DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	209964
Drug Name:	Ivabradine
Indication(s):	Stable Symptomatic Heart Failure Due to Dilated Cardiomyopathy (DCM) in Pediatric Patients
Applicant:	AMGEN
Date(s):	10/25/2018
Review Priority:	Priority
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1 EXECUTIVE SUMMARY

This NDA seeks marketing authorization of ivabradine for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged 6 months to less than 18 years who are in sinus rhythm with elevated heart rate (b) (4) Study CL2-16257-090, an international Phase II study was conducted in children aged from 6 months to less than 18 years, with a DCM, and symptomatic chronic heart failure. The study results showed:

- The target HRR (defined as a reduction of the heart rate from baseline of at least 20%, and without inducing a bradycardia and/or signs or symptoms related to bradycardia), was obtained in a larger proportion in the ivabradine group than in the placebo group at the end of the titration period, with a between-group comparison statistically significant in favor of the ivabradine group.
- In addition, a larger reduction in the heart rate at rest in the ivabradine group than in the placebo group, from baseline to the end of the titration period.

Above two conclusions observed for the overall population were not driven by a particular age subset.

2 INTRODUCTION

2.1 Overview

Ivabradine reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the cardiac pacemaker f-current, resulting in heart rate reduction. Ivabradine was approved in the United States on 15 April 2015. The approved indication in adults is to reduce the risk of hospitalization for worsening heart failure with stable, symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) $\leqslant$ 35%, who are in sinus rhythm with resting heart rate $\geqslant$ 70 bpm and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

This NDA is being submitted to support the proposed indication in pediatric patients aged 6 months to less than 18 years who are in sinus rhythm (b) (4) and in fulfillment of the Written Request. As part of a Pediatric Investigation Plan, a pediatric study CL2-16257-090 in subjects of age 6 months to ≤ 18 years with DCM and symptomatic chronic heart failure receiving an optimal background treatment for chronic heart failure. It was conducted in pediatric subjects to address the following primary objectives:

- To determine the optimal dose of ivabradine to reach the target HRR of ≥ 20% without inducing bradycardia and/or signs of symptoms related to bradycardia.
- To assess the PK parameters of ivabradine and its active metabolite S18982 after repeated oral administrations.
- To assess the pharmacokinetic/pharmacodynamics (PK/PD) relationship of ivabradine and its active metabolite S18982 using heart rate as evaluation criterion.

In Study CL2-16257-090, ivabradine treatment resulted in a statistically significant and clinically meaningful reduction in resting heart rate. In the Full Analysis Set, target heart rate reduction

was achieved by 51 subjects (69.9%) in the ivabradine group versus 5 subjects (12.2%) in the placebo group, with an odds ratio (95% CI) of 17.24 (5.91; 50.30).

A larger reduction in the heart rate at rest was observed in the ivabradine group compared with the placebo group, from baseline to the end of the titration period, with a between-group difference statistically significant in favor of ivabradine (treatment difference [95% CI] of -18.99 bpm [-23.75; -14.23].

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\CDSESUB1\evsprod\NDA209964\0012 .

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The study CL2-16257-090 was performed in compliance with GCP guidelines, including the archiving of essential documents. Amgen's quality assurance and quality control procedures provide reassurance that the clinical study program was carried out in accordance with GCP guidelines. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each center.

Four quality control audits were carried out on the study documents: investigator's brochure, clinical study protocol, substantial amendments, corresponding amended protocols case report form and study report according to the internal procedures.

3.2 Evaluation of Efficacy

3.2.1 STUDY CL2-16257-90

The primary objectives of this study were:

- 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 parameters of ivabradine and its active metabolite S18982 after repeated oral administrations.
- To assess the PK/PD relationship of ivabradine and its active metabolite S18982 using heart rate as evaluation criterion.

3.2.1.1 Study Design

This was an international, multicenter, randomised, double-blind, placebo controlled, phase II/III study, with two parallel and non-balanced treatment arms (for each age subset), using a randomization ratio of two patients on ivabradine to one patient on placebo. The randomization was stratified by age-subset and was centralized by (b) (4)

A total of 116 subjects were enrolled, including 17 subjects of ages 6 months to < 1 year, 36 subjects of ages 1 to < 3 years, and 63 subjects of ages 3 to < 18 years. Subjects were randomly assigned to ivabradine or placebo in a 2:1 ratio. Study drug was titrated over a period of 2 to 8 weeks, with doses adjusted to the subject's age and weight, to reach an effective dose, defined as the dose that resulted in 20% heart rate reduction without going below pre-specified heart rates depending on age (and without inducing signs and symptoms of bradycardia).

