CLINICAL REVIEW

Application Type	NDA Resubmission After Refuse to File
Application Number(s)	209964
Priority or Standard	Priority
Submit Date(s)	25 October 2018
Received Date(s)	25 October 2018
PDUFA Goal Date	25 April 2019
Division/Office	ODE1/DCaRP
Reviewer Name(s)	Shetarra Walker, MD, MSCR
Review Completion Date	01 April 2019
Established/Proper Name	Ivabradine
(Proposed) Trade Name	Corlanor
Applicant	Amgen
Dosage Form(s)	Oral solution
Applicant Proposed Dosing Regimen(s)	(b) (4)
Applicant Proposed Indication(s)/Population(s)	Pediatric: Treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients aged 6 months to less than 18 years, who are in sinus rhythm with elevated heart rate (b) (4)
Recommendation on Regulatory Action	Approval contingent on Amgen's agreement with proposed changes to dosing regimen and Prescriber Information
Recommended Indication(s)/Population(s) (if applicable)	Oral solution for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients aged 6 months and older, who are in sinus rhythm with elevated heart rate (b) (4) ; for approved indications in adults who are unable to swallow tablets

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Glossary

ACEI	angiotensin-converting enzyme inhibitor
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
AV	atrioventricular
BID	twice daily
BPCA	Best Pharmaceuticals for Children Act
BPM	beats per minute
CHF	chronic heart failure
CI	confidence interval
CM	cardiomyopathy
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CV	cardiovascular
DCM	dilated cardiomyopathy
DSMB	data safety monitoring board
EAE	emergent adverse event
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
HRR	heart rate reduction
IFU	Instructions for Use
IND	Investigational New Drug
LV	left ventricular/ventricle
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction

LVESV	left ventricular end-systolic volume
LVSF	left ventricular shortening fraction
MAED	MedDRA-based Adverse Event Diagnostics
MedDRA	medical dictionary for regulatory activities
MG	Medication Guide
NDA	new drug application
NEAE	number of emergent adverse events
NME	new molecular entity
NYHA	New York Heart Association
OR	odds ratio
PCSA	potentially clinically significant lab abnormalities
PD	pharmacodynamics
PDCO	pediatric committee
PDUFA	Prescription Drug User Fee Act
PI	Prescribing Information
PIP	pediatric investigational plan
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	postnatal day
PP	per protocol
PPS	per-protocol set -- titration
PPSR	proposed pediatric study request
PREA	Pediatric Research Equity Act
PT	preferred term
QoL	quality of life
RS	randomized set
RTF	refuse-to-file
SAE	serious adverse event
SD	standard deviation
SEAE	serious emergent adverse event
SMQ	standardized MedDRA queries
SOC	system organ class
SS	safety set
US	United States
WR	Written Request

1. Executive Summary

1.1. Product Introduction

This review evaluates the safety of ivabradine oral solution in pediatric patients with DCM and HF ages 6 months to less than 18 years.

Approved by FDA in 2015 under NDA 206143, ivabradine oral tablet is approved for reduction of risk for hospitalization for worsening HF in adult patients with chronic HFrEF and resting HR of at least 70 bpm. To date, ivabradine has been approved for use in over 100 countries for treatment of CHF and chronic stable angina. Amgen acquired US commercial rights to ivabradine from Les Laboratoires Servier in August 2013.

FDA waived pediatric study assessments under PREA but issued a WR under NDA 206143 for a randomized, double-blind, placebo-controlled, multicenter, phase II/III dose-finding study with PK/PD characterization and 1-year efficacy/safety evaluation in pediatric patients ages 6 months to less than 18 years. Amgen developed an age-appropriate pediatric formulation, oral solution, for use in their pediatric studies.

Pertinent to this review, Amgen provided data from a PK/PD study in pediatric patients with DCM and HF. In addition, Amgen conducted a bioequivalence study comparing exposures between a 7.5 mg dose of a 1 mg/mL oral solution and tablet. Furthermore, Amgen conducted a validation study comparing PK parameters for ivabradine 10 mg tablet using dried blood spot microsampling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Refer to the Clinical Pharmacology review for conclusions on effectiveness of ivabradine for the pediatric indication and proposed pediatric dosing. In brief, study results demonstrate that ivabradine has similar efficacy on HRR in children with DCM and HF as seen in adults with DCM and HFrEF. These data support the effectiveness of ivabradine as a treatment for pediatric HF due to DCM in the context of elevated heart rate and sinus rhythm. FDA's proposed dosing regimen in children ages 6 months and older weighing less than 40 kg is different from the dosing regimen used in the study and proposed in Amgen's draft PI. In this population, we propose a starting dose of 0.05 mg/kg twice daily with food with adjustments every two weeks based on HR by intervals of 0.05 mg/kg/dose up to a maximum dose of 0.2 mg/kg/dose for infants younger than 1 year of age and 0.3 mg/kg/dose for patients 1 year and older.

Results for secondary efficacy endpoints including echocardiographic findings, NYHA/Ross classification, global clinical status (assessed by the investigator and subject/parents), NT-proBNP plasma concentration, and growth parameters generally supported the efficacy of ivabradine in treating pediatric DCM. These are described in Section 6.

1.3. Benefit-Risk Assessment

Benefit-Risk assessment for a pediatric DCM/HF population is provided below. See Dr. Preston Dunnmon's clinical review for NDA 206143 dated 04 December 2014 for a detailed benefit-risk assessment for the adult HFrEF indication for ivabradine oral tablet.

Benefit-Risk Integrated Assessment

Pediatric DCM is serious and life-threatening with no therapies approved for this indication. Compared to adult studies, CV clinical outcomes typically cannot be established in pediatric studies due to small sample sizes for comparable CV conditions. Based on ivabradine's proven effect on the bridging biomarker, HR reduction, it is reasonable to expect a clinically meaningful benefit in children similar to adults. The results of study CL2-16257-090 indicate that ivabradine is effective in lowering HR in pediatric patients, ages 6 months and older, with HF. There were no new or unexpected safety findings in pediatric patients studied. Not surprisingly, there were higher rates of bradycardia and first-degree AV block in the ivabradine group compared to placebo. These risks are modest compared to the benefit expected to result from a sustained reduction in HR in pediatric DCM/HF patients.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DCM is an intrinsic disease of heart muscle with resultant myocyte dysfunction and impaired ability of the myocardium to generate contractile force • DCM typically results in HF and LV dysfunction • Incidence of DCM in a pediatric population in North American is 44 per million per year in infants, younger than 1 year, and 3.4 per million per year in children 1 to 18 years of age • Etiology, pathophysiology, and symptoms of DCM, including edema, dyspnea, and exercise intolerance, generally overlap between adults and children • Pediatric DCM patients are at risk for hospitalization, cardiac transplant, and death	Pediatric DCM is a serious and life-threatening condition with poor prognosis; 1- and 5-year rates of death or transplantation are 31% and 46%, respectively. To date, there are no approved therapies for pediatric HF associated with DCM. Therefore, there is an unmet need for medical therapies.
Current Treatment Options	• Off-label use of medications with adult HF indications are typically used to treat pediatric DCM/HF including ACEI, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, and diuretics	No approved therapies for pediatric HF associated with DCM.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td><u>Benefit</u></td><td>Primary Efficacy Endpoint – Target HRR Results
<table>
<tr><th>Study Population</th><th>Ivabradine N (%)</th><th>Placebo N (%)</th><th>Treatment Effect [OR (95% CI)]</th><th>p-value</th></tr>
<tr><td>PPS</td><td>46/64 (71.9)</td><td>5/31 (16.1)</td><td>14.97 (4.79;46.77)</td><td><0.0001</td></tr>
<tr><td>FAS</td><td>51/73 (69.9)</td><td>5/41 (12.2)</td><td>17.24 (5.91;50.30)</td><td><0.0001</td></tr>
</table></td><td>Ivabradine treatment resulted in a statistically significant and clinically meaningful reduction in resting HR in pediatric DCM patients with HF.</td></tr>
<tr><td><u>Risk and Risk Management</u></td><td>By PT, AEs occurring with increased frequency in the ivabradine treatment group compared to placebo included nasopharyngitis, bronchitis, gastroenteritis, decreased HR, AV block 1st degree, bradycardia, and photopsia.

No risk management plan is being proposed for the pediatric HF indication because safety information pertaining to monitoring of HR, heart rhythm, and visual AEs already included in current product labeling for the adult indication would be applicable to the proposed pediatric HF indication.</td><td>Compared to adult ivabradine data in the SHIFT trial, there were no new safety signals identified in this pediatric study. Similar to SHIFT, there was a higher proportion of subjects in the ivabradine group with on-target AEs compared to placebo. Based on the mechanism of action of ivabradine and no concerns for increased risk for immunosuppression in either nonclinical or prior human studies, it seems unlikely that the increased frequency of observed infections in the ivabradine group are study-drug related.</td></tr>
</table>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Section 6.1 Study Results
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6.1 Study Results
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

Amgen provided information on “global clinical status” of the patient by investigators and parents by asking the following question: “how do you qualify the general clinical status of your patient/your child?” (possible responses: very good/good/average/bad/very bad) at visits D0, M0, M03, M06, M09, and M012/final visit. In addition, Amgen conducted a QoL substudy to study CL2-16257-090 using a validated PedsQL™ 4.0 questionnaire given to parents or patients.

2. Therapeutic Context

2.1. Analysis of Condition

Pediatric cardiomyopathies are rare diseases resulting from various etiologies. The most common form of pediatric cardiomyopathy is DCM. DCM is characterized by a dilated LV and systolic dysfunction sometimes accompanied by diastolic dysfunction. Clinical presentation and disease progression may differ between adults and children and among pediatric patients depending on the underlying etiology for DCM and age at presentation. Compared to adults, pediatric patients with DCM are more likely to experience severe morbidity and mortality and require advanced heart failure therapies such as inotropic support, extracorporeal membrane oxygenation, or cardiac transplantation. However, neurohormonal pathophysiologic derangements are sufficiently similar between children and adults with DCM to expect similar responses to HF therapies targeting these neurohormonal pathways. There continues to be an unmet need for approved drug therapies to treat pediatric HF.

2.2. Analysis of Current Treatment Options

To date, there are no approved drugs specifically indicated for treatment of pediatric HF. Drug therapeutic classes approved in adults for chronic HFrEF include diuretics, ACEI, angiotensin-receptor blockers, aldosterone antagonists, beta blockers, digoxin, anti-arrhythmics, and anti-coagulants. Most of these drug therapies are used off-label to treat pediatric HF patients based on published guidelines.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

As of July 2018, ivabradine tablet is approved in 119 countries including the US for treatment of CHF and in 118 countries excluding the US for treatment of angina. Amgen's pediatric study was conducted in accordance with a WR agreement. Amgen's pediatric development program was designed to support a pediatric heart failure indication in children 6 months and older and fulfill conditions of the WR under BPCA.

Reviewer Comment: *Ivabradine has been approved and marketed in the European Union since 2005.*

3.2. Summary of Presubmission/Submission Regulatory Activity

The timelines of major regulatory milestones are below. Requirements of the pediatric WR are summarized in Table 1.

- April 2015: FDA approval of Corlanor (ivabradine) oral tablet, NME under NDA 206143, for treatment of chronic HFrEF in adults; FDA issues a WR
- February 2016: Revised WR to extend deadline for submitting study reports to FDA
- March 2016: FDA granted orphan-drug designation of ivabradine for treatment of pediatric patients with DCM
- December 2016: Initial NDA 209664 submission
- February 2017: FDA issued a RTF letter because validation information for drug product sterilization processes not provided
- May 2017: Type A meeting with Amgen to discuss issues raised in the RTF letter
- September 2017: A new WR issued to replace prior WR to extend deadline for study reports because the sponsor request for timeline extension was received after the prior agreed upon deadline has passed
- January 2018: Amended WR to further extend deadline for study report submission

Reviewer Comment: *Amgen had already completed study enrollment to fulfill a PIP agreement with EU at the time of FDA issuance of the WR in 2015.*

Table 1: Requirements of Pediatric Written Request

WR Section	Requirement
Required Study	Randomized, double-blind, placebo-controlled, multicenter PK/PD and dose-finding study
Study Objectives	• Primary ○ determine the optimal dose of ivabradine to reach the target heart rate reduction of 20%, without inducing bradycardia ○ assess the pharmacokinetic parameters of ivabradine and its active metabolite S 18982 after repeated oral administrations, and to assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship of ivabradine and its active metabolite S 18982 using heart rate as the evaluation criterion ○ safety information • Secondary ○ compare to placebo the effects of ivabradine at target dose on LVEF, LVSF, LVESV, LVEDV, HR, HF functional classification (NYHA or Ross), global clinical status, growth (weight and height), cardiovascular biomarker NT-proBNP, ○ long-term (1 year) safety of ivabradine ○ ancillary substudy is to assess quality of life

