged from 6 months to less than 18 years with dilated cardiomyopathy (DCM) and symptomatic chronic heart failure (CHF) receiving an optimal background treatment for CHF.

Primary objectives:
- 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 heart rate (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 pharmacokinetic-pharmacodynamic (PK/PD) relationship of ivabradine and its active metabolite S 18982 using heart rate as evaluation criterion.

Objectives (Cont'd):
Secondary objectives:
- To assess, compared to placebo, the effects of ivabradine at target dose, on:
  - Left ventricular ejection fraction (LVEF), as a measure of cardiac function measured by echocardiography.
  - Clinical symptoms by using the NYHA/Ross classification.
  - Global clinical status evaluated by the investigator/parents.
  - Cardiovascular biomarker by measuring NT-proBNP.
- To assess, compared to placebo, the long-term safety of ivabradine over 1-year.

Other objective was to assess in a specific sub-study in selected countries/centres the effect of ivabradine compared to placebo on quality of life by using a questionnaire (ancillary study).

Methodology:
International, multicentre, randomised, double blind, placebo controlled phase II/III study, with two parallel and non-balanced treatment arms (for each age subset), using a ratio of 2 patients on ivabradine to one patient on placebo. The randomisation was stratified by age-subset, and was centralised by Interactive Response System.
The study involved an International Scientific Board (ISB) and a Data Safety Monitoring Board (DSMB). The ISB had the overall scientific responsibility for the study. The DSMB made appropriate recommendations to the ISB concerning the conduct of the study, based on efficacy and safety results.

Number of patients:
Planned: at least 90 evaluable patients: ivabradine group: n = 60, placebo group: n = 30 (further to amendment No. 6, 90 patients were initially planned) as *"at least 90 evaluable patients" (i.e. 90 patients having at least three PK samples) were considered sufficient to investigate the PK/PD relationship in childhood adequately*:
- At least 10 infants in age-subset [6-12[months (further to amendment No. 6, 30 infants initially planned),
- At least 30 infants and children in age-subset [1-3[years (further to amendment No. 6, 30 infants and children initially planned),
- At least 30 children and adolescents in age-subset [3-18[years (further to amendment No. 6, 30 children and adolescents initially planned).

In each age subset, a non-balanced randomisation using a ratio of two patients on ivabradine and one patient on placebo was considered sufficient to investigate the PK/PD relationship in childhood adequately.
Included: 116 patients (ivabradine group: n = 74, placebo group: n = 42):
- 17 infants in age-subset [6-12[months (ivabradine group: n = 10, placebo group: n = 7).
- 36 infants and children in age-subset [1-3[years (ivabradine group: n = 24, placebo group: n = 12).
- 63 children and adolescents in age-subset [3-18[years (ivabradine group: n = 40, placebo group: n = 23).

Diagnosis and main criteria for inclusion:
Patients of both gender aged from 6 months to less than 18 years old, with DCM, in sinus rhythm, receiving their usual treatment for CHF at the optimal dose (*i.e.* stable dose since at least 4 weeks before entering the study in the absence of guidelines on paediatric optimal doses), informed consent obtained, and with:
- Resting heart rate (HR) corresponding to the following criteria:
  - HR ≥ 105 bpm in age-subset [6-12[months.
  - HR ≥ 95 bpm in age-subset [1-3[years.
  - HR ≥ 75 bpm in age-subset [3-5[years.
  - HR ≥ 70 bpm in age-subset [5-18[years.
- CHF Class II to IV New York Heart Association (NYHA) or Ross classification (Ross 1987), stable for at least 1 month prior to selection.
- Left ventricular (LV) dysfunction with Left Ventricular Ejection Fraction (LVEF) ≤ 45% documented by echocardiography.
- LV dysfunction consecutive to idiopathic DCM, post-viral myocarditis DCM, ischaemic DCM (provided it was an acquired disease not requiring surgery), left ventricular non-compaction with DCM as primary condition, and added by amendment No. 2: post-anthracyclines DCM (provided the treatment by anthracyclines was stopped at least two years prior to the entry in the study).

Diagnosis and main criteria for inclusion (Cont'd):
Main criteria for non-inclusion

- Class I NYHA or Ross classification (asymptomatic),
- History of symptomatic or sustained (≥ 30 sec) ventricular arrhythmia unless a cardioverter defibrillator was implanted,
- Patients with a past history of cardiac corrective surgery,
- Congenital structural heart defects,
- Uncorrected primary obstructive or severe regurgitative valvular disease, restrictive or hypertrophic cardiomyopathy, or significant systemic ventricular outflow obstruction,
- Dilated cardiomyopathies secondary to muscular dystrophies, hemoglobinopathies, HIV, carnitine deficiency, active myocarditis.
- Patients receiving unauthorised concomitant treatment: quinidine, disopyramide, bepiridil, sotalol, ibutilide, ketoconazole, macrolides and antiretroviral medication.

Test drug:

Ivabradine: administered as oral liquid paediatric formulation or tablet formulation twice daily (morning and evening), according to the age and the weight as specified hereafter. A maximum of five doses were tested in each age-subset.

The goal of the up-titration period was to reach the effective dose, *i.e.* the dose that achieved a 20% HR reduction without inducing a bradycardia (*i.e.* HR should be greater than a predefined HR threshold by age subset: 80, 70, and 50 bpm for respectively, [6-12[months, [1-3[years, and [3-18[years age subsets), and/or signs or symptoms related to bradycardia. This dose was continued throughout the 2-week maintenance period and then, throughout the 1-year treatment period. After inclusion, the study drug dose was to be, at each visit, either up-titrated, maintained, down-titrated or stopped according to titrations rules taking into account the age, the weight, the HR and/or the presence of symptoms.

