Office of Clinical Pharmacology Review

NDA or BLA Number	209,964
Link to EDR	\\cdsesub1\evsprod\nda209964\0012\
Submission Date	10/25/2018
Submission Type	*Priority*
Brand Name	Corlanor
Generic Name	Ivabradine
Dosage Form and Strength	Oral solution, (b) (4) 1 mg/mL Tablet 5 and 7.5 mg
Route of Administration	Oral
Proposed Indication	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 (b) (4) (b) (4)
Applicant	Amgen, Inc.
Associated INDs/NDAs	There are no INDs associated with the NDA, because the drug was never studied under an IND in the U.S. NDA 206,143 (Adult indication)
OCP Review Team	Eliford Kitabi, Chao Liu, Sudharshan Hariharan, Martina Sahre
OCP Final Signatory	Mehul Mehta, Director, Division of Clinical Pharmacology I

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1 EXECUTIVE SUMMARY

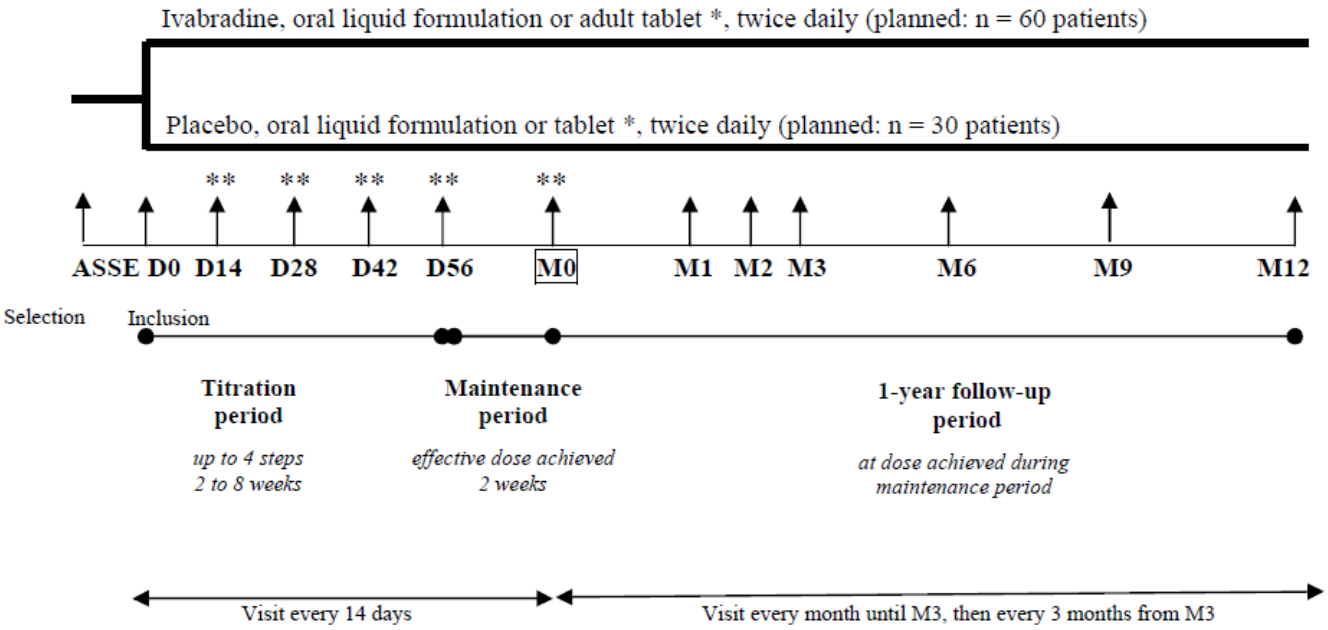
The Applicant is seeking approval of ivabradine for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients ages 6 months and older. This would make ivabradine the first drug to be approved in pediatric heart failure. The Agency had issued a Written Request (WR) in 2015, and subsequent revisions, mostly to delay the timeline in 2016, 2017, and 2018. The WR was for the assessment of effect of ivabradine on heart rate reduction in pediatric patients.