WR Section	Requirement
Study Population	• Pediatric subjects age 6 months to less than 18 years divided into three age groups: ○ 6 to <12 months ○ 1 to <3 years ○ 3 to <18 years • Number of subjects to be studied: at least 90 subjects (randomized 2:1 to ivabradine: placebo) with the following minimums per age group: ○ 6 months to less than 12 months - at least 10 patients ○ 1 to less than 3 years - at least 30 patients ○ 3 to less than 18 years - at least 30 patients • Representation of Ethnic and Racial Minorities: adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities OR description of efforts to do so and explanation for why unsuccessful
Study Endpoints	• Primary ○ characterization of PK parameters of ivabradine (S 16257) and S 18982 (active metabolite) plasma concentrations and corresponding heart rate values ○ target heart rate achieved - achievement of a heart rate reduction from baseline of at least 20% without inducing a bradycardia and/or signs or symptoms related to bradycardia • Secondary (efficacy) ○ echocardiographic parameters (LVEF, LVSF, LVESV, LVEDV) ○ HF symptom severity assessed by the NYHA or Ross classification ○ global clinical status evaluated by the investigator/parents ○ weight and height ○ cardiovascular biomarker NT- proBNP • Secondary (safety) ○ long-term (at least 1 year) safety of ivabradine in each age group and for the trial overall, to include analyses of all-cause mortality, CV mortality, arrhythmic mortality, HF mortality, all-cause hospitalization, CV hospitalization, arrhythmic hospitalization, hospitalization for worsening heart failure, and composite endpoint used in SHIFT (CV mortality and hospitalization for worsening HF) ○ occurrence of bradycardia ○ 12-lead ECG parameters ○ vital signs and AEs ○ clinical laboratory examination

WR Section	Requirement
Statistical Assessments	• Six subjects ages 6 to 12 months, 20 subjects ages 1 to 3 years, and 20 subjects ages 3 to <18 years treated with ivabradine were considered to be sufficient to assess the primary endpoint, the PK/PD characteristics in the pediatric population • Taking into account a randomization ratio of 2:1 for ivabradine: placebo, stratified by each age subset, at least 90 evaluable children were planned to be enrolled in the study (n= 60 for ivabradine group, n=30 for placebo group), including ≥ 10 infants ages 6 to 12 months, ≥ 30 infants and children ages 1 to 3 years, and ≥ 30 children and adolescents ages 3 to <18 years. • Descriptive statistics of plasma concentration-time data of ivabradine and its active metabolite as well as descriptive statistics of heart rate at rest should be presented at each time point for the entire study population and by age subgroup • Safety analyses should be performed on all subjects who received ≥ 1 dose of investigational product and by age subgroup • Treatment-emergent adverse events, ECG parameters, blood pressures, and laboratory parameters should be summarized using descriptive statistics • A detailed analysis of the ECG findings in each age group, and for the overall pediatric population, must be included with the final study report and datasets that you submit • Age-specific effects of ivabradine on the QT and the QTc should be described in detail • A detailed analysis of mortality and hospitalization should be included, as described above
Drug Safety Monitoring	Carefully monitor for bradycardia, QT/QTc prolongation, and the occurrence of worsening heart failure
Extraordinary Results	• If in the course of conducting the study, evidence indicating unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results; there may be a need to deviate from the requirements of this Written Request • For any scenario described above, the sponsor must contact the Agency to seek an amendment; although, it is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment
Drug Information	• An oral solution was developed for the pediatric study based on the agreed EU pediatric investigation plan in heart failure • Ivabradine dose was titrated according to age and heart rate • Older subjects in this trial received the adult active drug or matching placebo • Children < 40 kg or who were unable to swallow tablets received the oral solution

Reviewer Comments:

- *Additional requirements in the WR pertaining to pediatric formulation, labeling, format, types of reports to be submitted, and response to WR are consistent with standard FDA templated language.*
- *The sponsor has reasonably fulfilled all requirements of the WR.*
- *There was no IND opened in the United States until 2013 when the Pediatric Study Plan and PPSR were submitted for Agency feedback. Only juvenile nonclinical studies were submitted (b) (4) for the PPSR.*

3.3. Foreign Regulatory Actions and Marketing History

Ivabradine, including the oral solution, is not approved or marketed for children in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested.

4.2. Product Quality

The drug product used in the clinical drug development program is the same as the 'to be marketed' product. During internal discussions with CMC, it was discovered that the proposed (b) (4) ivabradine oral solution contains a leachable excipient, (b) (4) Accumulation of (b) (4) has been associated with adverse outcomes in young pediatric patients, especially infants, and increased risk for accumulation in individuals with renal or hepatic impairment. Based on the applicant's root cause analysis and subsequent corrective action regarding the (b) (4) CMC determined that they do not believe there will be a detectable amount of (b) (4) in the final drug product. Therefore, no information about trace (b) (4) will be included in product labeling. The CMC review is pending at time of this review.

4.3. Clinical Microbiology

The Clinical Microbiology review is not completed. However, there were no major clinical microbiology issues raised during this review cycle that would affect approvability or clinical conclusions on efficacy or safety.

4.4. Nonclinical Pharmacology/Toxicology

No new juvenile toxicity studies were submitted. Juvenile toxicity data in rats were previously reviewed under NDA 206143 by Dr. Jean Wu, dated 25 November 2014. Observations included neurobehavioral development, motor activity, learning and memory, sexual maturation, estrous cycling, reproductive capacity (fertility), and reproductive performance. There was no effect on the postnatal (pre-weaning) development and reproductive performance (post-weaning development) at doses up to 30 mg/kg/day. Other key drug-related findings included decreased white blood cell count, dose-dependent decrease in HR, increased heart weight in females given 30 mg/kg/day without correlated histopathologic changes, and cardiac histopathology findings similar to that observed in adult rats. The NOAEL was identified as 7.5 mg/kg/day. At this dose, exposures (AUC_{24h}) in males and female rats on PND77 were approximately 5 and 13-times the mean clinical exposure at steady state at the highest doses across age groups in pediatric patients, based on modeled AUCs. There were no nonclinical approvability issues discussed during this review cycle.

4.5. Clinical Pharmacology

Based on internal discussion, Clinical Pharmacology confirmed a PK/PD relationship between ivabradine and HRR in pediatric HF patients with DCM. Based on simulated PK modelling, Clinical Pharmacology concluded that the relationship between exposure and HRR was similar among pediatric age groups with similar findings in adults. Amgen proposed a complicated dosing table with (b) (4). However, Clinical Pharmacology proposed weight-based dosing with the same starting dose of 0.05 mg/kg twice daily (with food) for all ages but different maximum doses of 0.2 mg/kg/dose and 0.3 mg/kg/dose for pediatric patients less than 1 year of age and at least 1 year of age and older, respectively. At this time, Amgen has not yet responded to Clinical Pharmacology's proposed dosing regimen. The clinical pharmacology review is pending.

4.6. Devices and Companion Diagnostic Issues

Not Applicable.

4.7. Consumer Study Reviews/ Division of Medication Error Prevention and Analysis (DMEPA)

During discussion of their review, DMEPA had concern regarding failed labeling comprehension studies, particularly for prescribers and caregivers. In addition, accidental overdoses were reported during the study thought to be due to caregiver error. DMEPA considered the complicated dosing table proposed by Amgen in product labeling as a potential safety risk for dosing errors by prescribers and pharmacists. DMEPA verbally indicated to us that, if Amgen accepts the greatly simplified Clinical Pharmacology dosing proposal, there would be no need for Amgen to perform an additional labeling comprehension study. DMEPA's review is pending.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies included in this submission are summarized in Table 2.

Table 2: Listing of Clinical Trials Relevant to NDA 209964

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Study to Support Efficacy and Safety							
CL2-16257-090/ NP33304	-International, multicenter, randomized, double blind, placebo-controlled phase II/III study, with PK/PD characterization followed by a 1-year efficacy/safety evaluation. -Two parallel and non-balanced treatment arms (for each age subset), 2 (ivabradine):1 (placebo).	-Age- and weight-based dosing scheme with a prespecified starting dose given twice daily with up to 4 titrations -Oral liquid given to subjects ages 6 months to <3 years (< 40 kg); oral tablet (same as adult formulation) given to ages 3 to <18 years (≥ 40 kg)	Primary: Achievement of target HRR of at least 20%; PK/PD characterization Secondary Efficacy: LV function, functional class status, NT-proBNP, and growth, Safety QoL substudy	Duration of treatment up to 1 year.	116	Male and female children 6 months to < 18 years with DCM, Class II to IV NYHA/Ross CHF, LVEF ≤ 45% by echo, in sinus rhythm, on optimal CHF treatment, and age-based resting HR criteria	47 centers in 16 countries (all outside the US)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
PKH-086/ NP29920	Open-label, randomized, two-period cross-over study to assess relative bioavailability between ivabradine oral solution and marketed tablet	7.5 mg of either 1 mg/mL oral solution or marketed tablet	Relative bioavailability and safety	1	24	Healthy adult males	1 center
PKE-005/ NP33374, NP33354	Open-label and one-period study to compare plasma PK parameters of ivabradine and its active metabolite after repeated oral administration of ivabradine 10 mg to blood PK following sampling from capillary and venous dried blood spot microsampling method	10 mg ivabradine tablet oral twice daily x 5 days	PK and safety	5 days (no wash out period)	6	Healthy adult males	1 center
CL2-16257-090/ NP33312	Quality of Life sub-study of main study (NP33304)	Same as main study	Change in score from baseline at 6 and 12 months of follow-up comparing ivabradine to	Same as main study	69	Same as main study	34 centers in 13 countries (all outside the US)

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			placebo; Psychometric properties including quality of completion, clinical validity, and responsiveness				

5.2. Review Strategy

WR requirements were scrutinized to determine if Amgen met the terms of the WR. Analysis of adverse events was performed using MAED Release Version 1.9.1 and JReview Version 12.0.1-1067. The coding from verbatim to MedDRA PTs for AEs were verified. Descriptive safety and secondary efficacy data were summarized.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. CL2-16257-090

6.1.1. Study Design

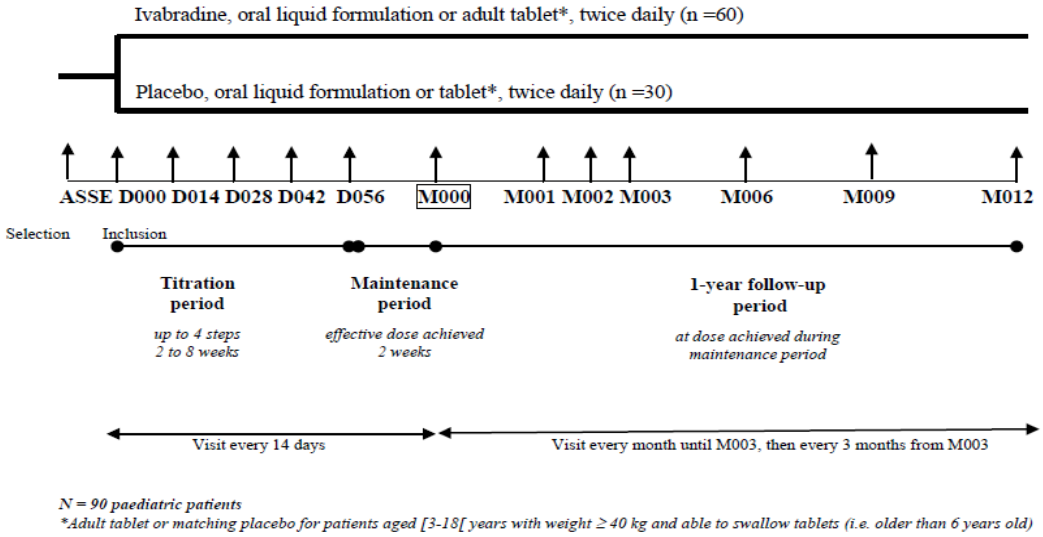
Overview and Objective

In Study CL2-16357-090, Amgen studied ivabradine in pediatric patients with DCM and HF on optimal background therapy, ages 6 months to less than 18 years, to determine efficacious and safe dosing.

Trial Design

A schematic of the study design for CL2-16257-090 is shown in Figure 1.

Figure 1: Study Design of CL2-16257-090



Source: Figure 8.2.1 in Protocol for CL2-16257-090

Study Objectives

Primary objectives of this study:

- To determine the optimal dose of ivabradine to reach the target HRR of 20% without inducing a bradycardia and/or signs or symptoms related to bradycardia
- To assess the PK parameters of ivabradine and its active metabolite S 18982 after repeated oral administrations
- To assess the PK/PD relationship of ivabradine and its active metabolite S 18982 using heart rate as evaluation criterion

Secondary/other objectives of this study:

- To asses, compared to placebo, effects of ivabradine at target dose on:
    - LVEF by echo
    - Clinical symptoms using NYHA/Ross classification
    - Global clinical status evaluated by investigators/parents
    - CV biomarker by measuring NT-proBNP
    - Weight and height
- To assess long-term safety of ivabradine over 1 year
- QoL sub-study using a questionnaire (children/parents)

Study Endpoints

Primary Efficacy

Target HRR achievement (see below for details)

PK/PD characterization

Secondary

- Efficacy
    - Echo parameters: LVEF, LVSF, LVESV, and LVEDV
    - NYHA/Ross classification
    - Global clinical status
    - NT-proBNP
    - Weight and height

- Safety: AEs, 12-lead ECGs, vital signs, clinical lab examination
- QoL sub-study - questionnaire

Reviewer Comments: *The primary efficacy endpoint was agreed upon at time of issuance of the WR as a suitable PD marker for this study based on the mechanism of action of ivabradine. Secondary efficacy endpoints chosen by Amgen were appropriate to study. However, Amgen did not propose adding information from secondary efficacy endpoints to labeling for the pediatric HF indication.*

Statistical Analysis Plan

Refer to the statistical review by Dr. Steve Bai dated 22 February 2019 for detailed SAP evaluation. There were no statistical issues noted during Dr. Bai's review of the design, conduct, or results of study CL2-16257-090 nor did I have concerns with the SAP from a clinical standpoint. No interim analyses were performed. The plan for missing data was to conduct secondary analyses with and without imputation using a last observation carried forward approach in patients of the FAS.

