Division of Cardiovascular and Renal Products
Cross-Discipline Team Leader Review

Date	April 12, 2019
From	Martin Rose, MD, JD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 209964 SD 14 (eCTD 012) - Resubmission following Refusal to File
Applicant	Amgen, Inc.
Date of Submission	10/25/2018
PDUFA Goal Date	04/25/2019
Proprietary Name	Corlanor
Established or Proper Name	Ivabradine
Proposed Dosage Forms	Oral solution [redacted] (b) (4) 5 mg scored oral tablets and 7.5 mg unscored oral tablets. (The tablets are currently marketed for adult use).
Applicant Proposed Indication(s)/Population(s)	"…the treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged 6 months to less than 18 years in sinus rhythm [redacted] (b) (4) "
Applicant Proposed Dosing Regimen(s)	A complex scheme with titrated dosing to achieve a target heart rate reduction. The scheme is too complicated to describe here.
Recommendation on Regulatory Action	Approve with PMCs relating to product quality
Recommended Indication(s)/Population(s)	As proposed by Applicant
Recommended Dosing Regimen(s)	OCP has proposed a greatly simplified, titrated dosing regimen, using an oral solution at a single strength (1 mg/mL) or the currently available oral tablets: *For the oral solution:* "The recommended starting dose … in pediatric patients 6 months of age and older and weighing less than 40 kg is 0.05 mg/kg twice daily with food. Assess patient at two-week intervals and adjust dose by 0.05 mg/kg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 0.2 mg/kg twice daily for patients 6 months to less than 1 year old, and 0.3 mg/kg twice daily for patients 1 years old and older." *For tablets in children with weight ≥ 40 kg:* "The recommended starting dose … is 2.5 mg twice daily with food. Assess patient at two-week intervals and adjust dose by 2.5 mg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 7.5 mg twice daily. In patients unable to swallow tablets, Corlanor oral solution can be used at recommended dose for tablets."

1. Benefit-Risk

(starts on next page)

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

I recommend approval of this resubmission. This recommendation is based on the results of a placebo-controlled, double blind trial in 116 patients age 6 months to < 18 years with symptomatic dilated cardiomyopathy and NYHA/Ross class II to IV heart failure, LV ejection fraction ≤ 45%, and baseline heart rate greater than age-specific limits. The randomization to ivabradine vs. placebo was 2:1. The study was conducted pursuant to a Pediatric Written Request (PWR). The goal of the trial was to compare the treatment arms in terms of the rate of achievement of a 20% reduction in heart rate (HR) from placebo, without induction of bradycardia, at the end of the titration period. HR reduction of this magnitude was also the target used in of the placebo-controlled SHIFT trial of ivabradine in 6505 adults with HFrEF, where it was associated with an 18% reduction in the rate of the composite primary endpoint of CV death and heart failure hospitalization. The treatment effect was driven by the results for HF hospitalization, but the results for CV death went in the same direction as HF hospitalization. Of note, 1349 subjects in SHIFT (21% of the total) had (non-ischemic) DCM as the etiology of their HFrEF. In the patients with DCM in SHIFT, there was a 25% reduction in the rate of the primary endpoint with ivabradine compared to placebo (nominal p=0.01). Like in the overall study population, this benefit was driven by effects on HF hospitalization, but deaths again went in the same direction. Also, the reduction in heart rate in SHIFT with ivabradine treatment from baseline to day 28 was identical in the overall SHIFT population and the SHIFT DCM subset: a mean reduction of 19% and a median reduction of 20% in both groups.

Adult and pediatric DCM have similar pathophysiology and symptoms, so it is reasonable to use HR reduction, the only known effect of ivabradine that might be relevant to HF outcomes, as a bridging biomarker. If ivabradine had effects on HR in patients with pediatric DCM like those observed in the SHIFT study, we were prepared to assume that it would also have beneficial effects in children with DCM on HF outcomes such as CV death and HF hospitalization. In the pediatric trial, the HR target reduction of 20% from baseline was achieved in 72% vs. 16% of the patients in the ivabradine and placebo arms, respectively (OR=14.97, 95% CI, 4.8, 46.8, p<0.0001). Deaths favored ivabradine over placebo (0/73 vs. 4/42). ADRs in the pediatric trial included symptomatic bradycardia (4% vs. 0%), asymptomatic bradycardia (7% vs. 2%). Risks in children appear similar to risks in adults. The trial results indicated that the benefits of ivabradine in the target pediatric population, based on the expected benefit in CV outcomes associated with the substantially greater rate of HR reduction, outweigh the modest risks compared to placebo that were observed in the trial.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pediatric cardiomyopathies are rare diseases resulting from various etiologies. The most common form of pediatric cardiomyopathy is dilated cardiomyopathy (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 heart failure (HF) due to pediatric DCM.	No drugs are approved to treat pediatric DCM. Approvals and evidence-based treatment recommendations are urgently needed.
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.	See comment above.
Benefit	• Prior to completion of the Applicant's placebo-controlled study 090 in children 6 months to <18 years old with DCM, HF and elevated heart rate, we agreed that success in an analysis of the primary endpoint, the rate of achievement of a 20% reduction in resting heart rate from baseline to the end of a 2- to 8-week titration period, could support approval of ivabradine for the studied condition. This agreement was based on the following: (1) reduction in HR through inhibition of I_f (the "funny" sodium current in the sinus node that drives spontaneous depolarization there and thus determines the heart rate) is the only known property of ivabradine that might beneficially affect outcomes in adults or children with HF and (2) in the SHIFT trial of ivabradine in adults with HFrEF that supported approval, similar reductions in HR were associated with a reduction in CV hospitalization. • The results of the primary endpoint analysis of Study 090 strongly favor ivabradine over placebo, as does the sensitivity analysis of mean change in resting heart rate over the same time period (see table below). Results in 3 subgroups of	The results of Study 090, which show a convincing reduction of heart rate in the studied population with pediatric DCM, create a link to the efficacy results in the SHIFT study that supported approval of ivabradine for the treatment of adults with HFrEF. Thus, we believe that they constitute substantial evidence of the efficacy of ivabradine for the pediatric indication proposed in the instant resubmission.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>children based on age from 6 months up to 18 years are consistent with the overall results (see Table 6).