While heart failure has a different etiology in pediatric patients, compared to adults, it has been agreed upon that the similarities between the dilated cardiomyopathy population in pediatric patients and adults are sufficiently similar to allow extrapolation of efficacy from adults to pediatrics via a bridging biomarker, in this case heart rate reduction. The reason that heart rate reduction was considered a reasonably good bridging biomarker is the fact that in adults, ivabradine is understood to mediate its benefit on clinical outcomes via the reduction in heart rate. Given that this mechanism of action is not different in pediatric patients, it was agreed that heart rate reduction could be used to bridge to efficacy in the adult population, provided that the exposure/response-relationship on heart rate would be reasonably similar between adults and pediatric patients.

The sponsor submitted an NDA in December 2016; however, the Agency found the application not sufficiently complete to permit substantive review. The reason was the lack of validated processes for manufacturing and sterilization of the product, which is a sterile, aqueous, non-preserved oral solution. With the resubmission of the product in 2018, that issue was considered addressed.

The sponsor has conducted study CL2-090, which is a pharmacokinetic/pharmacodynamic (PK/PD) study in pediatric patients with dilated cardiomyopathy. The study was conducted as an international, multicenter, randomized, placebo-controlled, double-blind, parallel arm study. The primary endpoint of the trial is the proportion of patients with a reduction in heart rate of 20% for ivabradine versus placebo. A target of 20% reduction in heart rate was based on the findings of the SHIFT trial in adult heart failure patients.

Briefly, the design of the study was as shown in Figure 1. The original protocol included enrollment goals of 30 children per age groups 6-12 months, 1-3 years, and 3-18 years. These goals were later revised to 10 in the youngest age group due to difficulty with enrollment. After screening, patients were randomized 2:1 to either ivabradine or placebo, followed by a titration period from Day 0 (randomization) to Week 8. The starting and subsequent doses were based on age (Table 1), and titration of drug would occur with the goal to reach the effective dose to achieve a 20% reduction of heart rate without causing the patient to fall below heart rate thresholds established for bradycardia. After the last titration visit, patients received ivabradine for 2 more weeks, to confirm tolerability at that dose. At Month 0 (representing 2 weeks after the last up-titration), began the one-year follow-up period.



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.*

Figure 1. Study schematic
[Source: CSR CL2-090, Adapted from Figure (9.1) 1]

The primary objectives of study CL2-090 were:

(1) To determine the optimal dose of ivabradine to reach the target heart rate reduction (HRR) of 20% without inducing bradycardia (i.e. HR should be greater than a predefined HR threshold by age subset) and/or signs or symptoms related to bradycardia.
(2) To assess the pharmacokinetic (PK) parameters of ivabradine and its active metabolite S18982 after repeated oral administrations.
(3) To assess the PK/PD relationship of ivabradine and its active metabolite S18982 using heart rate as evaluation criterion.

The dosage form used in the trial was an aqueous oral solution in a 0.1, 0.5, and 1.33 mg/mL strengths, however, the final to-be-marketed form is a 1 mg/mL (total 5 mL) ampule, of same formulation. The Applicant conducted a relative bioavailability study comparing tablets to oral solution (see Section 3.2.4). The two products show similar AUC, in that the geometric mean ratio and 90% confidence interval of AUC between oral solution and tablet falls within the 80-125% bioequivalence limits. Cmax is approximately 20% higher than with tablets, and the upper 90% confidence interval is 1.3, i.e., outside of BE limits (Figure 6). However, it is sufficiently close, and the exposure-response model does not indicate such steep relationship, that this increase would be considered clinically significant.

The dosing scheme that was used for the study is shown in Table 1. Physiologically based PK (PBPK) modelling approach was used to determine the ivabradine doses to be tested in the pediatric patients.

Table 1. Titration scheme in study CL2-090

Age subsets	Initial dose (D0)	1st titration (D14)	2nd titration (D28)	3rd titration (D42)	4th titration (D56)
[6-12[months	0.02 mg/kg *b.i.d.*	0.05 mg/kg *b.i.d.*	0.10 mg/kg *b.i.d.*	0.15 mg/kg *b.i.d.*	0.20 mg/kg *b.i.d.*
[1-3[years	0.05 mg/kg *b.i.d.*	0.10 mg/kg *b.i.d.*	0.15 mg/kg *b.i.d.*	0.20 mg/kg *b.i.d.*	0.30 mg/kg *b.i.d.*
[3-18[years					
Weight < 40 kg	0.05 mg/kg *b.i.d.*	0.10 mg/kg *b.i.d.*	0.15 mg/kg *b.i.d.*	0.20 mg/kg *b.i.d.*	0.30 mg/kg *b.i.d.*
Weight ≥ 40 kg	2.5 mg* *b.i.d.*	5 mg* *b.i.d.*	7.5 mg* *b.i.d.*	10 mg* *b.i.d.*	15 mg* *b.i.d.*