The following populations were used for analyses:

- RS - all randomized patients
- FAS - all randomized patients having received at least one dose of study drug with at least two evaluations of resting HR, one at baseline and one post-baseline.
- PPS - 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.
- SS - all patients having received at least one dose of study drug.

The following subsets were included in study analyses:

- Age cohorts – 6 months to <12 months, 1 to <3 years, 3 to <18 years old
- Patients having achieved target HRR at end of titration period (yes/no)

Target HRR was defined as a reduction in HR of at least 20% from baseline. Target HRR achievement and HR change were evaluated at the end of the titration period by treatment group for the PPS and FAS. For target HRR achievement, a logistic regression model adjusted for age class was used to estimate the OR between treatment groups and 95% CI. For HR change, mean difference between treatment groups and 95% CI were estimated using a parametric covariance analysis adjusted for age class and with baseline value as a covariate. In addition, this same analysis was conducted for HR change at M6 and M12 on patients in the FAS. A non-parametric approach rank-based analysis (Wilcoxon scores) adjusted for age class with baseline as covariate was used to check for robustness of results.

For LVEF, the estimate and 95% CI for treatment effect on change from baseline to M06 and on change from baseline to end of treatment period between treatment groups were calculated using a parametric covariance analysis adjusted for age class and with baseline value as a covariate on patients in FAS. LVEF analyses were also carried out by subset of target HRR achievement. For other secondary endpoints, descriptive statistics were performed on patients in the FAS and by subset of target HRR achievement. For NT-proBNP, a log-transformation was used. A non-parametric approach rank-based analysis (Wilcoxon scores) adjusted for age class with baseline as covariate was used to check for robustness of results.

Protocol Amendments
The original protocol was finalized on 10 June 2011. The protocol was amended six times with key changes summarized below. Certain protocol amendments were specific to study sites.

Amendment 1 (15 November 2011 – no subjects enrolled) (France)

- Addition of exclusion criterion of female with childbearing potential and sexually active but not on contraception
- Addition of withdrawal criterion of unwillingness to use contraception for females of childbearing potential and sexually active
- Dose adaptation rule for procedure in case of untolerated bradycardia while under treatment described
- Addition of ophthalmologic visit in case of visual AE with recommendation to stop study drug if required

Amendment 2 (14 February 2012 – two subjects enrolled (International/All)

- Addition of LV non-compaction with DCM and post-anthracycline DCM added to inclusion criteria (provided anthracyclines stopped at least 2 years prior to selection for study)
- Clarification that estimated duration of enrollment period (12 months) may be extended should 90 evaluable patients for PK/PD characterization not be recruited within this time
- Addition of contraception check, ophthalmologic visit for reported visual AE, and addition of a 4-hour medical observation after second study drug intake at D0
- Removal of exclusion criteria of patients on transplantation list and patients with post-anthracyclines DCM
- Addition of withdrawal criteria of heart transplantation or corrective heart surgery during study and unwillingness to use contraception for females of childbearing potential and sexually active
    - Addition of exclusion criterion of female with childbearing potential and

sexually active but not on contraception
- Addition of paragraphs containing dose adaptation rules and procedure in case of untolerated bradycardia under treatment

Amendment 3 (22 May 2012 – 16 subjects enrolled) (Germany)
- Addition of specific premature discontinuation criteria
- Addition of exclusion criteria for exclusion of person committed to an institution
- Addition of individual withdrawal criteria for patients
- Clarification of Visit 2 procedures timing
- Clarification of Visit 4A timing
- Clarification of height measurement

Amendment 4 (07 September 2012 – 29 subjects enrolled (International/All)

- Addition of potassium-depleting diuretics as treatment to be used with precautions in patients receiving ivabradine and having long QT interval

Amendment 5 (22 November 2012 – 74 subjects enrolled) (International/All)
- Administrative changes

Amendment 6 (23 May 2013 – 116 subjects enrolled) (International/All)
- Update of planned study completion date
- Update of distribution of patients per age subset
- Description of DSMB recommendations concerning patients with QTcB > 450 ms
    - ECG central reading implemented for all ECGs
    - Addition of withdrawal criterion for patients having QTcB > 450 ms confirmed by central reading at most recent visit
    - In patients withdrawn due to QTcB > 450 ms, need to assess the evolution of QTcB at least 3 days after last study drug intake, on ECG performed in frame of the final visit or during next routine check-up visit
- Clarification that 1 month is to be considered as 28 calendar days in the study
- Definition of an “evaluable” patient

Reviewer Comments: *These protocol amendments are appropriate and do not affect the interpretation of trial results. Due to difficulties in patient recruitment in the infant cohort (ages 6 months to <12 months), Amgen requested that the PDCO defer study completion to allow recruitment of at least 10 infants instead of 30 while still maintaining an overall sample size of at least 90 patients. The EMA approved this request. The sponsor supported their request by stating that the diagnosis of DCM is mostly made after 1 year of age and*

patients younger than 1 year of age are frequently too hemodynamically unstable to be eligible for the study.

Prior to protocol amendment 6, in January 2013, the DSMB received reports of asymptomatic cases of QTcB >450 ms from investigators. At that time, the DSMB reviewed all unblinded data of the patients for whom the QTcB >450 ms had been reported. The DSMB subsequently recommended that, because this study represent the first administration of ivabradine in children, a safety threshold QTcB >450 ms should not be crossed due to concern that HR reduction caused by ivabradine might exacerbate QT prolongation and precipitate severe arrhythmias. DSMB recommended that investigators manually measure QT interval again for all ECGs where a QTcB >450 ms was reported to confirm or correct the value. Then investigators were instructed to send these ECGs to a central ECG reviewer to confirm the abnormal value and evaluate patient risk.

6.1.2. Study Results

The study was conducted in accordance with the principles of GCP, including the archiving of essential documents. Before the study, the investigator had to allow study monitor visits to sites and facilities where the study would take place to ensure compliance with protocol requirements. Investigators subsequently received study monitors at regular intervals at the investigation sites for visits during which study monitors undertook source data verification on site according to internal procedures and monitoring plan.

When the database had been declared to be complete and accurate, it was locked on 11 April 2014 and the blind was broken on 14 April 2014. On the 29 April 2014, the database was unlocked due to the following: incorrect visit code calculation for ECG performed at M9, incorrect visit code calculation for biological parameters performed at M9, missing origin of pathology for 2 subjects, and 3 missing multi-coded AEs in the database due to a technical issue. After the data listed above were corrected, the database was locked again on 30 April 2014.

A quality control was carried out on study documents including investigator's brochure, clinical study protocol, substantial amendments, corresponding amended protocol case report forms, and study report according to internal procedures. Four audits were performed at investigational sites in France (0701), Italy (0901), Poland (1103), and Portugal (2203) with an additional two audits of contract research organizations in France.

Compliance with Good Clinical Practices

An Independent Ethics Committee reviewed the study protocol and subsequent amendments with study initiation only after Ethics Committee approval. The study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with the protocol, GCP, and applicable regulatory requirements. All parent(s)/legal representative of patients or

patients themselves (depending on the age of the minor, according to local regulations) provided written informed consent before patient selection. Depending on the age of the patient, an assent was obtained.

Financial Disclosure

Amgen provided a statement regarding financial certification (FDA Form 3454).

Reviewer Comment: *No disclosable financial information was reported by any of the clinical investigators participating in the trials.*

Patient Disposition

One hundred sixteen (116) patients were randomized to either ivabradine or placebo with a planned unbalanced randomization of 2:1. One subject (ivabradine group) was excluded from the SS because that subject did not receive study drug. Two subjects (in each treatment group) were excluded from the FAS because the resting HR at baseline or post-baseline was not evaluated. Nineteen (19) subjects (nine in ivabradine and 10 in placebo) were excluded from the PPS mainly for not completing the titration period and unauthorized treatment for CHF for which the dose was not stable within 4 weeks before selection. Overall, most subjects [105/116 (90.5%)] completed the titration period including 68/74 (91.9%) and 37/42 (88.1%) subjects in ivabradine and placebo groups, respectively. Most subjects completed the study with 89/116 (76.7%) overall and 61/74 (82.4%) and 28/42 (66.7%) in ivabradine and placebo groups, respectively.

The rate of discontinuation due to any reason was higher in the placebo group [14/42 (33.3%)] compared to ivabradine group [13/74 (17.6%)] leading to an imbalance in the proportion of subjects who completed the study between treatment groups. This imbalance was mainly driven by withdrawal due to AEs of which there was a higher proportion in the placebo group, 13/42 (31.0%), compared to ivabradine, 10/74 (13.5%). The 6 months to < 12 months cohort had the lowest proportion of study completers with 10/17 (58.8%) compared to 30/36 (83.3%) and 49/63 (77.8%) in 1 to <3 years and 3 to <18 years of age cohorts, respectively. Across all age cohorts, more subjects completed the study in the ivabradine group compared to placebo with the largest difference between treatment groups noted in the 6 months to < 12 months age cohort with 7/10 (70.0%) and 3/7 (42.9%) completing the study in ivabradine and placebo groups, respectively. As observed overall, the most common reason for study withdrawal across all age cohorts was AEs. See Section 8 for a summary of AE data. Subject Disposition is summarized in Table 3 below.

Table 3: Overall Subject Disposition

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 (89.7)
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)

n: number of patients affected
% calculated according to the number of patients included in each treatment group
**: 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*

Source: Sponsor's Table 10.1.1 in the CSR for CL2-16257-090

Reviewer Comments: *Differences in the proportion of study completers among age cohort subgroups are not expected to significantly affect safety or efficacy data. However, given that the sample size in the 6 to <12 months of age cohort was much smaller than older cohorts, interpretation of efficacy and, to a lesser extent, safety data might be limited.*

Protocol Violations/Deviations

Overall, 15/116 (12.9%) patients had 22 protocol deviations after study inclusion with a slightly lower proportion of subjects in the ivabradine group [8/74 (10.8%)] compared to placebo [7/42 (16.7%)]. The most frequent reasons for protocol deviations included blind broken, missing weight, and missing HR measurement for PK measurement. Major protocol deviations are summarized in Table 4.

Table 4: Summary of Major Protocol Deviations

Protocol deviations	Ivabradine (N = 74)			Placebo (N = 42)			All (N = 116)		
	NPD	n	%	NPD	n	%	NPD	n	%
Blind issue	**3**	**3**	**4.1**	**2**	**2**	**4.8**	**5**	**5**	**4.3**
Blind broken	3	3	4.1	2	2	4.8	5	5	4.3
Vital signs	**2**	**2**	**2.7**	**3**	**3**	**7.1**	**5**	**5**	**4.3**
Weight is missing	2	2	2.7	3	3	7.1	5	5	4.3
Pharmacokinetics	**2**	**2**	**2.7**	**5**	**2**	**4.8**	**7**	**4**	**3.4**
HR measurement for PK1 is not done	-	-	-	1	1	2.4	1	1	0.9
HR measurement for PK2 is not done	-	-	-	1	1	2.4	1	1	0.9
HR measurement for PK3 is not done	-	-	-	1	1	2.4	1	1	0.9
HR measurement for PK4 is not done	-	-	-	1	1	2.4	1	1	0.9
HR measurement for PK5 is not done	1	1	1.4	-	-	-	1	1	0.9
The time of HR measurement for PK5 is not reported	1	1	1.4	1	1	2.4	2	2	1.7
Electrocardiogram	**2**	**2**	**2.7**	**1**	**1**	**2.4**	**3**	**3**	**2.6**
ECG not carried out	2	2	2.7	1	1	2.4	3	3	2.6
Concomitant treatment	**1**	**1**	**1.4**	**1**	**1**	**2.4**	**2**	**2**	**1.7**
Unauthorised treatment:CYP3A4 INHIBITORS	1	1	1.4	1	1	2.4	2	2	1.7
ALL	**10**	**8**	**10.8**	**12**	**7**	**16.7**	**22**	**15**	**12.9**

N: number of patients in each considered treatment group.
NPD: number of protocol deviations before or at inclusion.
n: number of patients with at least one protocol deviation before or at inclusion.
*%: (n/N)*100.*
Source: Table 10.2.2 in CSR for CRL-16257-090

Reviewer Comments: *Three (4.1%) and two subjects (4.8%) in ivabradine and placebo groups, respectively, had a blind broken protocol deviation. For all three subjects in the ivabradine group, the investigator wanted to know the assigned treatment because subjects seemed to have a favorable response. All three subjects completed the M12 visit before the blind was broken. The two subjects in the placebo group had their blind broken because they withdrew from the study due to AEs including low cardiac output syndrome, weight decrease, pericardial effusion, and atrial flutter. Similar efficacy results were obtained when the data were analyzed using the FAS or PPS. Therefore, these major protocol deviations did not influence study results. Although there was a higher proportion of protocol deviations in the placebo group, I would not expect conclusions about safety or efficacy to be significantly affected.*

Table of Demographic Characteristics

As shown in Table 5, patients in all three age cohorts had similar demographic characteristics.