Study 090- Primary Endpoint and Sensitivity Analysis Results
<table><tr><th colspan="3">Endpoints</th><th>Ivabradine</th><th>Placebo</th><th>Treatment Effect</th></tr><tr><td>Target HRR Achievement (Primary endpoint)</td><td colspan="2">PPS</td><td>46/64 (71.9%)</td><td>5/31 (16.1%)</td><td>OR=14.97
95% CI: [4.79, 46.77]
p<0.0001</td></tr><tr><td></td><td colspan="2">FAS</td><td>51/73 (69.9%)</td><td>5/41 (12.2%)</td><td>OR=17.24
95% CI: [5.91, 50.30]
p<0.0001</td></tr><tr><td rowspan="4">Mean Reduction in Heart Rate at Rest (bpm)</td><td rowspan="2">PPS</td><td>BL</td><td>100.8±20.2</td><td>96.7±18.5</td><td rowspan="2">Diff= -19.59 (2.29)
95% CI: [-24.14, -15.04]</td></tr><tr><td>ET</td><td>78.1±17.7</td><td>94.6±19.8</td></tr><tr><td rowspan="2">FAS</td><td>BL</td><td>102.0±20.8</td><td>98.9±18.2</td><td rowspan="2">Diff= -18.99 (2.40)
95% CI: [-23.75, -14.23]</td></tr><tr><td>ET</td><td>80.7±19.8</td><td>97.5±20.7</td></tr></table>HRR=heart rate reduction; PPS=Per protocol set; FAS=Full analysis set (both analyses were specified as primary endpoints). BL=baseline; ET= end of titration period.
HR is expressed as mean ± SD.</td><td></td></tr>
<tr><td>Risk and Risk Management</td><td>No new risks of ivabradine were observed in the pediatric DCM trial. Known risks (bradycardia, conduction abnormalities, and visual disturbances) were observed, but overall, discontinuations for AES and SAES were more frequent in the placebo arm than in the ivabradine arm.

(b) (4) which is harmful in young children, was found as a low-level impurity in the drug product. The available data indicate that its source is the (b) (4) The Applicant provided data that indicates that (b) (4). Going forward, the Applicant will not store the (b) (4), and there is a PMC in place to assess (b) (4) in the finished product. If 3 lots of finished product have suitably low levels of (b) (4), the Applicant will not need to continue to test for (b) (4)</td><td>No new risks of ivabradine were observed. Tolerability of ivabradine in pediatric patients seems similar to its tolerability in adults. No REMS or AE-related PMR or PMC is needed.

However, there is a PMC to test for (b) (4), which was found as an impurity in the drug product.</td></tr>
</table>

2. Background

Ivabradine reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f-current (I_f), resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility. It was approved in the US under NDA 206143on 4/15/2015 "…to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use." Current labeling indicates that safety and effectiveness in pediatric patients have not been established. Ivabradine has been approved for treatment of heart failure and angina in the EU and elsewhere.

In the US, it is available as 5 mg, scored oral tablets and 7.5 mg, unscored oral tablets. The recommended starting dose in adults is 5mg bid, with dose adjustment based on HR, with a target of 50-60 BPM. The maximum dose is 7.5 mg bid.

In the US, the sole contraindication is acute decompensated HF. Warnings include an increase in the risk of atrial fibrillation and bradycardia. The latter is the most important risk of the product.

Regulatory history of this submission

- April 2015: FDA approval of Corlanor (ivabradine) oral tablet, a new molecular entity (NME) under NDA 206143, for treatment of chronic HFrEF in adults; FDA issues a WR. The Sponsor had already completed study enrollment to fulfill a PIP agreement with EU at the time of the WR was issued.
- 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. The submission sought to add an indication similar to the one sought in the instant resubmission.
- February 2017: FDA issued an RTF letter primarily because validation information for the drug product (b) (4) was not provided. The letter also included a comment from DMEPA stating, "… a Human Factors (HF) validation study is necessary to demonstrate that the intended users can use the product safely and effectively. However, you have not submitted a HF validation study."
- 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
- October 25, 2018: FDA received the resubmission that is the object of this review.

3. Product Quality

The product quality team recommends approval with a PMC related to [(b) (4)] which was present in the drug product as an impurity. The team consisted of the following individuals:

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rao Kambhampati	Wendy Wilson-Lee	ONDP
Drug Product			
Labeling			
Environmental			
Manufacturing	Mark Johnson	Rapti Madurawe	OPF
Microbiology	Wendy Tan	Bryan Riley	
Biopharmaceutics	Qi Zhang	Jing Li	ONDP
Regulatory Business Process Manager	Grafton Adams		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Critical review issues for the OPQ team included: 1) sterility assurance, 2) appropriateness of the product design, including the container closure system, and formulation for the intended population, 3) formulation, design, and process attributes to mitigate potential risks associated with known degradation pathways (acidic, alkaline, photolytic, and thermal), and 4) dosing accuracy, especially in the context of multistep administration instructions.

Drug Substance: The Applicant references NDA 206143 for all drug substance CMC information. There are no issues.

Drug Product: The drug product is a simple formulation with only [(b) (4)] and water as excipients. Because of potential sensitivities of pediatric patients to preservatives, the Applicant has chosen sterile manufacture the drug product. The container closure is single use ampules, now to contain only one product strength, 1 mg/mL X 5 mL.

[(b) (4)] is an impurity in the drug product that originates from the [(b) (4)] ure. Data presented in the NDA showed [(b) (4)] leaching into the drug product [(b) (4)]. A safe level of [(b) (4)] could not be determined for this product given the proposed target population of neonates and pediatric patients. The applicant instituted corrective actions to reduce the amount of [(b) (4)] in the [(b) (4)]. A root cause analysis found that the [(b) (4)] originated from the exposure of the [(b) (4)]. The correction action instituted by the [(b) (4)] was to cease [(b) (4)]. The applicant provided data demonstrating that [(b) (4)] content was higher in [(b) (4)] compared to the resin manufactured using the new process. The applicant confirmed that all future batches [(b) (4)] would be manufactured using [(b) (4)] from the new process.

OPQ considers the Applicant's root cause analysis and subsequent corrective action at the source for the [(b) (4)] to be sufficient to support approval of the NDA. Based on the preliminary finding that the new corrective action reduces the amount of [(b) (4)] in the

resin to < (b) (4)ppm, they do not believe that any detectable amount of (b) (4) will be present in the final drug product. Because they now expect to see no detectable (b) (4) in the product, OPQ will not include information about trace (b) (4) in Section 11 of the prescribing information. This is in keeping with current OPQ policy to only include in Section 11 ingredients intentionally added to the product such as the active ingredients and excipients.

OPQ and the Applicant agreed to a product quality related post-marketing committing provide confirmatory data that replicates the success of the corrective action and low (b) (4) result in additional (b) (4) and final drug product batches (PMC # 3597 Confirmation of (b) (4) Content in Ivabradine Oral Solution). (See **12** for the text of the PMC agreement). As part of the PMC, the Applicant agrees to provide additional data for three, distinct (b) (4) lots manufactured using the new process to confirm that the mitigation strategies consistently provide (b) (4) with low (b) (4) content. The applicant agrees to provide some of this information within one year. Because the projected volume of manufacture for the drug product is low, the Applicant projects that it may take up to (b) (4) to manufacture three drug product batches using additional lots of (b) (4) from the new process. OPQ and the Applicant agreed that (b) (4) content data for drug product batches could be included as part of the annual report, as data become available with a target completion of 2027. A validated HPLC method will be used to monitor (b) (4) content with a limit of NMT (b) (4)mcg/mL. This proposed limit was found acceptable by both the nonclinical and clinical review teams.