- **2 to 8-week titration period**:
  - In age subset [6-12[months: ivabradine, oral liquid paediatric formulation, at the starting dose of 0.02 mg/kg twice daily, then 4 titrations, *i.e.* 0.05, 0.10, 0.15 and 0.20 mg/kg twice daily.
  - In age subset [1-3[years and [3-18[years with weight < 40 kg: ivabradine, oral liquid paediatric formulation, at the starting dose of 0.05 mg/kg twice daily, then 4 titrations, *i.e.* 0.10, 0.15, 0.20 and 0.30 mg/kg twice daily.
  - In age subset [3-18[years with weight ≥ 40 kg and able to swallow tablets (age > 6 years old): ivabradine, adult tablet formulation, at the starting dose 2.5 mg twice daily, then 4 titrations, *i.e.* 5, 7.5, 10 and 15 mg twice daily.
- **2-week maintenance treatment period**: ivabradine, oral liquid paediatric formulation or adult tablet formulation at the target dose, twice daily.
  In case of bradycardia (*i.e.* HR lower than a pre-defined HR threshold) and/or signs or symptoms of bradycardia occurred at a given dose during the titration period, the dose had to be decreased and continued for 2 weeks, during the maintenance period, until M0.
- **1-year treatment period**: ivabradine, oral liquid paediatric formulation or adult tablet formulation, at the dose of the maintenance period adapted to the weight, twice daily. In all patients, and at each visit (or unscheduled visit), the study drug dose was to be decreased or stopped in case of bradycardia and/or symptoms related to bradycardia or for safety reason (according to the investigator's opinion).

Batch Nos.:

- Oral solution: *1 mg*: L0039205, L0039211, L0043945, L0043958, L0043970; *5 mg*: L0039207, L0039213, L0043949, L0043962, L0043974; *13.3 mg*: L0039257, L0039259, L0043954, L0043966, L0043978.
- Oral tablets: *2.5 mg*: L0037264, L0044336; *5 mg*: L0038676, L0040468; *7.5 mg*: L0038024, L0038975, L0044386, L0044844; *10 mg*: L0038042, L0036266, L0038912, L0042413, L0044706.

Comparator (reference product and/or placebo):

Matching placebo, oral liquid paediatric formulation or adult tablet formulation, twice daily (morning and evening), in the same conditions as specified above for ivabradine.

Duration of treatment:

- A 2 to 8-week titration period.
- A 2-week maintenance period.
- A 1-year follow-up period.

Criteria for evaluation:
Primary endpoints
Target HRR achievement
Achievement of a HRR from baseline of at least 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. The HR reference value was the HR value measured at rest (any method was allowed provided the measurement was performed at rest, and the child being quite).

Characterisation of PK and PK/PD
- Characterisation of PK parameters of ivabradine (S 16257) and its active metabolite S 18982.
- Characterisation of PK/PD relationship between S 16257 and S 18982 plasma concentrations and corresponding HR values.

PK and PD measurements: PK measurements were performed within the titration and the maintenance periods using a sparse blood sampling strategy. Population PK and PK/PD analyses allowed the characterization of the PK parameters of ivabradine and its active metabolite, as well as the PK/PD relationship between plasma concentrations and heart rate reduction (HRR), in order to propose dosing recommendations.

Criteria for evaluation (Cont'd):

Secondary endpoints
Efficacy secondary endpoints
- Echocardiographic parameters, measured at selection, M0, M1, M2, M3, M6, M9 and M12 (or final) visits:
  - Left ventricular ejection fraction (LVEF, %).
  - Left ventricular shortening fraction (LVSF, %).
  - Left ventricular end-systolic volume (LVESV, mL).
  - Left ventricular end-diastolic volume (LVEDV, mL).
- NYHA/Ross functional class (I, II, III or IV), assessed at each visit.
- Global clinical status evaluated by the investigator/parents, at D0, M0, M3, M6, M9 and M12 (or final) visits.
- NT-proBNP at selection, M0, M6 and M12 (or final) visits.
- Weight and height at each visit.

Safety secondary endpoints:
- Adverse events at each visit.
- 12-lead ECG parameters: HR, PR interval, QRS, QT, QTc durations at each visit. *In this study, according to DSMB recommendations, a particular focus was done on the patients having at least one QT corrected with Bazett formula (QTcB) > 450 ms. As specified in amendment No. 6, a central reading was performed for all ECGs patients and in case of QTcB value > 450 ms confirmed by the central reading, the patients were to be withdrawn from the study and an adverse event to be reported by the investigator.*
- Vital signs at each visit.
- Clinical laboratory examination, performed at selection, M0, M6 and M12 (or final) visits.

Other endpoint: Quality of life questionnaire (sub-study attached to the main study). These results are fully described in a separate clinical report (NP 33312).

Statistical methods:
Pharmacokinetic and pharmacodynamic analyses:
- Descriptive statistics of plasma concentration-time data of ivabradine and its active metabolite, and descriptive statistics of HR at rest were performed at each time point, for the whole population and by age subgroup.
- A population modelling approach was used to describe the PK of ivabradine and its active metabolite, and to characterise the relationship between PK and PD (*i.e.* HR at rest). In the PK and PK/PD analyses, the influence of covariates was investigated. Results were presented in the whole population and by age subgroup.

A PK set was defined for the PK analysis.
Complete results are described in a separate report.

Study outcome: Descriptive statistics were provided.

Efficacy:
The following Sets were defined for efficacy analyses:
- FAS: 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;
- PPS titration: 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 objective: an estimate of the odds ratio of the target HRR achievement between treatment groups was provided, using a logistic regression model adjusted for age class, in patients of the Per Protocol Set Titration (main analysis).

As secondary analysis, the difference of HR change between treatment groups at the end of titration period was assessed using a parametric covariance analysis adjusted for age class and with baseline value as a covariate, in patients of the Per Protocol Set Titration.

These analyses were also carried-out on patients on the Full Analysis Set and the secondary analysis was carried-out for the HR change at M6 and M12 on patients on the Full Analysis Set.

Dose description: descriptive statistics of the dose prescribed at the end and during the titration period, on patients of the Per Protocol Set-Titration (PPS titration) and in the target HRR achievement subsets.

Secondary objectives: descriptive statistics of secondary endpoints (LVEF, LVSF, LVEDV, LVESV, NYHA/Ross class, global clinical status, NT-proBNP, weight and height) were performed on patients of the Full Analysis Set overall and by subset of patients having achieved the target HRR at the end of titration period or not.

In particular, the treatment effect on LVEF was assessed on the change between baseline and M6 and on the change between baseline and M12 *versus* placebo using a parametric covariance analysis adjusted for age class and with baseline as a covariate, on patients of the Full Analysis Set.