Table 5: Table of Key Demographic Characteristics (RS Population)

Demographic Characteristics	Ivabradine (N=74) n (%)	Placebo (N=42) n (%)	Total (N=116) n (%)
Sex			
Male	39 (52.7)	25 (59.5)	64 (55.2)
Female	35 (47.3)	17 (40.5)	52 (44.8)
Age			
Mean years (SD)	5.8 (5.1)	5.8 (4.6)	5.8 (4.9)
Age Cohort (n)			
6 - <12 months	10 (13.5)	7 (16.7)	17 (14.7)
1-<3 years	24 (32.4)	12 (28.6)	36 (31.0)
3-<18 years	40 (54.1)	23 (54.8)	63 (54.3)
Weight			
Mean kilograms (SD)	22.3 (18.1)	22.3 (16.2)	22.3 (17.4)
Race			
Caucasian	66 (89.2)	36 (85.7)	102 (87.9)
Black or African American	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)
Duration since CHF diagnosis Mean months (SD)	47.6 (51.2)	48.7 (47.8)	48 (49.7)
DCM as main cause of CHF	74 (100)	42 (100)	116 (100)
DCM subtypes			
Idiopathic	45 (60.8)	20 (47.6)	65 (56.0)
Post-viral myocarditis	16 (21.6)	9 (21.4)	25 (21.6)
Ischemic	-	2 (4.8)	2 (1.7)
LV non-compaction	11 (14.9)	11 (26.2)	22 (19.0)
Post-anthracycline	2 (2.7)	-	2 (1.7)
NYHA/Ross Classification			
Class I	-	-	-
Class II	59 (79.7)	34 (81.0)	93 (80.2)
Class III	12 (16.2)	6 (14.3)	18 (15.5)
Class IV	3 (4.1)	2 (4.8)	5 (4.3)
LVEF mean % (SD)	31.9 (8.3)	34.6 (7.6)	32.9 (8.1)
Mean NT-proBNP plasma concentration (pg/mL) (SD)	1492.6 (2451.3)	2010.4 (4260.5)	1682.1 (3223.9)

Source: Adapted from Tables (10.4.1) 1, (10.4.1) 2, and (10.4.1) 3 from CSR for CL2-16257-090

Reviewer Comments:

- *For most demographic characteristics, there were no significant imbalances between treatment groups except for a higher proportion of subjects with LV non-compaction in the placebo group, 26.2%, compared to ivabradine group, 14.9%. In addition, there was a*

significantly lower proportion of subjects with idiopathic DCM in the placebo group, 47.6%, compared to ivabradine, 60.8%. However, I would not expect differences in underlying DCM etiology to significantly affect safety or efficacy data.

- *Most randomized subjects were Caucasian, likely a reflection of the predominantly European enrollment. However, underrepresentation of minorities in the study would not be expected to affect safety or efficacy data because there is no evidence to suggest ethnic or racial differences in ivabradine's mechanism of action.*
- *Mean NT-proBNP baseline plasma concentrations were significantly lower in the 3 to <18 years of age cohort compared to younger cohorts, 647.1 ± 928.2 pg/mL versus 3091.7 ± 3684.5 pg/mL (6 months to < 12 months of age) and 2264.4 ± 3079.3 pg/mL (1 to <3 years of age).*

Other Baseline Characteristics

For baseline vital signs, HR, and baseline ECG measures for PR, QTcB, and QTcF intervals, there were no significant differences between study groups. Table 6 contains a summary of baseline HR and key ECG parameters.

Table 6: Baseline Heart Rate and Key ECG Parameters

	Ivabradine N=74	Placebo N=42	Overall N=116
Heart Rate (vital sign) ay Age Cohort Mean bpm (SD)			
6-<12 months	132.9 (20.7)	127.4 (7.4)	130.6 (16.4)
1-<3 years	112.0 (10.1)	110.1 (12.5)	111.4 (10.8)
3-<18 years	88.2 (11.7)	86.0 (8.6)	87.4 (10.7)
PR interval Mean ms (SD)	135.3 (23.3)	137 (26.5)	135.9 (24.4)
QTcB interval Mean ms (SD)	423.9 (33.6)	421.9 (26.3)	423.1 (31.0)
QTcF Interval Mean ms (SD)	390.2 (31.1)	389.2 (26.6)	389.9 (29.4)

Source: Adapted from Tables (10.4.1) 5 and (10.4.1) 6 in CSR for CL2-16257-090.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects were required to be on optimal and stable CHF therapy prior to study enrollment. The most common CHF concomitant therapy included ACEI, aldosterone antagonists, other diuretics, and beta-blockers. Other noteworthy concomitant medications used by subjects in the study included antithrombotic agents, mineral supplements, vitamins, and antianemia

preparations. Table 7 below contains a summary of concomitant medications.

Table 7: Summary of Concomitant Medications at Baseline

Concomitant Medications	Ivabradine N=73 n (%)	Placebo N=42 n (%)	Overall N=115 n (%)
ACEI	70 (94.6)	39 (92.9)	109 (94.0)
Angiotensin II Antagonists	2 (2.7)	2 (4.8)	4 (3.5)
Aldosterone Antagonists	63 (85.1)	28 (66.7)	91 (78.5)
Other diuretics	49 (66.2)	31 (73.8)	80 (69.0)
Beta-blockers	59 (79.7)	29 (69.1)	88 (75.9)

Source: CSR for CL2-16257-090, p90 of 205.

Reviewer Comment: *There are no important imbalances among CHF concomitant medications between treatment groups.*

In response to preliminary FDA comments (2015), Amgen provided a supplemental CSR containing additional analyses on beta-blockade use including information on guidelines supporting beta-blocker use in children with HF, local standard of care for dosing of beta-blockers at investigation sites, and occurrence of bradycardia and/or study withdrawal as a function of background beta blocker dosing. In brief, there were no published guidelines for beta-blocker use for pediatric HF at time of study initiation. In 2013 and 2014, two guidelines from the Canadian CV Society and International Society for Heart and Lung Transplantation, respectively, were published. Recommendations for beta-blocker use for pediatric HF are included in both guidelines although only the Canadian CV Society guideline includes a max dose for beta-blocker use. None of the participating countries in the study had local guidelines for beta-blocker use in pediatric HF. Based on US Pediatric CM Registry from 2000 to 2006, 18% of patients received beta-blockers compared to 70% receiving ACEI for symptomatic idiopathic DCM. Amgen did not collect any data to explain why certain pediatric patients were not on a beta-blocker or justification of doses for children who were on beta-blockers. In Table 8 are results of a post-hoc analysis performed by Amgen to stratify age cohorts by <50% (low dose), ≥50% to <100% (medium dose), and ≥ 100% (high dose) of the recommended target daily dose based on Canadian CV Society recommendations for carvedilol.

Table 8: Summary of Beta-Blocker Use Among Enrolled Pediatric Subjects

	Ivabradine (N = 74)	Placebo (N = 42)
Subjects on carvedilol and metoprolol taken at baseline	56	25
< 50% Recommended Target Daily Dose – N'	39	17
6 to 12 months,– n (%)	8 (20.5)	2 (11.8)
1 to 3 years	9 (23.1)	4 (23.5)
3 to 18 years	22 (56.4)	11 (64.7)
≥ 50% and < 100% Recommended Target Daily Dose – N'	13	7
6 to 12 months – n (%)	1 (7.7)	3 (42.9)
1 to 3 years	5 (38.5)	3 (42.9)
3 to 18 years	7 (53.8)	1 (14.3)
≥ 100% Recommended Target Daily Dose – N'	4	1
6 to 12 months – n (%)	0 (0.0)	0 (0.0)
1 to 3 years	1 (25.0)	1 (100.0)
3 to 18 years	3 (75.0)	0 (0.0)
Subjects on another type of BB taken at baseline – N'	3	4
Subjects without BB taken on baseline – N'	15	13

BB = Beta-blocker; N=total number of subjects in considered treatment group; N '=total number of subjects in each dose category; n=number of subjects in each age group; %=(n/N ') x 100.
Recommended target daily dose for carvedilol is 1 mg/kg/day and for metoprolol is 2 mg/kg/day.

Source: Table 7-1 in supplemental CSR with additional analyses for CL2-16257-090.

Reviewer Comments: *Amgen's stratification by dose in Table 8 is based solely on carvedilol dosing. It is unclear how Amgen determined whether a subject was on low, medium, or high dose for metoprolol. However, of the 71 subjects taking beta-blocker, only two were taking metoprolol with seven taking bisoprolol. Most of the patients were taking carvedilol.*

Efficacy Results – Primary Endpoint

The primary endpoint was PK characterization of ivabradine and its active metabolite, S18982, and corresponding HR values in addition to achievement of target HRR, at least 20% decrease in HR from baseline without inducing bradycardia. In the pivotal adult HF trial, SHIFT, ivabradine tablet was shown to reduce the risk of the combined endpoint of hospitalization for worsening HF or CV death based on a time-to-event analysis with hazard ratio: 0.82 [95% CI (0.75, 0.90), p < 0.000]. Because CV outcomes trials are not feasible to conduct in a pediatric HF population, the Division determined that HRR would be a reasonable PD marker to extrapolate efficacy from adults with DCM/HFrEF to pediatric HF patients with DCM. Refer to the Clinical Pharmacology review for detailed description and analyses of the primary efficacy endpoints.

According to the Biostatistics Review, ivabradine treatment resulted in a statistically significant and clinically meaningful reduction in resting HR. In the FAS, target HRR was achieved by 51

subjects (69.9%) in the ivabradine group versus five subjects (12.2%) in the placebo group, with an OR (95% CI) of 17.24 (5.91; 50.30). In addition, a larger reduction in the HR at rest was observed in the ivabradine group, compared with placebo, from baseline to the end of the titration period with a treatment difference [95% CI] of -18.9 bpm [-23.75; -14.23]. The p-value for target HRR and reduction in HR at rest (FAS and PPS) was <0.0001. Furthermore, the same trend in target HRR was observed across all age cohorts with no particular age cohort driving the results. Table 9 shows key primary endpoint results from the Biostatistical Review.

Table 9: Results of Target HRR Achievement and Reduction of HR at rest (FAS and PPS)

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]

Data Quality and Integrity

OSI did not conduct site inspections. There were no data quality or integrity concerns noted during this review.

Efficacy Results – Secondary and other relevant endpoints

Amgen did not plan to assess secondary endpoints with control of Type-1 error rate nor did Amgen propose including secondary endpoints for the pediatric labeled indication. There were no significant differences between treatment groups in growth parameters (growth data not shown in this review). Amgen conducted a substudy with a Pediatric QoL Inventory to asses for change in QoL measures from parents and patients (data not shown). There was a trend toward improvements for parent-reported scores but no improvement from baseline for child-reported scores. Overall, there was a trend toward improvement in left ventricular systolic function, clinical status, and NT-proBNP as shown in Figures 2-6 below.

Figure 2: Mean (SD) Changes from Baseline in Echocardiography Parameters

Echo-cardio-graphy Para-meters	CL2-090			SHIFT		
	Ivabradine Mean ± SD (N = 73)	Placebo Mean ± SD (N = 41)	Ivabradine vs Placebo Treatment Difference (SE)	Ivabradine Mean ± SD (N = 208)	Placebo Mean ± SD (N = 203)	Ivabradine vs Placebo Treatment Difference (SE)
LVEF (%)	Month 6: 11.43 ± 11.57 Month 12: 13.54 ± 13.14	Month 6: 5.29 ± 10.28 Month 12: 6.94 ± 11.44	Month 6:5.11 (2.14) 95% CI [0.87;9.35] Month 12: 5.57 (2.44) 95% CI [0.75;10.40]	Month 8: 2.4 ± 7.7	Month 8:-0.1 ± 8.0	Month 8: 2.7 (0.8) 95% CI: [1.3; 4.2], p<0.001
LVSF (%)	Month 6: 6.77 ± 6.06 Month 12:8.19 ± 7.37	Month 6: 3.07 ± 4.40 Month 12: 3.76 ± 7.02	-	-	-	-
LVESV (mL)	Month 6: -13.41 ± 21.83 Month 12: -15.03 ± 25.45	Month 6: -2.70 ± 13.66 Month 12: -2.20 ± 18.07	-	Month 8: -13.0 ± 31.6	Month 8: -1.3 ± 32.8	Month 8: -11.2 (3.0) 95% CI: [-17.1 ; -5.4], p < 0.001
LVEDV (mL)	Month 6: -7.39 ± 24.66 Month 12: -6.04 ± 32.35	Month 6: 3.69 ± 22.88 Month 12: 4.59 ± 24.86	-	Month 8: -14.7 ± 36.4	Month 8: -2.9 ± 36.8	Month 8: -10.9 (3.4) 95% CI:[-17.6 ; -4.2] p = 0.001

LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; LVSF = left ventricular shortening fraction; SD = standard deviation.
Source: Table (11.2.1) 1, Table (11.2.1) 3 of NP33304; Table (11.2.4) 1, Table (11.2.2) 1, Table (11.2.3) 1 of NP30294.