Shelf life was another issue during the review. The primary review assessment of stability data recommended a reduction in the proposed drug product shelf life based on the absence of statistical analysis of the data. This information was not requested during the review cycle to address this concern. However, given that the data for the drug product primary stability batches did not show any significant changes in any of the monitored parameters (i.e. description, assay, impurities, pH, density, nominal volume, uniformity of dosage, sterility, (b) (4) in the intended commercial packaging, statistical analysis is not needed as noted in ICH Q1E Evaluation of Stability Data. As such, the proposed 36-month drug product shelf life is accepted based on the 24-month long-term and 6-month accelerated stability data for the primary registration batches when the drug product ampules are stored in the (b) (4) foil pouches at USP Controlled Room Temperature, protected from light.

Sterility assurance was the major basis of the RTF of the original pediatric formulation NDA. The Applicant chose to develop a sterile, preservative free formulation given the known sensitivities of pediatric patients to preservatives. In the resubmission, the Applicant provided all required sterilization validation information. Based on the review by the OPQ Division of Microbiology Assessment, the manufacturing process is validated with respect to sterility assurance and the proposed packaging provides sufficient protection from microbial contamination during storage.

Biopharmaceutics: The Biopharmaceutics reviewers found that there was no need to for the Applicant to request a biowaiver because bridging of the clinical trial and to-be-marketed formulations has been established based on 21 CFR 320.24(b)(6). The review indicates that there are adequate in vivo PK and clinical data within the NDA to support the proposed commercial pediatric formulation.

Facilities: Six facilities are described that are involved in manufacturing, testing and/or packaging the drug substance or drug product. All are recommended for approval based on previous history.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewers were Drs. John Koerner and Jean Wu. The pediatric resubmission contained no additional preclinical studies, and none were expected. However, based on non-clinical information submitted in the first ivabradine NDA (206143, for the treatment of HFrEF in adults), the nonclinical reviewers proposed an addition to labeling in Sec. 8.4 regarding cardiac and white blood cell findings in juvenile rats exposed to ivabradine at levels 5X (males) and 13X (females) the highest levels achieved across age groups in pediatric clinical studies. This language was adopted with some modifications for the agreed-upon labeling. I believe this language will not materially deter use of ivabradine in children with DCM.

5. Clinical Pharmacology

The Clinical Pharmacology review was performed by Drs. Eliford Kitabi, Chao Liu, Sudharshan Hariharan, and Martina Sahre. The Office of Clinical Pharmacology recommends approval of this NDA with a modified dosing scheme than what was proposed. The applicant has agreed with the review team's proposal for dosing.

Pharmacokinetics

The review contains limited information regarding ivabradine PK in children with HF. The review states the following:

> "Therapeutic exposure (AUC) at the maintenance dose was approximately 197 ng*h/mL for ivabradine and 64 ng*h/mL for S18982 [*note: this an active metabolite of ivabradine*]. Mean Cmax at the maintenance dose was 28 and 5.1 ng/mL, for ivabradine and S18982, respectively. Following maintenance doses, the exposure of ivabradine and S18982 is similar between adult and pediatric heart failure patients."

The pediatric data described above came from Study 090, the PK/PD study performed by Amgen to satisfy our PWR.

Adult PK are described as follows in the current labeling of ivabradine.

> Pharmacokinetics
>
> Absorption and Bioavailability
>
> Following oral administration, peak plasma ivabradine concentrations are reached in approximately 1 hour under fasting conditions. The absolute oral bioavailability of ivabradine is approximately 40% because of first-pass elimination in the gut and liver.
>
> Food delays absorption by approximately 1 hour and increases plasma exposure by 20% to 40%. Corlanor should be taken with meals [see Dosage and Administration.

Ivabradine is approximately 70% plasma protein bound, and the volume of distribution at steady state is approximately 100 L.

Metabolism and Excretion

The pharmacokinetics of ivabradine are linear over an oral dose range of 0.5 mg to 24 mg. Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours.

The total clearance of ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~ 4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine….

Specific Populations

Age

No pharmacokinetic differences (AUC or Cmax) have been observed between elderly (≥ 65 years) or very elderly (≥ 75 years) patients and the overall patient population [see Use in Specific Populations (8.5)].

Hepatic Impairment

In patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of Corlanor were similar to that in patients with normal hepatic function. No data are available in patients with severe hepatic impairment (Child-Pugh C) [see Contraindications (4)].

Renal Impairment

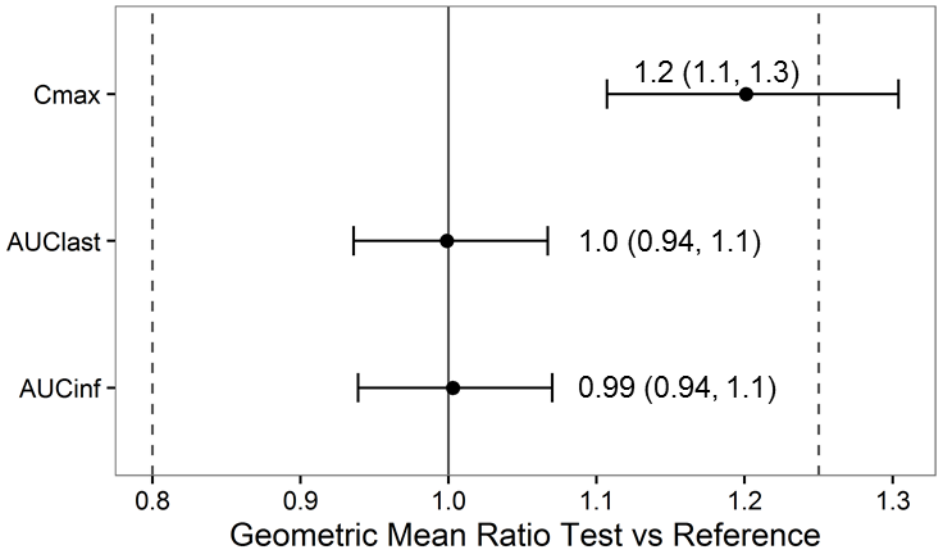
Renal impairment (creatinine clearance from 15 to 60 mL/min) has minimal effect on the pharmacokinetics of Corlanor. No data are available for patients with creatinine clearance below 15 mL/min.

Pediatrics

The pharmacokinetics of Corlanor have not been investigated in patients < 18 years of age.

The OCP review described the results of a two-period, two-sequence crossover study in 24 healthy adult volunteers of the relative bioavailability of ivabradine oral solution (7.5 mL of a 1 mg/mL solution) and 7.5 mg ivabradine tablets (Study PKH-086). Summary results are shown below.