Statistical analyses of the secondary endpoints were also carried-out by subset of patients having achieved target HRR at the end of titration period or not.

Note: Adjustment for age class is not applicable when the analysis was performed by age subset.

All statistical analyses were also carried-out by subset of age.

Quality of Life sub-study (conducted in patients from 2 to less than 18 years of age): statistical analyses are detailed and presented in a separate report.

Safety:
Descriptive statistics were provided in the Safety Set.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 116 patients were included in the CL2-16257-090 study, and randomly assigned to ivabradine or placebo groups, with a planned unbalanced ratio (2:1) reached:

- Ivabradine group: 74 patients (10 patients in the [6-12[months age subset, 24 patients in the [1-3[years age subset, and 40 patients in the [3-18[years age subset).
- Placebo group: 42 patients (7, 12, and 23 patients, respectively, in each subset).

Disposition of included patients by group - Overall patients

Status	Ivabradine	Placebo	All
	n (%)	n (%)	n (%)
Included	**74**	**42**	**116**
In compliance with the protocol	65 (87.8)	36 (85.7)	101 (87.1)
With a protocol deviation before or at inclusion	9 (12.2)	6 (14.3)	15 (12.9)
Withdrawn due to	**13 (17.6)**	**14 (33.3)**	**27 (23.3)**
Adverse event	10 (13.5)	13 (31.0)	23 (19.8)
Protocol deviation	2 (2.7)	-	2 (1.7)
Non-medical reason	-	1 (2.4)	1 (0.9)
Lack of efficacy*	-	-	-
Lost to follow-up	-	-	-
Other protocol withdrawal criteria*	1 (1.4)	-	1 (0.9)
Titration period completed **	**68 (91.9)**	**37 (88.1)**	**105 (90.5)**
In compliance with the protocol	68 (91.9)	36 (85.7)	104 (99.0)
With a protocol deviation after inclusion	-	1 (2.4)	1 (0.9)
Study completed	**61 (82.4)**	**28 (66.7)**	**89 (76.7)**
In compliance with the protocol	55 (74.3)	25 (59.5)	80 (69.0)
With a protocol deviation after inclusion	6 (8.1)	3 (7.1)	9 (7.8)
Randomised Set (RS) [1]	**74 (100)**	**42 (100)**	**116 (100)**
Full Analysis Set (FAS) [1]	**73 (98.6)**	**41 (97.6)**	**114 (98.3)**
Per Protocol Set Titration (PPS) [2]	**64 (87.7)**	**31 (75.6)**	**95 (83.3)**
Safety Set (SS)	**73 (98.6)**	**42 (100)**	**115 (99.1)**

% calculated according to the number of patients included in each treatment group; n: number of patients affected; *: Only applicable during follow-up period; **: to note 2 patients (1 in each group) withdrawn at M0 were not considered as having completed the titration period according to the following definition as the duration between the 2 last visits of the titration period were inferior to 3 days; (1) % calculated as % of the Randomised Set; (2) calculated as % of the FAS

During the study, 23.3% (27 patients) were withdrawn, with a lower frequency reported in the ivabradine group than in the placebo group: 17.6% *versus* 33.3%, respectively. The main reason for patients' withdrawal was adverse events in both groups, with a lower frequency of patients affected in the ivabradine group than in the placebo group (13.5% *versus* 31.0%, respectively), mostly due to electrocardiogram QT prolonged (9.5% in both groups), that was emergent in 4.1% *versus* 7.1%, respectively. No patient was lost to follow-up. Of note, most of the patients were withdrawn after the titration period, with a lower proportion of patients in the ivabradine group than in the placebo group: 10.8% *versus* 23.8%, respectively.

The percentage of patients with protocol deviations at inclusion was similar in both treatment groups (12.2% *versus* 14.3%, respectively), in the Randomised Set. They concerned mostly previous treatments for CHF for which the dose was not stable (according to the investigator's judgment) within 4 weeks before selection, mainly diuretics (4 patients in each group, 5.4%, and 9.5%, respectively).

Demographic and other baseline characteristics fulfilled with the inclusion criteria defined in the study protocol.

In the Randomised Set, patients were on average 0.74 ± 0.15 years old (approximately 8.9 ± 1.8 months) in the [6-12[months age subset, 2.1 ± 0.6 years in the [1-3[years age subset, and 9.3 ± 4.2 years in the [3-18[years age subset, and 55.2% of them were male (52.7% *versus* 59.5%, respectively). Patients had CHF since 48.0 ± 49.7 months on average (ranging from 1 month to 16.7 years, median = 25.5 months), with no relevant between-group difference. All patients had a stable condition regarding CHF symptoms for at least 4 weeks before selection, and the cause of the CHF was DCM for all patients. For more than half of the patients, the DCM was idiopathic (60.8% *versus* 47.6%, respectively).

At baseline, patients had mostly CHF class II (80.2%), and no patient had a CHF class I (NYHA or Ross classification). CHF was rated class III in 15.5% and class IV in 4.3%. No relevant difference between-group was observed.

SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

The mean **LVEF** was 31.9 ± 8.3%, median = 32.0% in the ivabradine group *versus* 34.6 ± 7.6%, median = 37.0% in the placebo group. The mean **NT-proBNP** plasma concentration was 1682 ± 3224 pg/mL (1493 ± 2451 pg/mL in the ivabradine group *versus* 2010 ± 4261 pg/mL in the placebo group), and the geometric mean was 484 pg/mL (478 pg/mL *versus* 495 pg/mL, respectively).

The **Global Clinical Status** assessed by parents and children, or by the investigator was mostly judged "good", respectively, 65.5% and 61.2%. No relevant between-group difference was observed.

Concomitant treatments received at inclusion for CHF were mainly ACE inhibitors (94.6% *versus* 92.9%, respectively), beta-blockers (79.7% *versus* 69.1%, respectively), aldosterone antagonists (85.1% *versus* 66.7%, respectively), diuretics other than aldosterone antagonists (66.2% *versus* 73.8%, respectively), and digitalis (52.7% *versus* 45.2%, respectively).