The Investigational medicinal products are:
Ivabradine: administered twice daily (morning and evening), at the starting dose of:

- 0.02 mg/kg for the 6-12 months, as oral liquid pediatric formulation.
- 0.05 mg/kg for the 1-3 years and 3-18 years with weight < 40 kg, as oral liquid pediatric formulation.
- 2.5 mg for the 3-18 years with weight ⩾ 40 kg, as an adult tablet formulation.

Placebo: matching placebo was administered in the same condition as for ivabradine, pediatric oral solution or adult tablet formulation, twice daily (morning and evening).

3.2.1.2 Statistical Methodologies

The analysis sets of patients were defined as:
Randomised Set (RS): all patients to whom a therapeutic unit was randomly assigned using IRS.

Full Analysis Set (FAS): Patients of the Randomised Set having received at least one dose of study drug, and with at least two evaluations of resting HR.

Per Protocol Set Titration (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.

Safety Set (SS): All patients having received at least one dose of study drug.

Primary Endpoints and Analyses
The primary efficacy endpoints were target heart rate reduction achievement (yes/no) and heart rate at rest (bpm).

The main analysis on target heart rate reduction achievement was estimated using a logistic regression method adjusted for age class. The estimate of the odds ratio, its standard error and its 95% confidence interval were provided.

The treatment effect of ivabradine versus placebo on heart rate at rest was estimated using a parametric covariance analysis adjusted for age class and baseline value. The estimate of the difference between treatment groups, its standard error and its 95% confidence interval were provided.

Secondary Endpoints and Analyses

The secondary endpoints were:

- Echocardiography criteria: Left Ventricular Ejection Fraction (LVEF, %), Left Ventricular Shortening Fraction (LVSF, %), Left Ventricular End-Systolic Volume (LVESV, %), and Left Ventricular End-Diastolic Volume (LVEDV, %).
- NYHA or Ross classification (class I/II/III/IV).
- Global clinical status.
- Weight and height.

All secondary endpoints were provided with descriptive statistics at baseline, at each post-baseline visit and on change from baseline to each post-baseline value by treatment group.

3.2.2 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The first visit of the first patient was on 21 December 2011 and the date of the last visit for the last patient was on 26 February 2014. A total of 122 patients were selected for the study. Among them, 116 patients were included and randomly assigned, with a planned unbalanced ratio 2:1 between Ivabradine and Placebo group. The Safety Set consisted of 115 patients. One patient of the Randomised Set was excluded from the Safety Set as he did not receive any study drug. The Full Analysis Set (FAS) consisted of 114 patients. Two patients of the Randomised Set were excluded from the FAS as the resting HR at baseline or post-baseline was not evaluated. The Per Protocol Set (PPS) titration consisted of 95 patients. See Table 3-1.

Table 3-1 Analysis Sets by treatment group

Analysis Sets	Ivabradine	Placebo	Total
Randomized Set	74	42	116
Safety Set	73	42	115
FAS	73	41	114
PPS	64	31	95

[Source: Reviewer's results]

The main demographic characteristics are summarized in Table 3-2. Patients were in average 0.74±0.15 years old in the 6-12 months age subset, 2.14 ± 0.56 years in the 1-3 years age subset, and 9.28 ± 4.16 years in the 3-18 years age subset. Patients were mainly Caucasian (87.9%, 102 patients). A slightly more patients were male (64) versus 52 female patients.

Table 3-2 Demographic Characteristics

	Statistics	Ivabradine	Placebo	All
Age		5.82, 5.10, 74	5.80, 4.59, 42	5.82, 4.90, 116
6-12 months age	**Mean, SD, N**	0.74, 0.17, 10	0.74, 0.13, 7	0.74, 0.15, 17
1-3 years age		2.15, 0.58, 24	2.13, 0.55, 12	2.14, 0.56, 36
3-18 years age		9.30, 4.60, 40	9.26, 3.35, 23	9.28, 4.16, 63
Gender: M/F	**N:N**	39:35	25:17	64:52
Race				
Caucasian		66 (89.2)	36 (85.7)	102 (87.9)
Black	**n (%)**	3 (4.1)	2 (4.8)	5 (4.3)
Asian		-	1 (2.4)	1 (0.9)
Other		5 (6.8)	3 (7.1)	8 (6.9)

[Source: Reviewer's results]

3.2.3 RESULTS AND EXPLORATORY ANALYSES

In this study, Ivabradine treatment resulted in a statistically significant and clinically meaningful reduction in resting heart rate. This review focused the main analysis of target HRR achievement in the FAS. In the FAS, target heart rate reduction at end of the titration period was achieved by 51 subjects (69.9%) in the ivabradine group versus 5 subjects (12.2%) in the placebo group, with an odds ratio (95% CI) of 17.24 (5.91; 50.30).