Figure 1 Results of Study PKH-086



The results met the traditional BE 80%-125% standard for BE for AUC, but not for C_{max}, which had a point estimate of 1.2 for solution vs. tablet. This result was not unexpected and was considered acceptable by OCP in terms of switching patients from the solution to tablets and vice-versa at the same nominal mg dose of ivabradine.

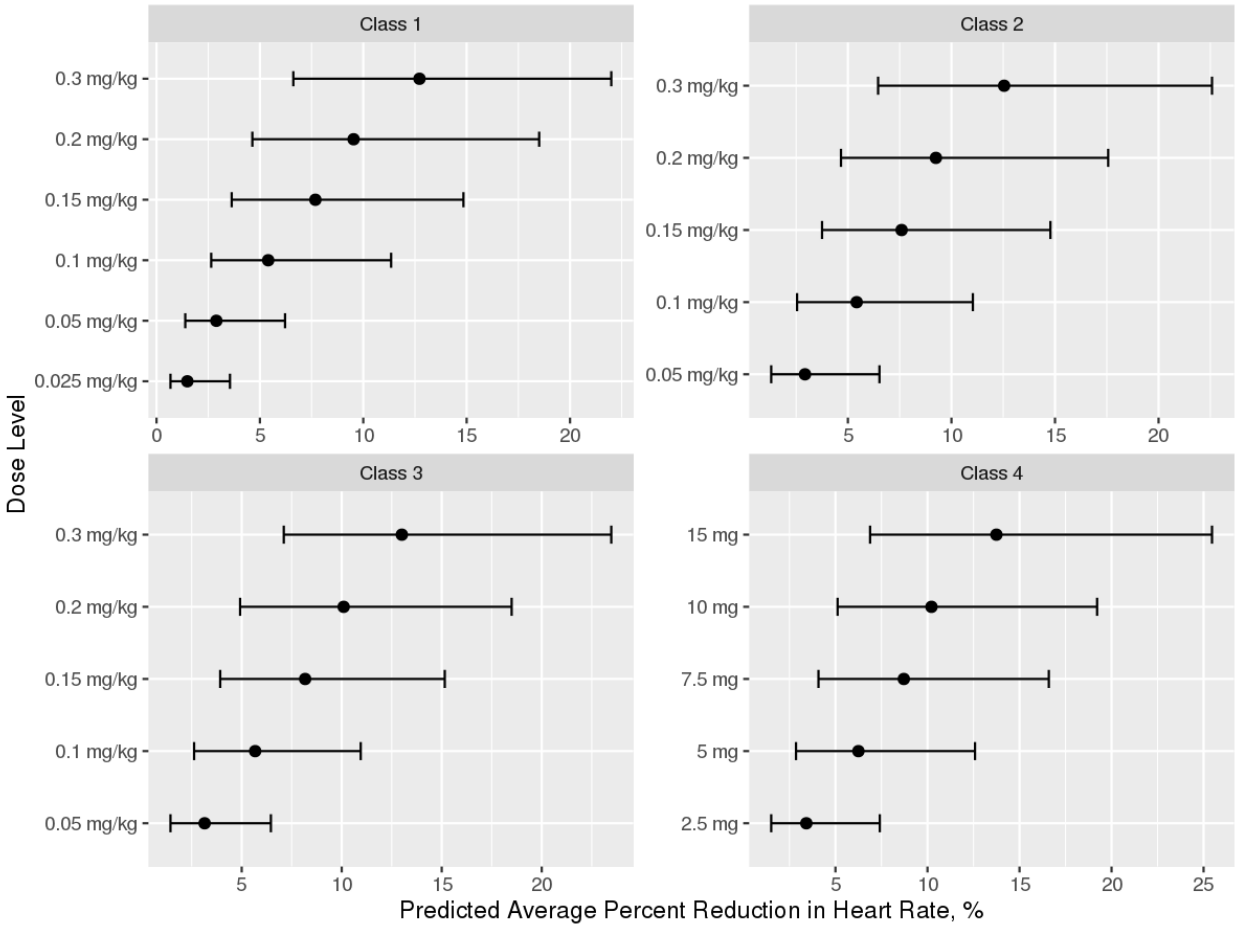
The OCP reviewers independently confirmed that compared to placebo, ivabradine was superior in reducing heart rate at multiple time points starting at Month 00 through Month 12 in the 4 age- and weight-based patient bands that they examined (data not shown). In these analyses, heart rate was analyzed as a continuous variable.

The OCP review included modeling of the exposure-response (i.e., heart rate reduction) relationships in adults with HFrEF and children. In adults, they found:

- Higher baseline heart rates were associated with greater absolute reductions in heart rate on treatment
- A dose response for relative (%) heart rate reduction that appeared to linear over the dose range of 2.5 to 10 mg but flattened out as the dose was increased to 20 mg.
- After cessation of dosing, the heart rate returns to baseline values with no rebound

The OCP reviewers appeared not to disagree with the Applicant's conclusions regarding PK/PD relationships in pediatric patients. Figure **2** is the Applicant's plot of modeled dose vs. HR response in different pediatric age groups.

Figure 2 Ivabradine Dose vs. Expected HR Response in Pediatric Age Groups



Age groups: Class 1 – 6 to 12 months; Class 2 – 1 to 3 years; Class 3 – 3 to 18 years and weight < 40 kg; Class 4 – age 3 to 18 years and age ≥ 40 kg.
Source: Applicant's Summary of Clinical Pharmacology Studies, Table 6 (file://cdsesub1/evsprod/nda209964/0012/m2/27-clin-sum/summary-clin-pharm.pdf)

In addition, the OCP reviewers divided the study population into 4 age- and weight-related strata and independently analyzed the heart rate data from Study 090 in these strata . They found a statistically significant reduction in heart rate with ivabradine compared to placebo starting at Month 00 (two weeks after the end of the titration period) through Month 12. In these analyses, heart rate was analyzed as a continuous variable. (Data not shown).

Like Amgen, OCP found that age and body weight are meaningful covariates of the dose response in children. However, the OCP reviewers concluded that the Applicant's dosing scheme in the proposed labeling was overly cautious and would result in delays in reaching therapeutic blood levels for patients 6 to 12 months. The complete text of the Applicant's pediatric dosing scheme in the proposed Corlanor package insert can be found **below** on p. 14-15.