*All patients received an oral liquid paediatric formulation except * in the age subset [3-18[years with a weight ≥ 40 kg, whom were to receive oral tablet formulation of ivabradine or placebo, if they were older than 6 years and able to swallow tablets.*

[Source: CSR 03-3-14-body.pdf, Table (9.4.1) 1]

The results of the study are as follows:

- In the per protocol population, the proportion of patients achieving a heart rate reduction of 20% was 71.9% (46/64) of patients in the ivabradine arm compared to 6.1% (5/31) of patients in the placebo arm. The results were reasonably similar across age groups.
- In the age group of children 6 to 12 months of age, in the PPS set, only 4 of 8 children reached target heart rate. Out of the 4 patients who responded, only 1 achieved target heart rate following the starting dose of 0.02 mg/kg, however, the patient's heart rate response returned to baseline at subsequent visit. Three of the 4 patients responded with the 3rd or 4th titration.
- In the 1- to 3-year-old patients, 14 of 20 children in the ivabradine arm reached target heart rate. Eight patients were titrated to the highest dose, while only one reached the target at the starting dose, 0.05 mg/kg.
- In children 3 to 18 years of age, achievement of target heart rate occurred more often at lower doses, including the starting doses.

The results from the younger children, particularly 6- to 12-month-old, led the review team to consider labeling a higher starting dose supported by modelling and simulations. The heart rate response was simulated for a starting dose of 0.05 mg/kg (2.5 times higher than studied in CL2-090) to assess whether there would be unacceptable reduction in heart rate predicted after the first dose. The results suggested that the likelihood of greater heart rate reductions would be higher than with a lower starting dose, but that the level of reductions would still be no lower than what is clinically manageable. Please refer to Appendix 4.3 for more details.

Moreover, the applicant's proposal for dosing in the product label attempted to provide (b) (4) Please see Appendix 4.1 for the full dosing instructions as proposed by the applicant. The resulting (b) (4) became (b) (4) . Based on a labeling comprehension study, it was found that these instructions were too complicated to allow for safe labeling. For full context on the results of the comprehension study, please refer to the review by DMEPA. Hence, the review team switched to dosing in 'mg/kg' as studied in the CL2-090.

To address the increase in starting dose for patients 6 months to 1 year of age and to reduce the complexity of the dosing recommendation proposed by the applicant, the labeling language for pediatric patients (Section 2.2. of the USPI) was therefore changed to the following:

> Section 2.2 Pediatric Patients
>
> 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.
>
> Dose Reduction for Bradycardia
>
> If bradycardia develops, reduce the dose to the previous titration step. In patients who develop bradycardia at the recommended initial dosage, consider reducing the dosage to 0.02 mg/kg twice daily.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the contents of this NDA and recommends 'approval' with a modified dosing scheme than what was proposed. The applicant is in agreement with the review team's proposal for dosing.

1.2 Post-Marketing Requirements and Commitments

None.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

This review is an abbreviated assessment of efficacy and safety in pediatric heart failure patients. For further relevant clinical pharmacology information, please see the clinical pharmacology review for the original indication (NDA 206143, DARRTS 11/26/2014 and 4/11/2014)

ADME Table (Information summarized from clinical pharmacology review for NDA 206,143)