Figure 3: Change in NYHA or Ross Classification from Baseline to Month 12

Overall patients and age subsets - FAS (N = 114)

NYHA or ROSS classification			Ivabradine (N = 73)	Placebo (N = 41)
Overall patients				
Evolution from baseline to M12		n_{obs}	61	28
	Improvement	n (%)	23 (37.7)	7 (25.0)
	Stability	n (%)	38 (62.3)	21 (75.0)
	Worsening	n (%)	-	-
Subsets				
[6-12[months (N = 16)		n_{obs}	7	3
Evolution from baseline to M12	Improvement	n (%)	5 (71.4)	1 (33.3)
	Stability	n (%)	2 (28.6)	2 (66.7)
	Worsening	n (%)	-	-
[1-3[years (N = 36)		n_{obs}	21	9
Evolution from baseline to M12	Improvement	n (%)	7 (33.3)	3 (33.3)
	Stability	n (%)	14 (66.7)	6 (66.7)
	Worsening	n (%)	-	-
[3-18[years (N = 62)		n_{obs}	33	16
Evolution from baseline to M12	Improvement	n (%)	11 (33.3)	3 (18.8)
	Stability	n (%)	22 (66.7)	13 (81.3)
	Worsening	n (%)	-	-

Baseline: last available value before the first study drug intake
*N: number of patients in each considered treatment group; n_{obs}: number of patients with a value observed at baseline and at the considered visit ; %=(n/n_{obs})*100; improvement: increase by at least one level of NYHA or Ross classification from baseline to M12; stability: same level of NYHA or Ross classification from baseline to M12; worsening: decrease by at least one level of NYHA or Ross classification from baseline to M12*

Source: Table (11.2.2) 2 in CSR for CL2-16257-090.

Figure 4: Change in NT-proBNP Plasma Concentrations (pg/mL) from Baseline to Months 0, 6, and 12

Evolution from baseline to M0, M6 and M12 - Overall patients - FAS (N = 114)

NT-proBNP plasma concentration (pg/mL)		Ivabradine (N = 73)	Placebo (N = 41)
M0 - Baseline	n_{obs}	64	35
	Mean ± SD	-371.4 ± 1001.0	134.6 ± 3451.5
	Median	3.0	-12.4
	Min ; Max	-4257.7 ; 568.1	-15435.0 ; 7873.0
M6 - Baseline	n_{obs}	62	28
	Mean ± SD	-737.8 ± 1691.7	-25.3 ± 1122.7
	Median	-42.0	-28.3
	Min ; Max	-8257.0 ; 1584.0	-1983.8 ; 5257.0
M12 - Baseline	n_{obs}	59	27
	Mean ± SD	-710.1 ± 1478.4	-367.4 ± 576.5
	Median	-128.3	-128.70
	Min ; Max	-5556.3 ; 1148.0	-1980.7 ; 783.6

Baseline: last available value before the first study drug intake
N: total number of patients in each considered treatment group
n_{obs} = number of patients with a value observed at baseline and at the considered visit

In the age subsets, same trends were observed for NT-proBNP, with a decrease over time in both groups, from baseline to M12, in the FAS:

- [6-12[months: -814.543 ± 1269.240 pg/mL (median = -237.600 pg/mL) in the ivabradine group *versus* -583.900 ± 1382.383 pg/mL (median = -554.600 pg/mL) in the placebo group.
- [1-3[years: -1489.053 ± 1959.324 pg/mL (median = -451.800 pg/mL) *versus* -794.425 ± 445.541 pg/mL (median = -762.450 pg/mL), respectively.
- [3-18[years: -239.458 ± 953.384 pg/mL (median = -3.000 pg/mL) *versus* -113.288 ± 230.402 pg/mL (median = -27.000 pg/mL), respectively.

Source: Table (11.2.4) 1 in CSR for CL2-16257-090.

Figure 5: Change in Global Clinical Status from Baseline to Month 12 (Investigator)

Evolution from baseline to M12 - Overall patients and age subsets - FAS (N = 114)

Global clinical status			Ivabradine (N = 73)	Placebo (N = 41)
Overall patients				
Baseline		n_{obs}	73	41
	Very good	n (%)	5 (6.9)	1 (2.4)
	Good	n (%)	43 (58.9)	27 (65.9)
	Average	n (%)	18 (24.7)	10 (24.4)
	Bad	n (%)	4 (5.5)	3 (7.3)
	Very bad	n (%)	1 (1.4)	-
	Not performed	n (%)	2 (2.7)	-
M12		n_{obs}	61	28
	Very good	n (%)	21 (34.4)	7 (25.0)
	Good	n (%)	33 (54.1)	16 (57.1)
	Average	n (%)	7 (11.5)	4 (14.3)
	Bad	n (%)	-	1 (3.6)
	Very bad	n (%)	-	-
	Not performed	n (%)	-	-
Evolution from baseline to M12		n_{obs}	61	28
	Improvement	n (%)	31 (50.8)	10 (35.7)
	Stability	n (%)	28 (45.9)	16 (57.1)
	Worsening	n (%)	2 (3.3)	2 (7.1)
Subsets				
[6-12[months				
Evolution from baseline to M12		n_{obs}	7	3
	Improvement	n (%)	5 (71.4)	1 (33.3)
	Stability	n (%)	2 (28.6)	2 (66.7)
	Worsening	n (%)	-	-
[1-3[years				
Evolution from baseline to M12		n_{obs}	21	9
	Improvement	n (%)	13 (61.9)	4 (44.4)
	Stability	n (%)	8 (38.1)	3 (33.3)
	Worsening	n (%)	-	2 (22.2)
[3-18[years				
Evolution from baseline to M12		n_{obs}	33	16
	Improvement	n (%)	13 (39.4)	5 (31.3)
	Stability	n (%)	18 (54.6)	11 (68.8)
	Worsening	n (%)	2 (6.1)	-

Baseline: last available value before the first study drug intake
N: total number of patients in each considered treatment group
n_{obs} = number of patients with a value observed at baseline and at the considered visit
%=$(n/n_{obs})*100$

Source: Table (11.2.3) 1 in CSR for CL2-16257-090.

Figure 6: Change in Global Clinical Status from Baseline to Month 12 (Patient/Parent)

Evolution from baseline to M12 - Overall patients and age subsets - FAS (N = 114)

Global clinical status			Ivabradine (N = 73)	Placebo (N = 41)
Overall patients				
Baseline		n_{obs}	73	41
	Very good	n (%)	8 (11.0)	5 (12.2)
	Good	n (%)	48 (65.8)	27 (65.9)
	Average	n (%)	12 (16.4)	6 (14.6)
	Bad	n (%)	1 (1.4)	1 (2.4)
	Very bad	n (%)	-	-
	Not performed	n (%)	4 (5.5)	2 (4.9)
M12		n_{obs}	61	28
	Very good	n (%)	22 (36.1)	9 (32.1)
	Good	n (%)	34 (55.7)	17 (60.7)
	Average	n (%)	5 (8.2)	2 (7.1)
	Bad	n (%)	-	-
	Very bad	n (%)	-	-
	Not performed	n (%)	-	-
Evolution from baseline to M12		n_{obs}	61	28
	Improvement	n (%)	20 (32.8)	9 (32.1)
	Stability	n (%)	37 (60.7)	13 (46.4)
	Worsening	n (%)	4 (6.6)	6 (21.4)
Subsets				
[6-12[months				
Evolution from baseline to M12		n_{obs}	7	3
	Improvement	n (%)	2 (28.6)	-
	Stability	n (%)	5 (71.4)	3 (100.0)
	Worsening	n (%)	-	-
[1-3[years				
Evolution from baseline to M12		n_{obs}	21	9
	Improvement	n (%)	9 (42.9)	3 (33.3)
	Stability	n (%)	12 (57.1)	3 (33.3)
	Worsening	n (%)	-	3 (33.3)
[3-18[years				
Evolution from baseline to M12		n_{obs}	33	16
	Improvement	n (%)	9 (27.3)	6 (37.5)
	Stability	n (%)	20 (60.6)	7 (43.8)
	Worsening	n (%)	4 (12.1)	3 (18.8)

Baseline: last available value before the first study drug intake
N: total number of patients in each considered treatment group
n_{obs}: number of patients with a value observed at baseline and at the considered visit
% = $(n/n_{obs})*100$.

Source: Table (11.2.3) 2 in CSR for CL2-16257-090.

Dose/Dose Response

Refer to the Clinical Pharmacology review for detailed discussion of the ivabradine dose-

response relationship.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not Applicable.

7.1.1. Primary Endpoints

Refer to Section 6.1.2.

7.1.2. Secondary and Other Endpoints

Refer to Section 6.1.2.

7.1.3. Subpopulations

Refer to Section 6.1.2.

7.1.4. Dose and Dose-Response

Refer to Section 6.1.2 and Clinical Pharmacology Review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Refer to Clinical Pharmacology review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Not Applicable.

7.2.2. Other Relevant Benefits

Not Applicable.

7.3. Integrated Assessment of Effectiveness

Amgen relied on a single adequate and well controlled pediatric study and extrapolated data from an ivabradine trial in adults with HFrEF, SHIFT, to support approval of ivabradine oral solution in pediatric patients with DCM and HF. SHIFT was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study in adults with symptomatic HFrEF. SHIFT was

adequately powered to demonstrate a treatment effect of long term ivabradine treatment on CV outcomes in adults with HFrEF. SHIFT demonstrated a 26% reduction in risk of hospitalization for worsening HF with similar results in a post-hoc analysis in adults with DCM. Similar to adults with HFrEF, hospitalization for worsening HF contributes to significant morbidity in pediatric patients with DCM and HF.

In 116 pediatric patients with DCM and HF on optimal background therapy, compared to placebo, treatment with ivabradine resulted in a 20% or greater reduction in baseline HR with a confirmed OR of 17.24 (95% CI: 5.91; 50.30) and p-value <0.0001 (FAS population). A similar robust treatment effect was observed in the PPS population with an OR 14.97 (95% CI: 4.79; 46.77). Treatment effect appeared durable. The pediatric study was not powered to detect clinical outcomes however, we believe that the PD marker of target HRR is predictive of the CV clinical outcome of reduction in risk for HF hospitalizations observed in SHIFT.

To date, there are no approved products with a labeled indication for pediatric HF treatment. Overall, ivabradine-induced HRR to at least 20% of baseline, as shown in study CL2-16257-090, represents a clinically meaningful treatment effect in pediatric patients with DCM and HF. Refer to Section 6 for details of study CL2-16257-090. The safety profile in pediatric patients is similar to the AE profile observed in the SHIFT trial. Overall, the robust treatment effect with no new or unexpected safety signals provide supportive evidence to support approval of ivabradine for use in pediatric patients, ages 6 months and older, with DCM/HF on optimal background therapy and in sinus rhythm.

8. Review of Safety

8.1. Safety Review Approach

One hundred sixteen (116) subjects were randomized in study CL2-16257-090 with 115 of these subjects included in the SS. One subject was excluded from the SS because that person did not receive any study drug. No patient was lost to follow up.

All safety results are presented for study CL2-16257-090 including deaths, EAEs, SEAEs, and drug discontinuations/dose reduction/study withdrawal due to EAEs. AE terms used are PTs included in MedDRA. PTs were coded using primarily MedDRA version 16.0 except PTs for coding of “severe ventricular arrhythmias” for which MedDRA version 17.0 was used.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The number of patients required for the safety database was agreed upon in a WR. Amgen only submitted a single study providing safety information in a pediatric population. Refer to Dr.

Dunnmon's clinical review of NDA 206143 for safety database information in adults with HFrEF treated with ivabradine.

The intended duration of study CL2-16257-090 was 13 to 14.5 months. Based on analysis of the PPS, overall mean and median exposure to double-blind study drug was similar between treatments in the PPS both in titration and overall treatment periods. There was no open label extension phase either in this study or as a separate study.

Titration Period by Age cohort

By age cohort, mean and median duration of the titration period in the ivabradine group was similar between the 6 to <12 months and 1 to <3 years of age cohorts. However, compared to younger age cohorts, the ivabradine mean and median durations were significantly shorter for the 3 to <18 years of age cohort. For the placebo group, mean and median durations were similar between 1 to <3 years and 3 to <18 years of age cohort but significantly shorter for the 6 to <12 months of age cohort.

Treatment Period by Age cohort

As to be expected, there was more variation among the mean and standard deviations for duration of the maintenance treatment period among all age cohorts. However, median number of days in the overall treatment period was similar among all age cohorts.

See Table 10 for mean and median study durations of the titration and overall treatment periods.