To design a better-performing dosing scheme, OCP built a prediction model to assess the effects on heart rate of various starting doses and titration strategies in children across a range

of ages and weights. Results of their modeling in patients from 6 to 12 months are shown in Table 1. The first row (in green) shows predicted results for the scheme actually used in Study 090, with a starting dose of 0.02 mg/kg and a maximum ending dose 0.2 mg/kg after 4 up-titrations. The blue-shaded row is the one preferred by OCP to be recommended in labeling because the model predicts the most favorable combination of benefits (success in HRR) and risks (bradycardia). In addition, this regimen includes a maximum of 4 dose levels, compared to 5 for the one used in Study 090 (b) (4)

Table 1. Results of OCP Prediction Model - Probabilities of Success and Bradycardia with Various Dosing Schemes in Patients Age 6 to 12 months

TITRATION SCHEMES	CANDIDATE DOSING SCHEMES				SUCCESSFUL SUBJECTS	
	START DOSE	END DOSE	INCREMENTS	NUMBER OF STEPS	SUCCESS PROBABILITY	BRADYCARDIA PROBABILITY
Clinical trial titration scheme	0.02	0.2	NA	5	0.23 (0.16 - 0.3)	0.015 (0 - 0.04)
Alternative titration schemes	0.125	0.2	0.025	4	0.23 (0.16 - 0.32)	0.015 (0 - 0.04)
	0.15	0.2	0.025	3	0.24 (0.16 - 0.32)	0.017 (0 - 0.04)
	0.05	**0.2**	**0.05**	**4**	**0.24 (0.16 - 0.32)**	**0.014 (0 - 0.03)**
	0.1	0.2	0.05	3	0.24 (0.17 - 0.32)	0.016 (0 - 0.05)
	0.05	0.2	0.075	3	0.23 (0.16 - 0.32)	0.015 (0 - 0.04)

Doses are expressed in mg/kg.
"Success" refers to attainment of a 20% reduction in HR.
The blue-shaded data row corresponds to the regimen favored by OCP for labeling.

The starting dose in the OCP proposed regimen is the same, 0.05 mg/kg, across the range of pediatric ages from 6 to 18 with weight < 40 kg. However, they concluded that the maximum dose should be different in younger vs. older children. They also agreed with DMEPA that that the Applicant's proposed dosing scheme was needlessly complicated and could be simplified by expressing the recommended doses in mg/kg, like in many other pediatric labels (see Sec. 12 for information on DMEPA's review). Finally, OCP believed that any pediatric dose could be delivered using one concentration of ivabradine solution: 1 mg/kg. The entire dosing scheme proposed by OCP is shown below. This was incorporated into draft labeling that was accepted by the Applicant.

"Recommended Dosage

"Pediatric Patients 6 Months of Age and Older Weighing Less than 40 kg (Oral Solution)
The recommended starting dose of Corlanor oral solution in pediatric patients 6 months of age and older and weighing less than 40 kg is 0.05 mg/kg twice daily with food. Assess patient at two-week intervals and adjust dose by 0.05 mg/kg to target a heart rate (HR) reduction of at least 20%,

based on tolerability. The maximum dose is 0.2 mg/kg twice daily for patients 6 months to less than 1 year old, and 0.3 mg/kg twice daily for patients 1 years old and older.

"Pediatric Patients Weighing 40 kg and Greater (Tablets)
The recommended starting dose of Corlanor tablets in pediatric patients weighing more than 40 kg is 2.5 mg twice daily with food. Assess patient at two-week intervals and adjust dose by 2.5 mg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 7.5 mg twice daily. In patients unable to swallow tablets, Corlanor oral solution can be used at recommended dose for tablets".

Note that the lowest single dose to be delivered using the OCP dosing scheme is for a 5 kg infant: 5 x 0.05 mg/kg, or 0.25 mg (0.25 mL of the 1.mg/mL solution). This can be readily drawn up and delivered in a 1 mL syringe with suitable barrel markings. Higher doses, up to the maximum dose of 7.5 mg (7.5 mL), could be given with larger syringes. Plastic syringes to deliver volumes in the range of 1-10 mL are widely available in pharmacies and could be dispensed with each refill.

Sara Thomas of DMEPA has indicated that because of the relative simplicity of this dosing scheme and its similarity to many current pediatric dosing schemes that recommend mg/kg dosing, OCP's proposal would be acceptable to DMEPA without an additional labeling comprehension study.

The Applicant's initially-proposed pediatric dosing scheme in labeling is reproduced below and continues onto the next page:

(b) (4)

Table 2. Recommended Dosing of Oral Solution (Each Dose to be Given Twice Daily)

(b) (4)

(b) (4)

As noted in Sec. **12** of this review, the results of the labeling comprehension study required by DMEPA to cure a deficiency that contributed to our RTF of the original submission of this application were unacceptable.

6. Clinical Microbiology

See Sec. **3** for a discussion of sterility issues.

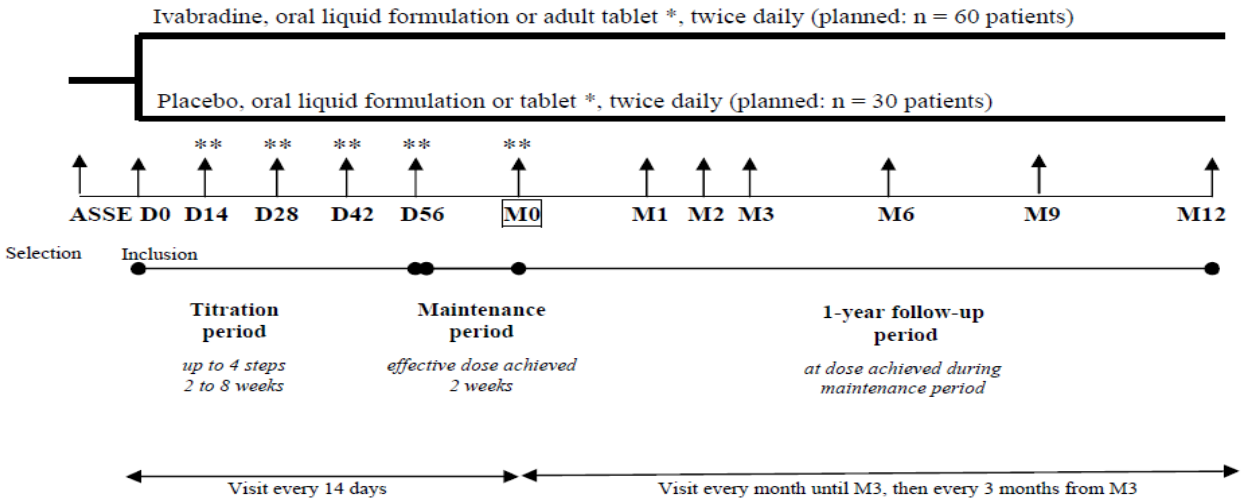
7. Clinical/Statistical- Efficacy

The clinical reviewer was Dr. Shetarra Walker and the statistical reviewers were Drs. Steve Bai and James Hung. My review borrows heavily from their reviews, especially Dr. Walker's.