As regards to **ECG** parameters at baseline, no relevant between-group difference was observed. The mean heart rate was 101.0 ± 23.2 bpm in the ivabradine group and 99.7 ± 21.9 bpm in the placebo group. The mean QT corrected with Bazett formula (QTcB) was 423.1 ± 31.0 ms, and the mean QT corrected with Fridericia formula (QTcF) was 389.9 ± 29.4 ms, with no relevant between-group difference. Similar trends were observed in the age subsets.

No relevant between-group difference was observed for **vital signs** at baseline, in the Randomised Set. The mean supine **SBP and DBP** were 95.1 ± 12.3 mmHg and 57.0 ± 10.1 mmHg, respectively. The overall mean **heart rate** was 130.6 ± 16.4 bpm in the [6-12[months subset, 111.4 ± 10.8 bpm in the [1-3[years subset and 87.4 ± 10.7 bpm in the [3-18[years subset. The BMI was 16.3 ± 3.0 kg/m², ranging between 10.8 kg/m² and 26.3 kg/m².

Demographic and other baseline characteristics in the PPS titration were close to those described in the Randomised Set.

The mean overall **treatment duration** was 363.9 ± 86.6 days (median = 397.0 days), 374.3 ± 67.1 days (median = 397.0 days) in the ivabradine group *versus* 342.6 ± 115.5 days (median = 399.0) in the placebo group, in the PPS titration. The global compliance during the treatment period was good (98.3 ± 4.5%), with no relevant difference between groups.

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Statistical results have to be interpreted with caution because the multiplicity of analyses has not been controlled in this study and could lead to false positive conclusion. Therefore, to reduce the probability of positive results due to the chance, only 95% CI far away from 0 for criteria expressed as difference (change) and from 1 for criteria expressed as ratio (OR) would be interpreted as statistically significant.

Primary assessment criteria

Target HRR achievement
Main analysis: target HRR achievement during the titration period

The target HRR was obtained, in a larger proportion of patients in the ivabradine group than in the placebo group at the end of the titration period: 46 patients 71.9% *versus* 5 patients, 16.1%, in the PPS titration. The between-group comparison was statistically significant in favour of ivabradine in the PPS titration (Odds Ratio: E = 14.97, 95% CI = [4.79 ; 46.77]). The mean time to reach this target HRR was 43.9 ± 23.0 days in the ivabradine group.
Results observed for the overall population were not driven by a particular age subset.
None of the patients who did not achieve the target HRR reported signs or symptoms related to bradycardia in both treatment groups. Of note, no patient reached the target HRR in the [1-3[years in the placebo group.

**Target Heart Rate Reduction (HRR) achievement during the titration period -
Treatment effect - Overall patients and age subsets patients - PPS titration (N = 95)**

Target HRR achievement at the end of titration period		Ivabradine (N = 64)	Placebo (N = 31)
Overall patients	n_{obs}	64	31
	n (%)	46 (71.9)	5 (16.1)
Statistical analysis			
Odds Ratio	E [1]	14.97	
	95% CI [2]	[4.79 ; 46.77]	
Time to reach target HRR (days)	Mean ± SD	43.9 ± 23.0	28.8 ± 10.0
	Median	43.0	28.0
	Min ; Max	12 ; 77	16 ; 44
[6-12[months	n_{obs}	8	2
	n (%)	4 (50.0)	1 (50.0)
Statistical analysis			
Odds Ratio	E [1]	1.00	
	95% CI [2]	[0.05;22.18]	
Time to reach target HRR (days)	Mean ± SD	53.3 ± 27.2	29.0 ±
	Median	63.0	29.0
	Min ; Max	14 ; 73	29 ; 29
[1-3[years	n_{obs}	20	10
	n (%)	14 (70.0)	-
Statistical analysis			
Odds Ratio	E [1]	NA	
	95% CI [2]	NA	
Time to reach target HRR (days)	Mean ± SD	54.8 ± 22.1	-
	Median	70.0	-
	Min ; Max	13 ; 77	-
[3-18[years	n_{obs}	36	19
	n (%)	28 (77.8)	4 (21.1)
Statistical analysis			
Odds Ratio	E [1]	13.12	
	95% CI [2]	[3.39;50.84]	
Time to reach target HRR (days)	Mean ± SD	37.2 ± 21.0	28.8 ± 11.5
	Median	29.0	27.5
	Min ; Max	12 ; 76	16 ; 44

*N: number of patients in each treatment group considered; n_{obs}: Number of observed values; %:(n/nobs) * 100; Statistical analyses are presented with imputation using a Last Observation Carried Forward (LOCF) approach as these results were consistent with the analyses without imputation, using the complete case approach; (1) Estimate (E) of the odds ratio between ivabradine and placebo groups based on a logistic regression model adjusted for age class, and Standard Error (SE) of the estimate (for overall patients); (2) 95% confidence interval of the estimate (two-sided); NA: Not Applicable*

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

The sensitivity analysis to statistical approach performed in the PPS titration and sensitivity analysis to the choice of the patient's set performed in the FAS showed consistent results for the overall patients (PPS titration: Odds ratio, E = 12.94, 95% CI = [4.22 ; 55.55], FAS: Odds Ratio: E = 17.24, 95% CI = [5.91 ; 50.30]). Results observed for the overall population were not driven by a particular age subset.

Secondary analyses

- **Heart rate at rest during the titration period:** change and relative change from baseline to the end of the titration period.
    A larger reduction in the heart rate at rest was observed in the ivabradine group compared to the placebo group, from baseline to the end of the titration period, in the PPS titration:
    - The change was: -22.7 ± 10.8 bpm in the ivabradine *versus* -2.2 ± 12.0 bpm in the placebo group, with a between-group difference statistically significant in favour of ivabradine (E (SE) = -19.59 (2.29), 95% CI = [-24.14 ; -15.04]).
    - The relative change was -22.3 ± 10.1% *versus* -1.9 ± 12.5%, respectively.
    Same trends were observed in the age subsets, except in the [6-12[months subset (where the reduction in heart rate was similar in both groups).
    The sensitivity analysis to the statistical approach performed in the PPS titration and sensitivity analysis to the choice of the patient's set performed in the FAS showed similar results.