Table 10: Treatment Duration (days) During Study in PPS Population

Treatment duration (days)	Ivabradine (N=64)	Placebo (N=31)	All (N=95)
Titration Period			
N	64	31	95
Mean ± SD	52.2 ± 23.3	64.4 ± 16.6	56.2 ± 22.0
Median	64.0	71.0	70.0
Min; Max	13; 79	17; 86	13; 86
6-<12 months			
Mean ± SD	62.8 ± 20.1	49 ± 28.3	60.0 ± 20.9
Median	71.0	49.0	71.0
1-<3 years			
Mean ± SD	60.8 ± 20.4	71.6 ± 2.4	64.4 ± 17.4
Median	71.0	71.0	71.0

3-<18 years			
Mean ± SD	45.1 ± 23.4	62.3 ± 18.7	51.0 ± 23.2
Median	45.0	70.0	60.0
Overall Treatment Period			
N	64	31	95
Mean ± SD	374.3 ± 67.1	342.6 ± 115.5	363.9 ± 86.6
Median	397.0	399.0	397.0
Min; Max	85; 426	80; 428	80; 428
6-<12 months			
Mean ± SD	352.4 ± 96.8	389.5 ± 13.4	359.8 ± 86.9
Median	399.5	389.5	399.0
1-<3years			
Mean ± SD	390.1 ± 34.6	327.3 ± 134.8	369.1 ± 85.6
Median	402.0	405.0	403.5
3-<18 years			
Mean ± SD	370.4 ± 72.9	345.7 ± 113	361.9 ± 88.5
Median	388.5	396.0	395.0

Source Adapted from Table (10.5.1)1 and p99 or 205 in CSR for CL2-16257-090.

Reviewer Comments: *It is unclear why the oldest age cohort tended to have a shorter duration in the titration period compared to younger cohorts. However, the overall treatment duration was comparable among age cohorts. Therefore, these numerical differences in titration period among age cohorts would not be expected to affect interpretation of the safety data.*

8.2.2. Relevant characteristics of the safety population:

Safety and efficacy populations are essentially the same. Demographic and other baseline disease characteristics are summarized in Table 5 in the efficacy discussion. As previously stated, most randomized subjects were Caucasian however, underrepresentation of minorities in the study would not be expected to affect safety or efficacy data because there is no evidence to suggest ethnic or racial differences in ivabradine's mechanism of action in either the SHIFT or pediatric trials.

8.2.3. Adequacy of the safety database:

Considering that pediatric DCM is a rare condition, the totality of safety information from SHIFT and pediatric trials is adequate for a safety database.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Not Applicable.

8.3.2. Categorization of Adverse Events

An AE was defined as any untoward medical occurrence in a subject participating in the clinical study, whether or not there is a causal relationship with the study drug and/or experimental procedures, occurring or detected from the time of participant's/parent's signature of information and consent form. EAEs were defined as all AEs which occurred between the first study drug intake date (included) and the last study drug intake date + 3 days (included), or which occurred before the first study drug intake date and which worsened (in terms of intensity) or became serious between the first study drug intake date (included) and the last study drug intake date + 3 days (included).

Study drug included the investigational drug under evaluation, ivabradine or placebo, given during any period of the study. Medical conditions/diseases present before starting study drug were only considered AEs if they worsened after starting study drug. Abnormal laboratory values or test results constituted AEs only if the investigator considered them clinically significant. Although any event resulting in inpatient hospitalizations or prolongation of hospitalization was reported as an AE, the two overnight hospitalizations required by protocol for visits D0 and D014 were not considered AEs. Excessive intake of study drug by a patient or pregnancy required immediate notification. Similarly, study drug intake by someone other than the patient required immediate notification only if there were signs or symptoms, if the person was a minor regardless of symptoms, or intake was more than 40 mg of study drug within 24 hours regardless of symptoms.

A SEAE was defined as an event which was fatal, life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly or a birth defect, or medically important i.e. any event not immediately life-threatening or resulting in death or hospitalization but may have jeopardized the subject and required an intervention to prevent one of these outcomes.

EAEs were summarized by SOC, PT, maximum severity, relationship to the trial treatment, and discontinuation due to EAEs. **The sponsor requested that investigators provide additional information regardless of severity or causality for the following AEs: bradycardia, rhythm/conduction disorders, blood pressure increases, and visual AEs.** For a bradycardia AE, the investigator was required to check the QT interval and calculate the corrected QT, using both Bazett (QTcB) and Fridericia (QTcF) formulas, and include confounding factors such as electrolyte disturbance or baseline bundle branch block on the AE form and/or CRF. For rhythm/conduction disorders, the investigator was required to report all signs and symptoms, method of diagnosis e.g. ECG, Holter, and information regarding possible etiologies. A similar level of additional detail was required for blood pressure increases and visual AEs on the AE form or CRF. Investigators were to follow-up AEs until resolution or stabilization even after the final study visit. Investigators were also required to follow a standardized procedure for

reporting and following up "immediate notification" AEs that occurred during the study, within 30 days after the final study visit, or beyond 30 days irrespective of time of onset after end of study if the event was thought likely due to research.

8.3.3. Routine Clinical Tests

Biochemistry and hematology individual parameters were assessed locally with site-specific normal ranges. The sponsor only provided descriptive out-of-reference range values and PCSA values in the CSR.

8.4. Safety Results

8.4.1. Deaths

Four deaths occurred in the study, but only in the placebo group. Death(s) occurred in each age cohort with one subject in 6 to <12 months of age, two subjects in 1 to <3 years of age, and 1 subject in 3 to <18 years of age cohorts. Below are brief summaries of study deaths based on narratives provided by Amgen.

- 2-year-old female with ischemic DCM died in hospital from ventricular tachycardia-induced cardiac arrest precipitated by intense crying after a "sample collection" on day 159 of study
- 15-year-old male with idiopathic DCM died from sudden cardiac death at home on day 79 of study after taking a walk on a very hot day with resultant sudden onset of breathlessness
- 8-month-old male with idiopathic DCM died on day 29 due to septic shock resulting in hypotension then cardiac arrest
- 13-month-male with LV noncompaction DCM died on day 93 from a ventricular fibrillation arrest after a persistent complicated hospital course including treatment for decompensated heart failure and multisystem organ failure precipitated by adenoviral upper respiratory infection

8.4.2. Serious Adverse Events

Ninety-four (94) SEAEs were reported by 38 (33.0%) subjects overall with 22 (28.8%) subjects reporting 32 SEAEs in the ivabradine group compared to 17 (40.5%) subjects reporting 62 SEAEs in the placebo group. There was a higher proportion of SEAEs requiring hospitalization or prolongation of hospitalization for any cause in the placebo group with 16 subjects (38.1%) compared 19 subjects (26.0%) in the ivabradine group. Similarly, a higher proportion of subjects in the placebo group compared to ivabradine required hospitalization or prolongation of hospitalization for CV causes, arrhythmias, or worsening HF.

The most frequently reported SEAE PT was CV evaluation i.e. planned hospitalization for evaluation of DCM reported in four subjects each in ivabradine and placebo groups, 5.5%

versus 9.5%, respectively (See Table 11 below). Other SEAEs in the ivabradine treatment arm included upper respiratory tract infections, pneumonia, concussion, accidental overdose, bradycardia, QTc prolongation, pericardial effusion, and heart transplant. There was one sudden cardiac death reported but only in the placebo group. Select narratives for cardiac SEAEs and Serious Adverse Drug Reactions in the ivabradine group are summarized below.

- **Cardiac decompensation:** Patient 090-(b) (6) (12-year-old male) was admitted to the hospital for pulmonary edema in the setting of cardiac decompensation on day 56 (max tolerated ivabradine dose 2.5 mg). The patient was maintained on ivabradine and responded favorably to diuretic therapy.
- **Ventricular tachycardia/cardiac arrest/cardiac failure/pulmonary hypertension/)/heart transplant:** Patient 090-(b) (6) (24-month-old male) started dosing with ivabradine in (b) (6) and in (b) (6) was listed for heart transplantation and permanently hospitalized while awaiting transplant. While hospitalized, the patient presented with cardiac arrest in the setting of ventricular tachycardia to 220 bpm requiring cardiopulmonary resuscitation on day 277 from which he recovered. He was maintained on the same dose of ivabradine, 0.30 mg/kg BID. Post resuscitation, the patient's QTcB was prolonged to 486 ms, so ivabradine was held. Eight days later, the QTcB improved to 435 ms but 8 days after that increased again to 499 ms while off ivabradine. The patient presented with cardiac failure and pulmonary hypertension 21 days after last study drug dose. The patient recovered.
- **Decreased heart rate:** Patient 090-(b) (6) (6-year-old male) was hospitalized on day 56 for asymptomatic bradycardia, the same day he was uptitrated to 0.3 mg/kg BID of ivabradine. Prior to receiving the 0.3 mg/kg dose, the patient had a HR of 80 bpm but after study drug intake, on the same day, his HR was measured at 68 bpm. The patient received inpatient ECG monitoring most notable for low nocturnal HRs averaging 52-66 bpm with the lowest HR of 41 bpm but maximum HR 99 bpm. By the next day, the HR improved to 76 bpm and the patient was discharged and considered recovered. The study drug dose was not changed or interrupted.
- **Bradycardia/convulsive episode:** Patient 090-(b) (6) (2-year-old female) was uptitrated to 0.30 mg/kg BID ivabradine but on day 346 she experienced generalized non-febrile convulsions immediately after taking ivabradine. The patient was transported by ambulance to the ER where she was conscious and asymptomatic with a HR of 90 bpm. A diagnosis of "convulsive crisis probably due to bradycardia was made." The patient was hospitalized during which she maintained a normal HR and blood pressure with no concern for worsening cardiac echocardiogram. She had two normal 24-hour Holters that only revealed nocturnal sinus bradycardia to a minimal HR of 56 bpm but max HR 131 bpm. The patient was maintained on the same dose of ivabradine.

Table 11: Most Common SEAEs by SOC and PT

SOC or PT	Ivabradine N = 73 n (%)	Placebo N = 42 n (%)
Infections/Infestations	**8 (11.0)**	**9 (21.4)**
Investigations	**5 (6.8)**	**8 (19.0)**
Cardiovascular evaluation	4 (5.5)	4 (9.5)
HR decreased	1 (1.4)	-----
ECG QT prolongation	------	2 (4.8)
Cardiac Disorders	**3 (4.1)**	**6 (14.3)**
Cardiac Failure	1 (1.4)	2 (4.8)
Ventricular tachycardia	1 (1.4)	2 (4.8)
Cardiac arrest	1 (1.4)	1 (2.4)
Bradycardia	1 (1.4)	-----
Cardiogenic shock		2 (4.8)
Atrial Flutter		1 (2.4)
Cardiac failure chronic		1 (2.4)
Low cardiac output syndrome		1 (2.4)
Pericardial effusion		1 (2.4)
Ventricular fibrillation		1 (2.4)
General disorder and administration site conditions	1 (1.4)	2 (4.8)
Sudden cardiac death	------	1 (2.4)

Source: Reviewer's analysis based on applicant's datasets, popset.xpt and aestu.xpt using the MAED adverse event tool. Cross-reference: Table (12.2.1)2 in CSR for CL2-16257-090.

Reviewer Comments: *It is not obvious that ivabradine played a role in any of these SEAEs except for the patient with isolated bradycardia. The sponsor considered the SAE, bradycardia with convulsions, as related to ivabradine because of a temporal association between the event and drug dosing. Based on the narrative provided, the child convulsed "immediately" after administration of ivabradine. Given that the drug must be adequately absorbed from the GI tract prior to effecting HR, it seems unlikely that this child would develop profound bradycardia and subsequent convulsions immediately after drug administration.*

There is no obvious correlation between incidence of SEAEs and age cohort in the ivabradine treatment group. Both 1 to < 3 years and 3 to < 18 years of age cohorts had the same

proportion of SEAEs (7.8%) compared to a lower proportion in the 6 to < 12 months cohort (1.6%).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

EAEs leading to treatment withdrawal occurred in 4/73 (5.5%) subjects in the ivabradine group and 8/42 (19.0%) in the placebo group. The only AE PT reported for more than one subject who dropped out in either treatment group was QT prolongation. One subject (1.4%) and five subjects (11.9%) in the ivabradine and placebo groups, respectively, dropped out of the study due to a SEAE. SEAEs leading to withdrawal included: heart transplant (ivabradine) and atrial flutter, cardiogenic shock, chronic heart failure, decreased weight, low cardiac output syndrome, pericardial effusion, vomiting, diarrhea, and hypotension (all in placebo). Table 12 summarizes AEs/SEAEs leading to withdrawal.