Study CL2-16257-090 - Design

In the instant resubmission, the Applicant submitted the results of a single study, CL2-16257-090, to fulfill our PWR and support labeling for the treatment of pediatric patients with dilated cardiomyopathy, stable heart failure and elevated HR. The tri-partite primary objectives of the study were consistent with the PWR: 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, and to assess the PK/PD relationship of ivabradine and its active metabolite S 18982 using heart rate as the evaluation criterion. For additional information regarding the PWR, see Dr. Walker's review.

Figure 3. Study 090 Plan



N = 90 paediatric patients
**Adult tablet or matching placebo for patients aged [3-18[years with weight ≥ 40 kg and able to swallow tablets (i.e. older than 6 years old)*
*** heart rate, expressed as the target HRR achievement, defined as a reduction of the heart rate from baseline of at least 20% and without inducing a bradycardia (i.e. HR should be greater than a predefined HR threshold by age subset) and/or signs or symptoms related to bradycardia.*

The trial was a double-blind RCT comparing ivabradine to placebo in patients of either gender, age 6 months to <18 years. Subjects were randomized 2:1 to ivabradine or placebo and stratified at baseline by age and weight [6 months to <12 months, 1 year to <3 years, 3 years to <18 years (<40 kg and ≥ 40 kg)]. Subjects had LVEF ≥45%, and were NYHA/Ross classification II-IV, on optimal and stable CHF therapy and in sinus rhythm. Subjects were required to have baseline resting HRs at or above predefined HRs by age cohort, as follows:

- HR ≥ 105 bpm for age 6–12 months.
- HR ≥ 95 bpm for age 1–3 years.
- HR ≥ 75 bpm for age 3–5 years.
- HR ≥ 70 bpm for age 5–18 years.

Patients were excluded if they had a prior history that included the following: congenital heart disease, prior cardiac transplant or cardiac corrective surgery, symptomatic or sustained ventricular arrhythmia unless cardioverter defibrillator implanted, severe regurgitative valvular disease, significant ventricular outflow obstruction, or other prespecified cardiomyopathies.

The study plan is shown in Figure **3**. The study was divided into a pre-randomization period (subject selection visit to D0 of titration period) and post-randomization period. The post-randomization period had a duration of 13 to 14.5 months divided into the following three periods:

- Titration Period (D0 to D56): Study drug was titrated in a 2 to 8-week period during which age and weight-based starting doses were titrated up to a maximum of four times from the starting dose based on titration rules, HR, and symptoms of bradycardia. Dosing during this period is described in Sec. **5**.
- Maintenance Period (D56 to M0): 2-week period during which subjects continued the highest dose achieved during the titration period and were evaluated for bradycardia.
- Treatment Period (M0 to M12): up to 1-year during which dose could be adjusted according to weight; or decreased or stopped for bradycardia, symptoms of bradycardia, or safety reasons.

Consistent with the PWR, the primary endpoint was achievement of the target HR reduction (HRR), which was defined as a reduction ≥20% of the baseline value. This was assessed at the end of the titration period. The comparison between the study arms was performed using a logistic regression model adjusted for age class to estimate the OR and 95% CI.

In addition, change from baseline in HR was assessed at the end of the titration period, M6 and M12, using a parametric covariance analysis adjusted for age class and with baseline value as a covariate. A non-parametric approach (a rank-based analysis (Wilcoxon scores) adjusted for age class with baseline as covariate) was used to check for robustness of results.

The following analysis populations were specified in the protocol.

- RS – (randomized set) all randomized patients
- FAS – (full analysis set) all randomized patients who received at least one dose of study drug with at least two evaluations of resting HR, one at baseline and one post-baseline.
- PPS – (per protocol set) patients in 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 – (safety set) all patients who received at least one dose of study drug.

The primary efficacy analysis was to be performed in the per-protocol set (PPS). The analysis was then performed in the full analysis set (FAS) as a sensitivity analysis. Other efficacy analyses were also performed in these two populations, with the same hierarchy of importance.

No interim efficacy analyses were specified or reported.

Study CL2-16257-090 – Results

This study may be referred to as Study 090 or CL2-090. A total of 116 subjects were randomized into the study – 74 and 42 into the ivabradine and placebo arms, respectively. Baseline demographics and disease-related factors are shown in these subjects are shown in Table 2. In general, the arms were well-balanced. However, the baseline NTproBNP was higher in the placebo arm, although the standard deviations for this parameter are roughly 2 times the means. Also, there were some differences between the arms in the etiologies of DCM. Only ~15% of patients were in the youngest age group (6 to <12 months). Note that the RS population total, 116, is only 2 patients larger that the FAS population (N=114), which was the population analyzed in one of the two primary endpoint analyses. Demographic data were not provided for the FAS or PPS (per-protocol population, N=95, the subject of the other "primary endpoint" analysis).

Table 2. Patient Characteristics (RS Population)

Patient 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			
diopathic	45 (60.8)	20 (47.6)	65 (56.0)
Post-viral myocarditis	16 (21.6)	9 (21.4)	25 (21.6)
schemic	-	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)

Patient Characteristics	Ivabradine (N=74) n (%)	Placebo (N=42) n (%)	Total (N=116) n (%)
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)
Heart Rate - Age Cohort Mean bpm (SD) 6-<12 months 1-<3 years 3-<18 years	 132.9 (20.7) 112.0 (10.1) 88.2 (11.7)	 127.4 (7.4) 110.1 (12.5) 86.0 (8.6)	 130.6 (16.4) 111.4 (10.8) 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: Dr. Walker's review -- Adapted from Tables (10.4.1) 1, (10.4.1) 2, and (10.4.1) 3 from CSR for CL2-16257-090

Table 3 is a display of HF concomitant medications use at baseline, which was reasonably similar in the two treatment arms.

Table 3. Summary of HF Concomittant Medications at Baseline (Safety Population)

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.

Table 4 shows study disposition in the randomized population. About 90% of randomized subjects in each arm completed the titration period and thus were analyzable for the primary endpoint. This seems acceptable. The rate of study completion was 82% and 67% in the ivabradine and placebo arms, respectively.

Table 4. Study Disposition (RS Population)

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: Table 10.2.2 in CSR for CRL-16257-090

Table 5 is copied from the Statistical Review by Drs. Bai and Hung. It shows the HRR response rate (the primary endpoint) and the change in HR from baseline to the end of the titration period in the PPS (N=95) and the larger FAS (N=114). Both analyses strongly favor ivabradine over placebo in each of the two analysis sets.

Table 5. Results for Target HRR Achievement and Heart Rate at Rest during the Titration Period-FAS and PPS titration

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] p<0.0001
	FAS		51/73 (69.9%)	5/41 (12.2%)	OR=17.24 95% CI: [5.91, 50.30] p<0.0001
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	
Heart Rate at Rest (bpm)	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: Dr. Bai's results]

BL= Baseline; ET= End of titration period.