- **Target HRR achieved according to the dose**
    For patients with target HRR achieved in the ivabradine group, the mean doses prescribed during the titration period and the doses received at the end of the titration period were as follows, in the PPS titration:
    - [6-12[months: mean dose = 0.085 ± 0.044 mg/kg *b.i.d.*, 1 patient (25.0%) at the starting dose 0.02 mg/kg *b.i.d.*, 1 patient (25.0%) at 0.15 mg/kg *b.i.d.*, and 2 patients (50.0%) at the maximal dose 0.20 mg/kg *b.i.d.*,
    - [1-3[years: mean dose = 0.131 ± 0.040 mg/kg *b.i.d.*, 1 patient (7.1%) at the starting dose 0.05 mg/kg *b.i.d.*, 3 patients (21.4%) at 0.10 mg/kg *b.i.d.*, 1 patient (7.1%) at dose 015 mg/kg *b.i.d.*, 1 patient (7.1%) at dose 0.20 mg/kg *b.i.d.*, and 8 patients (57.1%) at the maximal dose 0.30 mg/kg *b.i.d.*,
    - [3-18[years < 40 kg: mean dose = 0.104 ± 0.040 mg/kg *b.i.d.*, 4 patients (23.5%) at the starting dose 0.05 mg/kg *b.i.d.*, 3 patients (17.6%) at 0.10 mg/kg *b.i.d.*, 3 patients (17.6%) at 0.15 mg/kg *b.i.d.*, 5 patients (29.4%) at 0.20 mg/kg *b.i.d.*, and 2 patients (11.8%) at the maximal dose 0.30 mg/kg *b.i.d.*,
    - [3-18[years ≥ 40 kg: mean dose = 4.06 ± 2.16 mg *b.i.d.*, 4 patients (36.4%) at the starting dose 2.5 mg *b.i.d.*, 5 patients, (45.5%) at 5 mg *b.i.d.*, and 2 patients (18.2%) at the maximal dose 15 mg *b.i.d.*
    The target HRR could be reached at the starting dose in at least one patient in each age subset.
    For all patients who did not reach the target HRR, the dose received at the end of the titration period was the maximal dose: 18 patients in the ivabradine group and 26 patients in the placebo group.
    During the follow-up period, the dose received by the patients was unchanged for most of the patients (87.5% in the ivabradine group and 100% in the placebo group) and few patients had a dose decreased (12.5% *versus* no patient, respectively).

- **Heart rate at rest during the follow-up period**
    From the baseline to the end of the follow-up, the reduction in the heart rate was larger in the ivabradine group than in the placebo group, with a between-group difference statistically significant in favour of ivabradine: change = -20.8 ± 15.9 bpm *versus* -3.0 ± 11.6 bpm (E (SE) = -16.63 (2.67) bpm, 95% CI = [-21.91;-11.34], in the FAS). Same trends were observed for the relative change (-24.17 ± 9.76% *versus* -3.50 ± 12.14%, in the FAS). Results showed same trends in the age subsets.
    Results of the sensitivity analysis to the statistical approach were similar.

PK results
The PK analysis showed that whatever the age class, the therapeutic exposure at the maintenance dose was comparable. Median AUC was 197 ng.h/mL and ▇▇▇▇▇▇▇ for ivabradine ▇▇▇▇▇▇▇▇▇▇▇▇, respectively. Median Cmax was ▇▇▇▇▇▇▇▇▇▇▇▇ for ivabradine ▇▇▇▇▇▇▇, respectively.

PK/PD results
The PK/PD model developed in adult (refer to the internal clinical report NP 32761) was applied with the HR baseline values in children, individual PK parameters in children and dosing history to predict HR at the different measurement times of the paediatric study. These predictions in children were in good agreement with observed heart rate in children from study CL2-16257-090. Thus the PK/PD relationship described in adult patients was conserved in pediatric population.

SUMMARY - CONCLUSIONS (Cont'd)

<u>EFFICACY RESULTS (Cont'd)</u>

Secondary efficacy criteria

The **echocardiographic parameters** showed a trend to an improvement over time, with ivabradine group *versus* placebo group:

- LVEF increased from baseline to M12 in both treatment groups, with a between-group difference indicating a trend in favour of ivabradine: 13.54 ± 13.14% *versus* 6.94 ± 11.44% in the placebo group (E (SE) = 5.57 (2.44)%, 95% CI = [0.75 ; 10.40]), in the FAS.
- LVSF increased from baseline to M6 and M12 in both groups, with a larger increase in the ivabradine than in the placebo group (M6: 6.8 ± 6.1% *versus* 3.1 ± 4.4%, respectively, M12: 8.2 ± 7.4% *versus* 3.8 ± 7.0%, respectively).
- LVESV decreased from baseline to M6 and M12 in both groups, with a larger reduction in the ivabradine than in the placebo group (M6: -13.4 ± 21.8% *versus* -2.7 ± 13.7%, respectively, M12: -15.3 ± 25.5% *versus* -2.2 ± 18.1%, respectively).
- LVEDV decreased from baseline to M6 and M12 in the ivabradine group, whereas it increased in the placebo group (M6: -7.4 ± 24.7% *versus* 3.7 ± 22.9%, respectively, M12: -6.0 ± 32.4% *versus* 4.6 ± 24.9%, respectively).

In the age subsets, a trend in favour of ivabradine was globally observed and similar results were observed in the sensitivity analyses.

Other secondary criteria showed a trend to an improvement of the patients, more marked in the ivabradine than in the placebo group.