The mean heart rate at rest decreased from baseline to the end of the titration period in the ivabradine group (From 102.0 to 80.7 bpm) whereas it remained stable in the placebo group (98.9 to 97.5 bpm). The between-group difference was statistically significant, in favor of ivabradine: E (SE) = -18.99 (2.40) bpm, 95% CI = [-23.75; -14.23].

Table 3-3 presented the results of Target HRR achievement and Heart rate at rest in both the FAS and PPS titration sets. In the PPS titration, the both results were in line with those obtained in the FAS.

Table 3-3 Results of Target HRR achievement and Heart rate at rest during the titration period-PPS titration and FAS

Endpoints			**Ivabradine**	**Placebo**	**Treatment Effect**
Target HRR Achievement	PPS		46/64 (71.9%)	5/31 (16.1%)	OR=14.97 95% CI: [4.79, 46.77]
	FAS		**51/73 (69.9%)**	**5/41 (12.2%)**	**OR=17.24 95% CI: [5.91, 50.30]**
Heart Rate at Rest (bpm)	PPS	BL	100.8±20.2	96.7±18.5	Diff=-19.59 (2.29) 95% CI: [-24.14, -15.04]
		ET	78.1±17.7	94.6±19.8	
	FAS	**BL**	**102.0±20.8**	**98.9±18.2**	**Diff=-18.99 (2.40) 95% CI: [-23.75, -14.23]**
		ET	**80.7±19.8**	**97.5±20.7**	

[Source: Reviewer's results]

Target HRR results observed for the overall population were not driven by a particular age subset:

- 6-12 months: 6 of 10 (60.0%) in the Ivabradine versus 1 of 6 (16.7%) in the placebo group.
- 1-3 years: 17 of 24 (70.8%) versus 0 of 12 (0.0%) patient in the placebo group, respectively.
- 3-18 years: 28 of 39 (71.8%) versus 4 of 23 (17.4%) in the placebo group, respectively.

Same trends were also observed in the age subsets for the heart rate at rest. The mean reduction over time was larger in the ivabradine group than in the placebo group for all three age subsets, see
Table 3-4.

Table 3-4 Heart rate at rest during the titration period – Age subsets patients

Age group		Ivabradine	Placebo
6-12 months	N	10	6
	Mean ± SD	-25.0±12.4	-4.2±16.5
1-3 years	N	24	12
	Mean ± SD	-26.4 ±11.2	1.3±10.5
3-18 years	N	39	23
	Mean ± SD	-17.1±13.6	-2.1±10.9

[Source: Reviewer's Results]

3.3 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Please find the age subgroup results for the Target HRR achievement and Heart Rate at rest in Section 3.2.3.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study CL2-16257-090 was a phase 2/3 study assessing pharmacokinetics, pharmacodynamics, efficacy, and safety of ivabradine oral solution and tablets in pediatric subjects with DCM. This study was designed with a primary objective to determine the optimal dose of ivabradine to reach the target heart rate reduction of 20% without inducing bradycardia and/or signs or symptoms related to bradycardia. The study also assessed the pharmacokinetic parameters of ivabradine and its active metabolite S18982 after repeated oral administrations; and to assess the PK/PD relationship of ivabradine and its active metabolite S18982 using heart rate as evaluation criterion. There are no statistical issues when reviewing the design, conduct, and results of CL2-16257-090.

5.2 Conclusions and Recommendations

In Study CL2-16257-090, ivabradine treatment resulted in a statistically significant and clinically meaningful reduction in resting HR. The target HRR was obtained in a larger proportion in the ivabradine group than in the placebo group at the end of the titration period, with a between-group comparison statistically significant in favor of the ivabradine group. In addition, a larger reduction in the heart rate at rest in the ivabradine group than in the placebo group, from baseline to the end of the titration period, in the FAS. The conclusions observed for the overall population were not driven by a particular age group.

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