Table 6 shows the results for target HHR achievement in the FAS and PPS by age group and indicates that the advantage of ivabradine over placebo over placebo in both these populations was not driven by the results in any particular age group.

Table 6. Results for Target HRR Achievement during the Titration Period-FAS and PPS Titration

FAS (N=114) n/N			PPS (N=95) n/N		
Age Group	**Ivabradine**	**Placebo**	**Age Group**	**Ivabradine**	**Placebo**
6 to <12 mo	6/10	1/6	**6 to <12 mo**	4/8	1/2
1 to <3 yr	17/24	0/10	**1 to <3 yr**	14/20	0/10
3 to <18 yr	28/39	4/23	**3 to <18 yr**	28/36	4/19
All	51/73	5/41	**All**	46/64	5/31

These data establish the efficacy of ivabradine in reducing heart rate in the target population of children with DCM, heart failure and an elevated HR. As described previously, we agreed to accept an effect on HRR in Study 090 as a bridging biomarker to the findings in adults with HFrEF in the SHIFT study, where compared to placebo, HRR with ivabradine was associated with a reduced rate of CV hospitalization. Thus, given the robust nature of the heart rate reduction findings in trial 090, the study results constitute substantial evidence of the efficacy of ivabradine for its proposed pediatric indication.

Death and either heart failure or CV hospitalization were not efficacy endpoints. For information on these events, see Sec. 8, Safety.

Secondary efficacy endpoints included a variety of parameters related to heart failure. These included several echocardiographic parameters, NYHA/Ross classification, global clinical status assessments, NT-proBNP concentration, and growth parameters. Results are summarized below, except for growth parameters. There was no alpha error allocated to the secondary endpoints. The Applicant is not proposing to include information about any of the secondary endpoints in labeling.

Table 7 shows changes from baseline to Month 6 and Month 12 for assessed echocardiographic parameters in Study 090 and also analogous data available from adults in SHIFT at Month 8. In each study, changes for all assessed parameters were more favorable with ivabradine than placebo.

Table 7. Changes from Baseline in Echocardiographic Parameters in Study CL2-090 and in Adults in SHIFT

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.

Table **8** shows evolution from baseline to Month 12 in NYHA/Ross classification by age group in the two treatment arms in Study 090. A higher percentage of patients in the ivabradine arm had improvement.

Table 8. Changes 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*

Table **9** shows changes in plasma NT-proBNP concentrations from baseline to Months 0, 6, and 12. Mean changes were more favorable (i.e., more greatly reduced) with ivabradine than with placebo. Median changes were modest in each arm.

Table 9. 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: CSR CL2-16257-090 Table (11.2.4) 1

8. Safety

No new risks of ivabradine were identified in the pediatric trial, Study 090.

Duration of Exposure

Of the 116 patients randomized to study drug in Study 090, 115 received at least one dose of study drug and constituted the safety population. Group statistics for treatment duration during the overall study period are shown in Table **10**. Data are shown for the entire safety population in the top 3 rows of data, and then for the 3 major age subgroups. The median exposure duration was slightly over 1 year and similar in both treatment arms, but the mean exposure tended to be higher with ivabradine than placebo.

Table 10: Treatment Duration (days) in the Safety Population during the Overall Study Period

	Ivabradine (N=73)	Placebo (N=42)	All (N=115)
Mean ± SD	351.0 ± 111.0	298.2 ± 151.9	331.7 ± 129.3
Median	396	393	393
Q1, Q3	368; 406	121; 407	359; 407
Age Subgroups -			
6 to<12 months	N=10	N=7	N=17
Mean ± SD	319.6 ± 140.7	195.6 ± 191.8	268.5 ± 170.0
Median	387	92	375
1 to <3 years	N=24	N=12	N=36
Mean ± SD	377.3 ± 78.0	336.6 ± 124.0	363.7 ± 96.0
Median	401	400.5	401
3 to <18 years	N=40	N=23	N=63
Mean ± SD	342.9 ± 119.2	309.5 ± 144.8	330.5 ± 129.2
Median	385	393	392

Source: Adapted from Study 090 CSR, Form 1-10, p. 376-379

Deaths

Deaths during the study occurred in 0/73 vs. 4/42 (9.5%) in the ivabradine and placebo arms, respectively. Dr. Walker describes the deaths as follows:

"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."

SAEs

The focus of the remainder of this section will be "emergent" adverse events, including serious emergent AEs (SEAEs) and emergent adverse events (EAEs). Emergent adverse events (EAEs) were defined as all adverse events 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).

Like the data for death, the data for SAEs, including overall cardiac SAEs, favor ivabradine over placebo. There was 1 vs. 0 SAE of bradycardia, and 1 vs. 0 SAE of "HR decreased" in the ivabradine and placebo arms, respectively. Note that the AE of "Cardiovascular Evaluation" refers to planned admissions.

Table 11. SEAEs by SOC or PT (occurring in at least 2 subjects in the ivabradine arm + all cardiac SAEs, Safety Population)

SOC or PT	Ivabradine N = 73 n (%)	Placebo N = 42 n (%)
Infections/Infestations	**8 (11.0)**	**9 (21.4)**
Pneumonia	2 (2.7)	3 (7.1)
Nasopharyngitis	2 (2.7)	-
Gastroenteritis viral	1 (1.4)	2 (4.8)
Adenoiditis	1 (1.4)	-
Gastroenteritis	1 (1.4)	-
RSV bronchiolitis	1 (1.4)	-
Tracheobronchitis	1 (1.4)	-
Viral infection	1 (1.4)	-
Upper respiratory tract infection	-	3 (7.1)
Adenoviral URI	-	1 (2.4)
Lower respiratory tract infection	-	1 (2.4)
Otitis media	-	1 (2.4)
Septic shock	-	1 (2.4)
Urinary tract infection	-	1 (2.4)
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)

The Study 090 protocol did not specify how heart transplants would be handled in terms of AE reporting. Subjects with a prior transplant or those anticipated to have a transplant or corrective heart surgery within one year of enrollment were excluded from the study. Also, patients undergoing heart transplant or corrective heart surgery during the study were to be withdrawn from treatment. As noted immediately below, one heart transplant in an ivabradine arm subject was coded as an SAE leading to study drug discontinuation. The CSR indicates that in the

ivabradine and placebo arms, respectively, there were a total of 2 (3% of subjects) and 2 (5%) heart transplants. Of these 4 procedures, 3 were treatment-emergent. The one that was not occurred 2 months after discontinuation of treatment in an ivabradine arm subject.

Discontinuations

Discontinuations also favored ivabradine. AEs (whether or not treatment-emergent) leading to treatment withdrawal occurred in 9 patients (12.3%) and 9 patients (21.4%) in the ivabradine and placebo arms, respectively. When only treatment-emergent events are counted, there were 4 patients (5%) and 8 patients (19%) who discontinued because of an AE in the ivabradine and placebo arms, respectively (Table **12**). Of note, treatment-emergent QT prolongation leading to discontinuation occurred in a higher percentage of patients in the placebo arm than in the ivabradine arm.