- **NYHA or Ross classification:** an improvement of the patients was observed, with a larger proportion in the ivabradine group than in the placebo group: 37.7% *versus* 25.0%, respectively. Most of the patients remained stable from baseline to M12: 62.3% in the ivabradine group *versus* 75.0%, in the placebo group. None of the patients in any group had a worsening.
- **Global clinical status:** most of the patients were improved from baseline to M12 in the ivabradine group, according to the investigator assessment, with a larger proportion in the ivabradine group than in the placebo group: 50.8% *versus* 35.7%, respectively. A total of 45.9% *versus* 57.1%, respectively, remained stable and 2 patients worsened (3.3% *versus* 7.1%, respectively). For the global clinical assessment evaluated by the children or the parents, patients were improved in 32.8% *versus* 32.1%, respectively, remained stable in 60.7% *versus* 46.4%, respectively, and worsened: 6.6% *versus* 21.4%, respectively.
- **NT-proBNP:** a decrease from baseline to M12 was observed in both groups (-710.1 ± 1478.4 pg/mL (median = -128.3 pg/mL) *versus* -367.4 ± 576.5 pg/mL (median = -128.70 pg/mL), respectively).
- **Weight**: as expected, an increase was observed from baseline to M12 in both groups. The change was 3.34 ± 2.48 kg *versus* 3.32 ± 2.08 kg, respectively. The mean BMI at M12 was similar in both groups: 16.8 ± 3.6 kg/m² *versus* 16.7 ± 3.2 kg/m², respectively, and was stable over the study.

 Same trends were observed in the age subsets.

Quality of life sub-study

This sub-study aiming to explore the effects of ivabradine compared to placebo on the health related quality of life, used Pediatric Quality of Life Inventory (PedsQL™ 4.0) questionnaires which was filled in by 69 parents and 36 children from age of 2 to less than 18 years. At baseline, the total score and the sub-scores (physical health and psychosocial summary scores) obtained either by the parents or children report were similar in both treatment groups, and were around 70 on a 0-100 scale. During the study, the questionnaires filled in by parents showed a trend to an improvement of the total score in favour of ivabradine (change of 9.09 ± 14.18) compared to placebo (change of 1.27 ± 15.34). Results of the two sub-scores (physical health and psychosocial summary scores) were also consistent. The questionnaires filled in by children did not show any relevant change during the study nor between-group difference for the total score and the sub-scores (for details please refer to the clinical report NP 33312).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

Adverse events

Summary of adverse events - Safety Set (N = 115)

Patients having reported at least one	Ivabradine (N = 73)		Placebo (N = 42)	
	n	%	n	%
Emergent adverse event (EAE)	63	86.3	37	88.1
Treatment-related EAE	21	28.8	8	19.0
Serious EAE (including death)	21	28.8	17	40.5
Treatment-related serious EAE	2	2.7	1	2.4
EAE leading to treatment withdrawal	4	5.5	8	19.0
SEAE leading to treatment withdrawal	1	1.4	5	11.9
Patients who died	-	-	4	9.5

N: number of patients in each treatment group considered.
%: (n*100/N).

Emergent adverse events were reported with similar frequency in both treatment groups (63 patients, 86.3% in the ivabradine group *versus* 37 patients, 88.1% in the placebo group).

In both treatment groups, the most frequently affected system organ classes (SOCs) were reported with a lower frequency in the ivabradine group than in the placebo group: Infections and infestations (50 patients, 68.5% *versus* 31 patients, 73.8%, respectively), Investigations (21 patients, 28.8% *versus* 16 patients, 38.1% respectively), and Gastrointestinal disorders (21 patients, 28.8% *versus* 15 patients, 35.7% respectively). Regarding the other SOCs, one was reported with a higher frequency in the ivabradine group than in the placebo group: Skin and subcutaneous tissue disorders (13 patients, 17.8% *versus* 4 patients, 9.5%, respectively). This between-group difference was mainly due to dermatitis atopic, dermatitis diaper, dry skin, and heat rash reported in 2 patients each (2.7%) in the ivabradine group only. Of note, the SOC eye disorders affected patients with similar frequency in both groups: 9 patients, 12.3% *versus* 6 patients, 14.3%, respectively. Details regarding phosphenes (2 patients, 2.7% *versus* 1 patient, 2.4%, respectively) and blurred vision (no patient affected in any treatment group) are provided hereafter in the potential or identified risk in the Risk Management Plan part.

The most frequent EAEs reported in the ivabradine group, with a higher frequency compared to placebo group were: nasopharyngitis (16 patients, 21.9% *versus* 7 patients, 16.7%, respectively), bronchitis (10 patients, 13.7% *versus* 3 patients, 7.1%, respectively), and gastroenteritis (9 patients, 12.3% *versus* 4 patients, 9.5%, respectively).

Cardiac disorders were globally less frequently reported in the ivabradine group than in the placebo group: 11 patients, 15.1% *versus* 13 patients, 31.0%, respectively. The preferred terms reported in the ivabradine group were mostly: atrioventricular block first degree (3 patients, 4.1% *versus* 1 patient, 2.4%, respectively), bradycardia (symptomatic) (3 patients, 4.1% *versus* no patient, respectively), and cardiac failure (2 patients in each group, 2.7% *versus* 4.8%, respectively). In the SOC Cardiac disorders, EAEs requiring hospitalisation or prolongation of hospitalisation were reported in 2 patients (2.7%) in the ivabradine group *versus* 4 patients (9.5%) in the placebo group, including:

- In the ivabradine group: cardiac failure and bradycardia (one patient each, 1.4%).
- In the placebo group: one patient had cardiac failure and atrial flutter, one patient had low cardiac output syndrome and pericardial effusion, one had cardiogenic shock, and one had cardiac failure, cardiogenic shock, ventricular tachycardia, ventricular fibrillation, and cardiac arrest.

A total of 4 **heart transplantation**, 2 in each treatment group, were performed during the study of which one in the ivabradine group and 2 in the placebo group were emergent (as one in the ivabradine group was performed about 2 months after the last study drug intake).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Overall potential or identified risk in the Risk Management Plan (RMP) of ivabradine consisted mainly in reports of bradycardia and ECG QT prolongations:

- Bradycardia was reported with a higher frequency in the ivabradine than in the placebo group (8 patients, 11.0% *versus* 1 patient, 2.4%, respectively), including bradycardia asymptomatic, *i.e.* heart rate decreased as preferred term (5 patients, 6.8% *versus* 1 patient, 2.4%, respectively) and symptomatic (3 patients, 4.1% *versus* no patient, respectively). Asymptomatic bradycardia were reported in patients aged [1-3[years in 2 patients, 8.3% in the ivabradine group *versus* 1 patient, 8.3% in the placebo group, in patients aged [3-18[years in 3 patients, 7.7% *versus* no patient, respectively. Symptomatic bradycardia were reported in the ivabradine group only, in 1 patient, 4.2%, aged [1-3[years and 2 patients, 5.1% aged [3-18[years.
- The ECG QT prolonged were less frequently reported in the ivabradine group than in the placebo group (6 patients, 8.2% *versus* 7 patients, 16.7%, respectively).