Table 12: SEAEs Leading to Treatment Withdrawal in Safety Set by SOC and PT

System Organ Class *Preferred Term*	**Ivabradine (N=73)**			**Placebo (N=42)**		
	NEAE	**n**	**%**	**NEAE**	**n**	**%**
Investigations	3	3	4.1	4	4	9.5
ECG – QT Prolongation	3	3	4.1	3	3	7.1
Weight decreased	0	0	0	1	1	2.4
Surgical/Medical Procedures	1	1	1.4	0	0	0
Heart transplant	1	1	1.4	0	0	0
Cardiac Disorders	0	0	0	5	4	9.5
Atrial flutter	0	0	0	1	1	2.4
Cardiac failure chronic	0	0	0	1	1	2.4
Cardiogenic shock	0	0	0	1	1	2.4
Low cardiac output syndrome	0	0	0	1	1	2.4
Pericardial effusion	0	0	0	1	1	2.4
Gastrointestinal disorders	0	0	0	2	1	2.4
Diarrhea	0	0	0	1	1	2.4
Vomiting	0	0	0	1	1	2.4
Vascular Disorders	0	0	0	1	1	2.4
Hypotension	0	0	0	1	1	2.4
All	4	4	5.5	12	8	19.0

Source: Adapted from Table (12.1.1.3)4 in CSR for CL2-16257-090

Below is a summary of narratives for withdrawal due to QT prolongation from the ivabradine group.

- Patient 090-(b) (6) (9-month-old male) titrated to 0.2 mg/kg BID ivabradine was withdrawn from study on day 297 due to QT prolongation evident prior to first dose of study drug. The patients' baseline ECG at time of screening had a QTcB of 447 ms however, on the day of randomization and first day of dosing, the QTcB was 485 ms. Follow up ECGs were routinely performed about every 2-3 weeks thereafter with QTcBs ranging from 423 to 487 ms. After reaching the max titration dose, QTcB intervals remained mostly under 450 ms. The patient remained asymptomatic.
- Patient 090-(b) (6) (15-year-old female) was initially started on 5 mg ivabradine but subsequently decreased to 2.5 mg for a HR of 54 bpm. She was withdrawn from the study on day 210 because of QT prolongation. Prior to dosing, the patient had a baseline QTcB of 489 ms, in the setting of left bundle branch block. By day 44, the patient was noted to have a QTcB of 470 ms for which the DSMB recommended temporarily stopping ivabradine while awaiting central ECG review. The central ECG reader confirmed a QTcB of 436 ms so the patient restarted ivabradine. Throughout the study, the patient's QTcB fluctuated between 427 ms to 480 ms. By day 186, the patient temporarily stopped ivabradine again for a QTcB of 451 ms while awaiting central ECG review. On day 210, the patient was withdrawn from the study because her baseline ECG had a QTc of 489 ms. Follow up ECGs performed during 5 weeks after last dose continued to have prolonged QTcB between 464 to 476 ms.
- Patient 090-(b) (6) (7-year-old male) was titrated to 0.15 mg/kg BID. He was withdrawn from the study on day 39 for QT prolongation due to left bundle branch block present before first study drug intake. This patient's baseline QTcB was 545 ms and remained elevated between 540 to 550 ms during the time he was enrolled in the study. He remained asymptomatic and his QTcB remained prolonged to 525 ms about 5 months after last study drug intake.
- Patient 090-(b) (6) 3-year-old female) was uptitrated to an ivabradine dose of 0.3 mg/kg BID. She was withdrawn from the study on day 30 for QT prolongation. Her baseline QTcB was 443 ms. Her QTcB peaked to 521 ms by day 28, the same day her dose was increased from 0.10 mg/kg BID to 0.15 mg/kg BID. Her ivabradine dose was further uptitrated to 0.3 mg/kg BID during which time her QTc fluctuated between 440 – 465 ms. She remained asymptomatic with subsequent normalization of the QTc to the 440's ms.
- Patient 090(b) (6) (2-year-old male) was uptitrated to an ivabradine dose of 0.2 mg/kg BID but was withdrawn for QT prolongation on day 42. His baseline QTcB was normal at 430 ms but peaked to 483 ms by day 42. He remained asymptomatic with follow up ECG performed about six weeks after last study drug dose that continued to show an elevated QTcB of 462 ms.
- Patient 090-(b) (6) (11-month-old male) was uptitrated to an ivabradine dose of 0.2 mg/kg BID. QTcB was normal at baseline however this patient had a left bundle

branch block. The QTcB remained normal on follow up ECGs until day 128 at which time the QTcB was measured at 477 ms by the central ECG reader. The patients remained asymptomatic. About 13 days after last study drug dose, the QTc remained elevated at 501 ms.

- Patient 090-[redacted] (b) (6) (3-year-old female) uptitrated to an ivabradine dose of 0.15 mg/kg BID with a baseline QTc 475 ms. During most of the study, the QTcB fluctuated but was mostly in the normal range. By day 177, the patient was withdrawn because of QT prolongation before first study drug intake. About a week after discontinuation of study drug, the QTcB increased further to 498 ms but eventually normalized about 3 months later to 433 ms.

Reviewer Comments:

- *Amgen did not specify whether all ECGs were obtained before or after study drug dose in their study report. However, per protocol, patients were instructed to not take the study drug on the morning of site visits with site visits scheduled as early as possible in the morning to allow the patient to take the adjusted dose, if applicable, during the visit. Therefore, I think it is likely that all ECGs described above were obtained prior to dosing.*
- *Although ivabradine tablet product labeling contains a warning about increased risk for QT prolongation in the setting of bradycardia, it is not obvious that ivabradine played a role in any of the AEs that led to treatment discontinuation or that ivabradine directly prolonged the corrected QT interval in pediatric HF patients.*

8.4.4. Significant Adverse Events

See Section 8.4.3.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, 100 of the 115 (87.0%) subjects in the SS reported 634 EAEs with 63 (86.3%) subjects reporting 379 EAEs in ivabradine group and 37 (88.1%) subjects reporting 255 EAEs in placebo group. Most EAEs were mild, 84.2% in ivabradine group compared to 72.5% in placebo group, or moderate, 12.4% in ivabradine group compared to 14.5% in placebo group. Severe EAEs accounted for 3.5% versus 12.9% in ivabradine and placebo groups, respectively. Overall, there were no new or unexpected AEs detected in this study. Most commonly affected SOCs overall were infections and infestations, followed by respiratory, thoracic and mediastinal disorders, and GI disorders (Table 13).

Table 13: EAEs by SOC Occurring in at Least 5% of Subjects in Ivabradine Treatment Group

	Ivabradine (n=74)		Placebo (n=42)	
SOC	Number of Events	Number of Subjects (%)	Number of Events	Number of Subjects (%)
Infestations and Infections	179	50 (67.6%)	95	31 (73.8%)
Respiratory, thoracic, and mediastinal disorders	131	48 (64.9%)	77	27 (64.3%)
GI disorders	67	33 (44.6%)	45	18 (42.9%)
Investigations	45	27 (36.5%)	32	18 (42.9%)
Skin and Subcutaneous tissue disorders	36	18 (24.3%)	11	7 (16.7%)
Cardiac disorders	28	14 (18.9%)	34	16 (38.1%)
Injury, poisoning and procedural complications	27	12 (16.2%)	17	8 (19.1%)
Ear and labyrinth disorders	19	11 (14.9%)	1	1 (2.38%)
Eye disorders	13	10 (13.5%)	7	6 (14.3%)
General disorders and administration site conditions	21	10 (13.5%)	15	8 (19.1%)
Nervous system disorders	13	10 (13.5%)	11	7 (16.7%)
Metabolism and nutrition disorders	9	9 (12.2%)	20	9 (21.4%)
Immune system disorders	13	8 (10.8%)	15	6 (14.3%)
Vascular disorders	19	8 (10.8%)	20	14 (33.3%)
Blood and lymphatic disorders	5	4 (5.4%)	3	3 (7.1%)
Musculoskeletal and connective tissue disorders	6	4 (5.4%)	4	3 (7.1%)
Psychiatric disorders	5	4 (5.4%)	7	3 (7.1%)

Source: Reviewer's analysis based on applicant's datasets, popset.xpt and aestu.xpt using the MAED adverse event tool.
Cross-reference: Table (12.1.1)1 in CSR for CL2-16257-090.

Reviewer Comment: *Frequency of EAEs were similar between treatment groups in each age cohort except the 6 to <12 months of age cohort where 7 (70.0%) subjects reported EAEs in the ivabradine group compared to 7 subjects (100 %) in placebo group.*

Table 14 contains the most common non-CV EAEs grouped by PTs with the most frequently occurring PTs including nasopharyngitis, bronchitis, gastroenteritis, and upper respiratory infection.

Table 14: EAEs (non-CV) by PT Occurring in at Least 5% of Subjects in Ivabradine

	Ivabradine (n=74)		Placebo (n=42)	
PT	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Nasopharyngitis	23	16 (21.6%)	10	8 (19.1%)
Bronchitis	14	10 (13.5%)	4	3 (7.1%)
Gastroenteritis	10	9 (12.2%)	6	4 (9.5%)
Upper Respiratory Tract Infection	17	9 (12.2%)	20	9 (21.4%)
Viral Infection	11	7 (9.5%)	5	3 (7.1%)
Diarrhea	6	6 (8.1%)	10	6 (14.3%)
Ear Infection	9	6 (8.1%)	0	0
Pyrexia	8	6 (8.1%)	5	4 (9.5%)
Rhinitis	7	6 (8.1%)	2	1 (2.4%)
Vomiting	7	6 (8.1%)	7	6 (14.3%)
Conjunctivitis	5	5 (6.8%)	1	1 (2.4%)
Constipation	5	5 (6.8%)	6	5 (11.9%)
Fall	10	5 (6.8%)	5	3 (7.1%)
Gastroenteritis viral	5	5 (6.8%)	4	3 (7.1%)
Pharyngitis	10	5 (6.8%)	0	0
Abdominal pain	6	4 (5.4%)	3	3 (7.1%)
Cough	5	4 (5.4%)	1	1 (2.4%)
Influenza	5	4 (5.4%)	3	2 (4.8%)
Laryngitis	4	4 (5.4%)	0	0
Otitis media	7	4 (5.4%)	1	1 (2.4%)
Respiratory Tract infection	4	4 (5.4%)	6	3 (7.1%)
Accidental Overdose	3	3 (4.1%)	3	3 (7.1%)

Source: Reviewer's analysis based on applicant's datasets, popset.xpt and aestu.xpt using the MAED adverse event tool.
Cross-reference: Table (12.1.2)1 in CSR for CL2-16257-090.

Reviewer Comments: *In a pediatric population, particularly one that is chronically ill, infectious illnesses would be expected. Based on the mechanism of action of ivabradine and no concerns for increased risk for immunosuppression in either nonclinical or prior human studies, it seems unlikely that increased frequency of observed infections in the ivabradine group are study-drug related.*

Table 15 and Table 16 contain events of special interest including cardiac and visual grouped by SMQs and PTs.

Table 15: Select Cardiovascular and Visual EAEs Grouped by SMQs

		Ivabradine (n=74)		Placebo (n=42)	
SMQs	**Broad/ Narrow**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Cardiac Arrhythmias	Broad	39	24 (32.4%)	22	14 (33.3%)
	Narrow	23	16 (21.6%)	18	12 (28.6%)
Cardiac Failure	Broad	8	5 (6.8%)	16	10 (23.8%)
	Narrow	5	4 (5.4%)	15	9 (21.4%)
Cardiomyopathy	Broad	11	6 (8.1%)	10	9 (21.4%)
	Narrow	1	1 (1.4%)	3	3 (7.1%)
Hemodynamic edema, effusions, and fluid overload	Broad	8	4 (5.4%)	6	3 (7.1%)
	Narrow	8	4 (5.4%)	6	3 (7.1%)
Retinal Disorders	Broad	2	2 (2.7%)	2	2 (4.8%)
	Narrow	2	2 (2.7%)	1	1 (2.4%)
Shock	Broad	16	12 (16.2%)	23	13 (31.0%)
	Narrow	16	12 (16.2%)	21	12 (28.6%)
Torsades de Pointes/QT prolongation	Broad	16	12 (16.2%)	17	10 (23.8%)
	Narrow	15	12 (16.2%)	13	9 (21.4%)

Source: Reviewer's analysis based on applicant's datasets, popset.xpt and aestu.xpt using the MAED adverse event tool.

Table 16: CV EAEs Grouped by PTs

	Ivabradine (n=74)		Placebo (n=42)	
PT	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**

	Ivabradine (n=74)		Placebo (n=42)	
QT prolongation (ECG)*	14	12 (16.2%)	11	8 (19.1%)
Cardiovascular Evaluation	8	6 (8.1%)	6	6 (14.3%)
Heart Rate decreased	7	5 (6.8%)	1	1 (2.4%)
AV block 1st degree	4	3 (4.1%)	1	1 (2.4%)
Bradycardia	3	3 (4.1%)	0	0
Photopsia	2	2 (2.7%)	1	1 (2.4%)

Source: Reviewer's analysis based on applicant's datasets, popset.xpt and aestu.xpt using the MAED adverse event tool. Cross-reference: Table (12.1.2)1 in CSR for CL2-16257-090.