Table 12. TEAEs Leading to Discontinuation of Study Drug (Safety Population)

Treatment Arm, AE Type	Patient Age and Gender	Onset Day of Event (a)	AE(s) Experienced
IVABRADINE	(N=73)		
SAE	12 yr, M	85	Heart transplant
NSAE	11 mo, M	127	Asymptomatic QT prolongation (QTP)
NSAE	2 yr, M	42	Asymptomatic QTP
NSAE	3 yr, F	29	Asymptomatic QTP
PLACEBO	(N=42)		
SAE	8 mo, F	92	Cardiogenic shock
SAE	11 mo, M	1	Vomiting, diarrhea, hypotension
SAE	15 mo, M	(b)	Worsening heart failure
SAE	8 yr, F	0	Hypotension, vomiting
SAE	14 yr, M	62	Atrial flutter, dyspnea
NSAE	8 yr, M	12	Asymptomatic QTP
NSAE	10 yr, M	85	Asymptomatic QTP
NSAE	8 yr, M	239	Asymptomatic QTP

Source: Study 090 CSR Tables (12.2.2) 1 and (12.2.2) 2
SAE= serious adverse event; NSAE=non-serious adverse event
(a) Onset day = Event onset date minus date of first dose of study drug
(b): Event date was not recorded, but a note in the CSR indicated that it probably occurred between 1.5 and 2.5 months after first dose of study drug.

AEs

Table **13** is a display of TEAEs occurring in at least 5% of patients in the ivabradine arm. Examination of these data revealed no new safety signals for ivabradine.

Table 13. EAEs (non-CV) by PT Occurring in at Least 5% of Subjects in the Ivabradine Treatment Group (Safety Population)

	Ivabradine (n=73)		Placebo (n=42)	
PT	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Nasopharyngitis	23	16 (21.9%)	10	8 (19.1%)
Bronchitis	14	10 (13.7%)	4	3 (7.1%)
Gastroenteritis	10	9 (12.3%)	6	4 (9.5%)
Upper Respiratory Tract Infection	17	9 (12.3%)	20	9 (21.4%)
Viral Infection	11	7 (9.6%)	5	3 (7.1%)
Diarrhea	6	6 (8.2%)	10	6 (14.3%)
Ear Infection	9	6 (8.2%)	0	0
Pyrexia	8	6 (8.2%)	5	4 (9.5%)
Rhinitis	7	6 (8.2%)	2	1 (2.4%)
Vomiting	7	6 (8.2%)	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 (5.5%)	3	3 (7.1%)
Cough	5	4 (5.5%)	1	1 (2.4%)
Influenza	5	4 (5.5%)	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%)

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.

We have already agreed with the Applicant on the presentation of risk information in labeling, including AE information.

9. Advisory Committee Meeting

The Division determined that an advisory committee meeting was not necessary.

10. Pediatrics

This submission was intended to satisfy a PWR. All the data are pediatric.

11. Other Relevant Regulatory Issues

See Sec. **12** for a discussion of the dosing instructions in labeling.

12. Labeling

We have reached agreement with the Applicant on labeling, and the Pediatric Review Committee (PeRC) has agreed to the labeling. However, one issue, now settled, merits discussion at a high level because it resulted in substantial work by DMEPA and OCP and several meetings of the review team. As noted in in the regulatory history in Sec. **2**, in our RTF letter to the Applicant DMEPA indicated that, " … a Human Factors (HF) validation study is necessary to demonstrate that the intended users can use the product safely and effectively." To respond to this requirement, the Applicant performed a label comprehension study (LCS) and included the results in the instant submission.

The study was performed for Amgen by a third party. DMEPA's review of the study report indicates,

> "The objective of the study was to assess if the Corlanor user interface, including the proposed Prescribing Information (PI), container labels carton labeling, and instructions for use (IFU), supports the safe and effective use by prescribers, pharmacists, and parents/caregivers. Specifically, the LCS examined the labeling by evaluating if:
>
> - Prescribers (pediatric cardiologists, nurse practitioners; n=16) can correctly answer questions about prescribing the correct dose, concentration, and volume based on the data provided in the PI based on the patient's weight, age, and heart rate.
> - Pharmacists (n=16) can correctly answer questions about dispensing the prescribed dose, verifying dose accuracy (dose, concentration, and number of cartons), and providing a suitably graduated syringe and medication cup.
> - Parents/Caregivers (n=33) can correctly answer questions on preparing and administering the correct dose, discarding the unused oral solution, and rinsing the cup and oral syringe after each use."

The Applicant's dosing instructions in the proposes labeling are descried in Sec. **5** of this review. These instructions have been drastically simplified, [redacted] (b) (4) of the oral solution (1 mg/mL) as a result of the efforts of the review team, including DMEPA, OCP, and DCRP. Accordingly, it would be little value to describe here in detail the results of the LCS study, except to note that there were unacceptable rates of failure to understand the dosing scheme described in labeling. The DMEPA review concludes as follows:

> "In summary, the product user interface is not safe and effective as proposed. Our evaluation of the LCS study results, proposed PI, container labels and carton labeling, and IFU identified areas of vulnerability that may lead to medication errors. Based on discussions with the DCRP review team, we are aware that the clinical data supports significant decreases in the complexity of the dosing table and removing [redacted] (b) (4). We agree with DCRP's intentions to decrease the complexity of the proposed product and expect these revisions will mitigate some of the risks for error seen in the LCS related to the prescriber and pharmacist's tasks…."

The DMEPA review team included Janine Stewart, Chi-Ming Tu, Quynh Nguyen, and Danielle Harris.

13. Postmarketing Recommendations

OPQ and the Applicant agreed to product quality related post-marketing commitments to provide confirmatory data that replicates the success of the corrective action and low (b) (4) result in additional (b) (4) and final drug product batches (PMC # 3597 Confirmation of (b) (4) Content in Ivabradine Oral Solution). A validated HPLC method will be used to monitor (b) (4) content with a limit of ≤ (b) (4) µg/mL. This proposed limit was found acceptable by both the nonclinical and clinical review teams. No REMS or other postmarketing studies are required.

The text of the Amgen's proposed and accepted PMCs follows:

"Amgen proposes the following PMCs for NDA 209964 related to confirmatory testing of (b) (4) content in the (b) (4)

(b) (4)

(b) (4)

14. Recommended Comments to the Applicant

Approval is recommended with the agreed-upon PMCs described immediately above.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTIN ROSE
04/15/2019 09:18:23 AM

NORMAN L STOCKBRIDGE
04/15/2019 09:20:15 AM