Phosphenes were reported with similar frequency in both groups: 2 patients, 2.7% *versus* 1 patient, 2.4%, respectively, and no patient reported blurred vision.

The other EAEs of the RMP were either reported with a lower frequency in the ivabradine group than in the placebo group (supraventricular tachyarrhythmia other than atrial fibrillation, severe ventricular arrhythmia), or reported with similar frequency in both treatment groups (immune system disorders).

Most of the EAEs were rated mild, with a higher frequency reported in the ivabradine group than in the placebo group (84.2% versus 72.5% of the EAEs, respectively). **Severe** EAEs were less frequently reported in the ivabradine group than in the placebo group (9 patients, 12.3% *versus* 8 patients, 19.0%, respectively). The most frequent SOC affected was infections and infestations (4 patients, 5.5% *versus* 3 patients, 7.1%, respectively). No particular preferred term was affected by severe EAEs. Severe EAEs of the cardiac disorders SOC were less frequently reported in the ivabradine group than in the placebo group (2 patients, 2.7% *versus* 5 patients, 11.9%, respectively).

A **recovery** was observed for most of the EAEs: 91.8% of the EAEs in the ivabradine group *versus* 84.7% in the placebo group.

EAEs considered as treatment-related according to the investigator's opinion were reported with a higher frequency in the ivabradine group than in the placebo group (21 patients, 28.8% *versus* 8 patients, 19.0%, respectively). They affected mainly the SOC investigations, and were more frequently reported in the ivabradine group than in the placebo group (11 patients, 15.1% *versus* 3 patients, 7.1%, respectively), including mostly heart rate decreased (5 patients, 6.8% *versus* no patient, respectively).

Emergent AEs leading to treatment withdrawal were reported with a lower frequency in the ivabradine group than in the placebo group (4 patients, 5.5% *versus* 8 patients, 19.0%, respectively). These EAEs were mainly electrocardiogram QT prolonged, with a lower frequency in the ivabradine group compared to the placebo group (3 patients in both groups: 4.1% *versus* 7.1%, respectively).
Serious EAEs leading to treatment withdrawal were reported in 1.4% (one patient) in the ivabradine group (heart transplant was not considered as treatment-related by the investigator) *versus* 5 patients, 11.9% in the placebo group (mainly due to cardiac disorders: 4 patients, 9.5%, including 1 patient each, 2.4%: atrial flutter, cardiac failure chronic, cardiogenic shock, and in one patient: low cardiac output syndrome and pericardial effusion).

Serious EAEs were reported with a lower frequency in the ivabradine group than in the placebo group (21 patients, 28.8% *versus* 17 patients, 40.5%, respectively). The SOCs Infections and infestations (8 patients, 11.0% *versus* 9 patients, 21.4%, respectively) and Investigations (5 patients, 6.8% *versus* 8 patients, 19.0%, respectively) were frequently reported. The most frequently reported SEAE was cardiovascular evaluation (corresponding to a planned hospitalisation for evaluation of DCM) reported in 4 patients in each group (5.5% *versus* 9.5%, respectively). Emergent SAEs were considered as treatment-related according to the investigator in 2 patients in the ivabradine group (heart rate decreased and in one patient: bradycardia and tonic convulsion) and one patient in the placebo group (vomiting, diarrhoea and hypotension).

None of the patients died in the ivabradine group and 4 patients in the placebo group had 5 EAEs leading to **death**: septic shock, sudden cardiac death, and ventricular tachycardia (each in one patient), and in one patient: cardiogenic shock and ventricular fibrillation.

In the age subsets, the safety profile was globally similar.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Laboratory parameters
Emergent PCSA values for biochemistry were detected in 5.5% in the ivabradine group *versus* 9.5% in the placebo group, respectively, for the following parameters: alkaline phosphatase (high value: 4.3% *versus* 2.8%, respectively), sodium (low value: one patient in each group), and ASAT and ALAT (high values: one patient in the placebo group only).
Emergent PCSA values for haematology were detected in 15.1% *versus* 9.5%, respectively. No particular parameter was affected.

Vital signs
No relevant change was observed from baseline to M12 in both groups for systolic or diastolic blood pressures.

Electrocardiogram (central review)
Heart rate
The HR markedly decreased in the ivabradine group over time, whereas no relevant changes were observed in the placebo group (change from baseline to M12: -27.6 ± 18.7 bpm in the ivabradine group *versus* -0.9 ± 9.5 bpm in the placebo group, in the Safety Set). The mean lowest HR values were 91.1 ± 9.4 bpm *versus* 111.7 ± 14.6, respectively, for the [6-12[months, 72.1 ± 11.4 bpm *versus* 96.8 ± 13.9 bpm, respectively, for the [1-3[years, 61.7 ± 12.2 bpm *versus* 73.0 ± 9.3 bpm, respectively, for the [3-18[years.
PR interval, QRS interval: no clinically relevant change over time was observed in both groups for the mean PR and QRS intervals.

QT interval
In the ivabradine group, the mean QT increased over time, whereas no relevant change was observed in the placebo group. The mean QT interval change from baseline to M12 was 37.1 ± 27.9 ms in the ivabradine group *versus* 2.7 ± 24.5 ms in the placebo group.
In the ivabradine group, the mean QTcB decreased over time, whereas it slightly increased in the placebo group. The change from baseline to M12 was -20.0 ± 25.0 ms *versus* 4.7 ± 19.2 ms, respectively.
In the ivabradine group, the mean QTcF slightly increased in both treatment groups over time. The change from baseline to M12 was 1.2 ± 20.5 ms *versus* 4.1 ± 19.7 ms, respectively.