Reviewer Comments: *Bradycardia, conduction disturbances, and phosphenes are known AEs described in product labeling for ivabradine tablet. As expected and observed in the adult ivabradine study, there was a higher proportion of subjects with these on-target effects in the ivabradine group compared to placebo.*

8.4.6. Laboratory Findings

Amgen provided a description of out-of-range biochemistry and hematology parameters. For biochemical parameters, there was a significantly higher proportion of ivabradine patients, compared to placebo, with elevated chloride, elevated total protein, elevated ASAT, and elevated alkaline phosphatase. PCSAs were described for alkaline phosphatase, plasma sodium, and liver function tests. One patient in each treatment group had clinically significant low plasma sodium values. In the ivabradine group, the patient with clinically significant low plasma sodium had a mildly low sodium level at baseline. For liver function tests, ASAT and ALAT, PCSA levels were detected in one patient in the placebo group who had an ASAT peak value of 543 IU/L and ALAT 241 IU/L in the setting of ischemic hepatitis. Three patients (4.3%) in the ivabradine group versus one patient (2.8%) in the placebo group had PCSA values for alkaline phosphatase. Only one patient with elevated alkaline phosphatase in the ivabradine group was reported as an EAE (non-serious) in the context of varicella. For out-of-range hematology values, blood counts and differential, 11 (15.1%) patients in the ivabradine group had PCSA values compared to four (9.5%) patients in the placebo group.

Reviewer Comment: *Given the mechanism of action of the drug and the significant and complex medical histories of enrolled patients, there is no clear relationship between ivabradine and the above lab abnormalities.*

8.4.7. Vital Signs

Evaluation of vital signs, particularly blood pressure, did not reveal clinically relevant changes from baseline to month 12 in the ivabradine group compared to placebo except for the 6 to < 12 months of age cohort. In this cohort, an increase in systolic and diastolic blood pressure from baseline to month 12 was larger in the ivabradine group compared to placebo as follows:

- Systolic blood pressure: 12.3 ± 13.4 mmHg versus 10.0 ± 6.2 mmHg, respectively
- Diastolic blood pressure: 18.4 ± 19.6 mmHg versus 11.0 ± 6.6 mmHg, respectively

Reviewer Comment: *Although increases in blood pressure were, on average, higher in the 6 to < 12 months of age cohort, there were no reports of hypertension AEs in any pediatric patient in this study. Furthermore, changes in hemodynamic status during the trial could explain increases in blood pressure over time in both treatment groups. Therefore, I do not find these changes in blood fluctuations in the youngest age cohort of clinical concern.*

8.4.8. Electrocardiograms (ECGs)

Compared to placebo, HR significantly decreased in the ivabradine group from baseline to the end of the titration period (M0), month 6 (M6) and month 12 (M12) of the maintenance period. Mean change in HR from baseline to Month 12 was -27.6 ± 18.7 bpm in the ivabradine group compared to -0.9 ± 9.5 in the placebo group. This trend is also observed across all age cohorts for mean lowest HR as shown in Table 17.

Table 17: Mean Lowest HR from Baseline to Month 12

	Ivabradine (bpm)	Placebo (bpm)
All Pediatric Patients	69.3 ± 15.2	85.6 ± 18.9
6 to < 12 months	91.1 ± 9.4	111.7 ± 14.6
1 to < 3 years	72.1 ± 11.4	96.8 ± 13.9
3 to < 18 years	61.7 ± 12.2	73.0 ± 9.3

Source: Study CL2-16257-090 CSR p. 177 of 205.

There were no clinically important changes in PR or QRS intervals from baseline to M0, M6, and M12.

8.4.9. QT

Although the mean change in QT interval is increased more in the ivabradine group compared to placebo by M12, the change in the mean corrected interval (QTc) is either decreased or similar to placebo. See Table 18 for a summary of the QT interval data.

Table 18: Summary of Overall QT/QTc Interval Changes

	Ivabradine	Placebo
Mean QT change overall M12-baseline	37.1 ± 27.9 ms	2.7 ± 24.5 ms
Mean QTcB change M12-baseline	-20 ± 25 ms	4.7 ± 19.2 ms
Mean QTcF change M12-baseline	1.2 ± 20.5 ms	4.1 ± 19.7 ms
	Ivabradine n (%)	**Placebo n (%)**
Emergent QTcB > 450 ms and increase in QTcB >30 ms from baseline	9 (12.5%)	9 (22.5%)
	Three subjects had EAE "ECG QT prolonged" reported by investigators with one (1.4%) in ivabradine (AE, recovered) and two (5%) in placebo (1 SAE and 1 AE, both recovered)	
Emergent QTcB > 500 ms or QTcB increase from baseline >60 ms	4 (5.6%)	2 (5%)
	No AE reported by investigator	
Emergent QTcF > 450 ms and QTcF prolongation increase from baseline >30 ms	4 (5.6%)	0
	One subject with EAE reported by investigator, recovered; same subject with QTcB > 450 ms and increase >30 ms from baseline	
Emergent QTcF values > 500 ms or QTcF increase > 60 ms from baseline	7 (9.7%)	1 (2.5%)
	No EAE reported for these patients	

Source: Adapted from Tables (12.4.2)3 and (12.4.2)4 and p181-187 of 205 in CSR for CL2-16257-090

Reviewer Comments: *Compared to the SHIFT trial data in adults, pediatric patients had a higher incidence of QT prolongation without an obvious association with bradycardia, 8.2% and 16.7% in ivabradine and placebo groups, respectively compared to 0.28% and 0.12% respectively in SHIFT. The sponsor postulates that differences in QT prolongation incidence between trials may be explained by a higher incidence of baseline conduction abnormalities in pediatric DCM patients.*

I agree that a significant proportion of children withdrawn from the study because of QT prolongation had a prolonged QT interval at baseline or known history of a left bundle branch block. Notwithstanding, I might also expect similar conduction disorders in an adult DCM population. Despite the increased prevalence of QT prolongation in the pediatric study, none of the patients with isolated QT prolongation (i.e. not in the context of an illness or electrolyte disturbances) developed arrhythmias as a result. It is also noteworthy that QT intervals in some patients intermittently fluctuated between normal and abnormal ranges despite continuing the same dose of ivabradine or remained elevated even after discontinuation of study drug. This suggests that it is unlikely that the QT prolongation was a direct toxicity effect of ivabradine. This observation is supported by ivabradine tablet labeling that states, "Ivabradine increases the uncorrected QT interval with heart rate slowing but does not cause rate corrected prolongation of QT."

Reviewer Comment: *QT prolongation is consistent with a labeled risk in product labeling for Corlanor (ivabradine) tablets. Comparison of safety data between pediatric and adult ivabradine trials are limited due to small sample sizes in the pediatric study*

8.4.10. Immunogenicity

Not Applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Bradycardia

Bradycardia was reported as either asymptomatic i.e. "heart rate decreased" or symptomatic i.e. "bradycardia." Overall, symptomatic and asymptomatic bradycardia had a higher incidence with ivabradine than placebo, eight (11.0%) patients versus one (2.4%) patient. Asymptomatic bradycardia was observed in five (6.8%) patients in the ivabradine group compared to one patient (2.4%) in the placebo group. Symptomatic bradycardia was observed in three patients (4.1%) in the ivabradine group versus no patients in placebo. There were no obvious trends by age group cohort in the incidence of bradycardia AEs. In the ivabradine group, asymptomatic bradycardia was reported in two (8.3%) patients aged 1 to < 3 years and in three patients (7.7%) aged 3 to <18 years. In the ivabradine group only, symptomatic bradycardia was reported in one patient (4.2%) aged 1 to <3 years and in two patients (5.1%) aged 3 to <18 years.

Amgen studied the effect of background beta-blocker dosing on the occurrence of bradycardia and associated study drug withdrawal in this pediatric study. Overall, while on background beta-blocker therapy, there were 2/115 (2.2%) subjects with symptomatic bradycardia and 4/115 (4.4%) with asymptomatic decreased HR. None of these cases occurred in subjects 6 to <12 months of age, but there was at least one subject in each of the older age cohorts with either symptomatic or asymptomatic bradycardia. All bradycardia or decreased HR events while on background beta-blocker therapy occurred in the ivabradine group. For subjects not on

background beta-blocker therapy, 1/115 (4.4%) reported symptomatic bradycardia in ivabradine group and 2/115 (8%) reported asymptomatic decreased HR, one subject each in ivabradine and placebo groups. Similar to patients on background beta-blocker therapy, none of the events occurred in the 6 months to < 12 months of age cohort. None of the subjects, regardless of presence or absence of beta-blocker background therapy, discontinued the study drug because of bradycardia or decreased HR.

8.5.2. Phosphenes

Phosphenes were observed in two patients (2.7%) in the ivabradine group versus one patient (2.4%) in the placebo group.

Reviewer Comment: *Findings of bradycardia and phosphenes are consistent with labeled risks in product labeling for Corlanor (ivabradine) tablets. Comparison of safety data between pediatric and adult ivabradine trials is limited due to small sample sizes in the pediatric study*

8.6. Safety Analyses by Demographic Subgroups

See Section 8.4.

8.7. Specific Safety Studies/Clinical Trials

Not Applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not Applicable.

8.8.2. Human Reproduction and Pregnancy

There were no pregnancies reported during the pediatric development program.

8.8.3. Pediatrics and Assessment of Effects on Growth

Refer to Section 6.1. In brief, there were no significant differences in growth parameters between ivabradine and placebo in study CL2-16275-090.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Although ivabradine is not approved in any country for pediatric use, Amgen reviewed postmarketing reports in the pediatric population from October 2005 through May 2018. Amgen retrieved 82 post-marketing reports with off-label use in pediatric patients. Of the 82 cases, 25 reports were from the US. Twenty-nine (29) of the 82 cases reported 83 AEs. Nine cases reported 9 SAEs including one fatal event, ventricular fibrillation occurring > 30 days after last dose. The sponsor provided narratives of serious reports.

Reviewer Comment: *There were no new safety concerns identified in these postmarketing events from off label use in pediatric patients.*

8.9.2. Expectations on Safety in the Postmarket Setting

Pediatric patients with tachycardia but not in the context of heart failure were not studied. Off-label use in patients with inappropriate sinus tachycardia or other tachyarrhythmias that might benefit from a reduction of the ventricular rate would be of concern. The PK/PD relationship established in this pediatric study cannot be generalized to other pediatric populations. Therefore, routine pharmacovigilance could be used to assess for increased frequency of AEs with postmarket off-label use.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues from other disciplines were raised during this review.

8.10. Integrated Assessment of Safety

The safety profile of ivabradine oral solution is similar to ivabradine tablets, which are already marketed to adults with HFrEF. The size and duration of the safety database, including pediatric and adult data, are adequate to characterize the safety of ivabradine for treatment of CHF in patients with DCM. Notable toxicities are bradycardia and phosphenes. These on-target toxicities have already been described in product labeling for ivabradine tablet. No new safety signals were observed in pediatric patients with DCM and HF. Therefore, I do not recommend a risk evaluation and mitigation strategy. Recommendations for safe and effective use of ivabradine oral solution, including simplification of dosing instructions and revised MG and IFU, have been proposed to Amgen.

9. Advisory Committee Meeting and Other External Consultations

Not Applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

At the time of this review, Amgen has not yet submitted revised product labeling based on our recommendations summarized below.

Key PI changes recommended to Amgen include new dosing regimen for ivabradine oral solution. We recommended weight-based dosing based on age, <1 year or ≥1 year, and weight, < 40 kg. In addition, we recommended a higher starting dose for use in infants than that used in study CL2-16275-090. In the study, Amgen started dosing at 0.02 mg/kg for infants compared to 0.05 mg/kg in older children dosed with ivabradine oral solution. Based on discussion with Clinical Pharmacology, there was concern that the HR response in infants was less robust with a starting dose of 0.02 mg/kg. Modelling and simulation data further supported this change in the dosing regimen with a goal to achieve target HRR sooner in the youngest age cohort. Clinical and Clinical Pharmacology concluded that based on simulated dose-response data and because infants along with other patients dosed ivabradine will be monitored for heart rate changes, there is no increased risk to starting infants on a higher dose of ivabradine. The new dosing regimen will also include simplified weight-based titration steps.

Amgen initially proposed [redacted] (b) (6) 1 mg/mL. We recommended that Amgen only market the 1 mg/mL concentration to limit potential exposure to a [redacted] (b) (4) leachable (this issue is now resolved) and minimize [redacted] (b) (6) which might be beneficial. Juvenile toxicity data and clarifying pediatric clinical trial information were also added to Sections 8.4 and 14.2 of the PI.

Other Prescription Drug Labeling

The Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) reviewed Amgen's proposed MG and IFU. DMPP and OPDP provided recommendations to Amgen to simplify wording, clarify concepts, and ensure that the MG and IFU are consistent with the PI. Key recommendations included including adding pediatric-specific information to the MG and IFU and to include age-appropriate information pertaining to supplies and drug packaging.

10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is indicated for the proposed indication.

12. Postmarketing Requirements and Commitments

After internal discussion, CMC proposes a PMC for confirmatory data that replicates the success of Amgen's corrective action for the (b) (4) leachable. Agreement on the terms of the PMC have not been reached with Amgen at time of this review. At time of this review, we do not recommend any PMRs. Because we believe that simplification of pediatric dosing for the oral solution aligns with typical pediatric dosing, weight-based, we do not believe that a PMR is necessary for a repeat human-factors assessment. Because our proposed dosing regimen is based on simulated data and modelling, any concerns for increased frequency of bradycardia or phosphenes AEs can be adequately addressed through routine pharmacovigilance. Therefore, a PMR to address this issue is not necessary.

13. Appendices

13.1. References

Not Applicable.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CL2-16275-090

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 175		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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