Emergent QTcB value > 450 ms and a QTcB prolongation from baseline > 30 ms: the rate of patients affected was lower in the ivabradine group than placebo group: 9 patients, 12.5% *versus* 9 patients, 22.5%, respectively. Among these patients, 3 patients had an EAE "electrocardiogram QT prolonged" reported by the investigator: one patient, 1.4% in the ivabradine group (not serious, not considered as treatment-related by the investigator, recovered), and 2 patients, 5.0% in the placebo group (including one EAE serious, both EAEs recovered).
Emergent QTcB value > 500 ms or a QTcB prolongation from baseline > 60 ms: no relevant between-group difference was observed for (4 patients, 5.6% *versus* 2 patients, 5.0% respectively). For these patients, no AE "electrocardiogram QTc prolonged" was reported by the investigator.
Emergent QTcB value > 500 ms and QTcB prolongation from baseline > 60 ms were detected in one patient in the ivabradine *versus* no patient in the placebo group. This patient had also a QTcF value > 500 ms and a QTcF prolongation > 60 ms. No AE electrocardiogram QT prolonged was reported for this patient.

Emergent *QTcF value > 450 ms with a QTcF prolongation from baseline > 30 ms* were detected in 4 patients, 5.6% in the ivabradine group only. Among these patients, one patient had an EAE "electrocardiogram QTc prolonged" reported by the investigator (not serious, not considered as treatment-related by the investigator, recovered). This patient had also a QTcB value > 450 ms and QTcB prolongation from baseline > 30 ms.
Emergent QTcF value > 500 ms or QTcF prolongation from baseline > 60 ms were detected in 7 patients, 9.7% *versus* 1 patient, 2.5% respectively. No EAE "electrocardiogram QTc prolonged" was reported for these patients.

Emergent ECG abnormalities
Most of patients had emergent ECG abnormalities, with similar frequency reported in both treatment groups (98.6% *versus* 97.6%, respectively). To note, sinus bradycardia was reported with a higher frequency in the ivabradine than in the placebo group (54.8% *versus* 4.8%, respectively).

CONCLUSION

This international Phase II study was conducted in children aged from 6 months to less than 18 years, with a dilated cardiomyopathy, and symptomatic chronic heart failure.

Results showed that the target heart rate reduction (HRR) was obtained at the end of the titration period, with a statistically significant higher achievement rate with ivabradine *versus* placebo (71.9% *versus* 16.1% respectively, Odds Ratio: E = 14.97, 95% CI = [4.79 ; 46.77]).

The mean dose prescribed during the titration period in patients with the target HRR achieved treated with ivabradine were 0.085 ± 0.044 mg/kg *b.i.d.* for the [6-12[months, 0.131 ± 0.040 mg/kg *b.i.d.* for the [1-3[years, 0.104 ± 0.040 mg/kg *b.i.d.* for the [3-18[years with a weight below 40 kg, and 4.06 ± 2.16 mg *b.i.d.*. for patients aged [3-18[years and with a weight above 40 kg, in the PPS titration. The target HRR could be reached at the starting dose in at least one patient in each age subset (1 patient (25.0%) in the [6-12[months, 1 patient (7.1%) in the [1-3[years, 4 patients (23.5%) in the [3-18[years < 40 kg, and 4 patients (36.4%) in the [3-18[years ≥ 40 kg).

A statistically significant reduction in HR was observed with ivabradine compared to placebo at the end of the titration period (-22.7 ± 10.8 bpm *versus* -2.2 ± 12.0 bpm respectively, E (SE) = -19.59 (2.29), 95% CI = [-24.14 ; -15.04]). In general, same trends were observed in the age subsets, although results in the [6-12[months are somewhat difficult to interpret due to the limited sample size (8 and 2 patients for ivabradine and placebo, respectively).

Secondary efficacy criteria showed also an improvement of the patients which was generally more marked with ivabradine compared to placebo group. For LVEF, the between-group difference showed a trend in favour of ivabradine (E (SE) = 5.57 (2.44%) 95% CI = [0.75 ; 10.40], at M12). Favorable trends were also observed for the other echocardiographic parameters (LVSF, LVESV, LVEDV). Regarding the evolution in NYHA or Ross classification, most of the patients remained stable while an improvement was observed with a higher frequency in patients with ivabradine compared to placebo. Consistent results were observed for the global clinical status assessed by the investigator or the parents/children.

The quality of life sub-study showed a trend to an improvement of the patients in the ivabradine compared to placebo group, regarding the total score and sub-scores issued from the PedsQL™ 4.0 questionnaires filled in by the parents. The questionnaires filled in by children did not show any relevant change during the study nor between-group difference.

The PK analysis showed that whatever the age class, the therapeutic exposures at the maintenance dose were in the same range. Median AUC was 197 ng.h/mL and 64 ng.h/mL for ivabradine and its metabolite (S 18982), respectively. Median Cmax was 28 ng/mL and 5.1 ng/mL for ivabradine and its metabolite, respectively. The results of the PK/PD analysis showed that the PK/PD relationship described in adult patients was conserved in paediatric population.

Regarding safety, emergent adverse events were reported with similar frequency in both treatment groups. Cardiac disorders were reported with a lower frequency with ivabradine compared to placebo. As expected, bradycardia was reported with a higher frequency with ivabradine (11.0% *versus* 2.4%, respectively), but most of them were asymptomatic. Cardiac disorders requiring hospitalisation or prolongation of hospitalisation were reported in 2.7% in the ivabradine group *versus* 9.5% in the placebo group. Heart transplantation was performed in 4 patients during the study (2 in each group). No patient died in the ivabradine group while 4 patients died in the placebo group, all for cardiac causes (mainly cardiac arrhythmias and shock).
Emergent QTcB values > 450 ms with a QTcB prolongation > 30 ms were less frequently reported with patients treated with ivabradine than placebo. Emergent QTcF values > 450 ms with a QTcF prolongation > 30 ms were reported in 4 patients in the ivabradine group only. One patient in the ivabradine group *versus* none in the placebo group had QTcB and QTcF value > 500 ms and a QTcB and QTcF prolongation > 60 ms, with no electrocardiogram QT prolonged reported as adverse event. The SOC eye disorders affected patients with similar frequency in both groups (12.3% *versus* 14.3%, respectively). Phosphenes were reported with similar frequency in both groups and no patient reported blurred vision. No relevant between-group difference was observed for the other events identified in the RMP.

Overall, in this paediatric population, the safety profile of ivabradine was the same that the one known in adults.

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