Pharmacology	
Mechanism of Action	Ivabradine acts as an inhibitor of hyperpolarization-activated cyclic nucleotide gated (HCN)-channels. These HCN-channels are typically, but not exclusively, found in tissues that have pacemaker function. Inhibition of the I_f current leads to slower depolarization and subsequently less propagated action potentials per minute. By this mechanism the heart rate is reduced. Ivabradine effect appears to be heart rate dependent, i.e. the greater the baseline heart rate, the greater the reduction.
Active Moieties	Ivabradine inhibits the I_f current in vitro with an IC_{50} of 1.5-3 µM and the HCN4 channel with an IC_{50} of 2 µM.
QT Prolongation	Ivabradine lowers heart rate. A reduction in heart rate is typically associated with a prolongation in QT and as such ivabradine has potential liability to prolong QT or QTc. Prior to submission of the NDA, the applicant was advised that a thorough QT study was not required because the reductions in heart rate were considered potential confounders in a thorough QT (TQT) study (See Meeting Minutes for January 23, 2014, available in DARRTS NDA 206143). (b) (4) [redacted]
General Information	
Bioanalysis	Plasma samples were analyzed using a validated LC/MS/MS method. The validation results and the performance during bioanalytical sample analysis conformed to the requirements. Venous blood samples from forearm (same blood draw as used for plasma samples) and capillary blood samples from finger sticks, fixated using dried blood spot sampling, were analyzed using a validated method. The validated method performed as intended during the bioanalytical sample analysis, however, it does not conform entirely to guidance issued in 2018, because hematocrit was not taken into account for validation or analysis. Given that the study was conducted prior to 2015, we consider that this is still acceptable. Refer to Appendix 0 for details
Healthy vs. Patients	The PK parameters of ivabradine and S18982 are reasonably similar between healthy subjects and heart failure patients.

<table>
<tr><td></td><td>The observed steady-state exposures in healthy subjects with 8 mg BID dose and predicted exposures in heart failure patients in the SHIFT trial receiving 7.5 mg BID are as follows:

<table>
<tr><th>Analyte</th><th>Parameter</th><th>Healthy Subjects* (8 mg BID Capsules)</th><th>Heart Failure Patients** (7.5 mg BID tablets)</th></tr>
<tr><td>Ivabradine</td><td>AUCτ [ng*h/mL]</td><td>111 ± 56</td><td>176 ± 101</td></tr>
<tr><td></td><td>Cmax [ng/mL]</td><td>31 ± 12</td><td>35 ± 18</td></tr>
<tr><td></td><td>Cmin [ng/mL]</td><td>3.3 ± 3.1</td><td>6.1 ± 5.3</td></tr>
<tr><td>S18982</td><td>AUCτ [ng*h/mL]</td><td>43 ± 10</td><td>54 ± 17</td></tr>
<tr><td></td><td>Cmax [ng/mL]</td><td>6.8 ± 2.0</td><td>7.5 ± 2.2</td></tr>
<tr><td></td><td>Cmin [ng/mL]</td><td>2.2 ± 0.9</td><td>1.7 ± 1.0</td></tr>
</table>

*Values derived from non-compartmental analysis, **Values predicted using population PK model

[Source: Clinical Study Report NP06870 (MAD study) Appendices D and E (healthy subjects) and SHIFT PK sub study report NP30429]</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen in pediatric patients</td><td>Therapeutic exposure (AUC) at the maintenance dose was approximately 197 ng*h/mL for ivabradine and 64 ng*h/mL for S18982. 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.</td></tr>
<tr><td>Range of effective dose or exposure</td><td>In pediatric patients, the exposure to achieve the intended 20% reduction in heart rate ranged from 0.085 to 0.131 mg/kg.</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>Maximally tolerated exposure will depend on individual patient characteristics. In adults and children, the maximal dose labelled is 7.5 mg BID. A dose limiting AE is the occurrence of phosphenes, which increases by dose.</td></tr>
<tr><td>Dose Proportionality</td><td>Ivabradine has been studied over a wide dose range in healthy subjects in single (0.5 to 40 mg) and multiple (8 to 32 mg BID) ascending oral dose studies. Ivabradine AUC and Cmax were dose-linear up to 24 mg. Peak and total systemic exposures at higher doses were less than dose proportional.</td></tr>
<tr><td>Accumulation</td><td>Following repeat administration, the accumulation of ivabradine is about 40-60%.</td></tr>
<tr><td>Variability</td><td>Adults: The inter-individual variability (% CV) for ivabradine was about 20% and 55%, respectively, for AUC and C_{max} after</td></tr>
</table>

	10 mg BID dosing in healthy subjects (Study PKH-16257-001). The inter-individual variability for PK parameters (clearance and volume of distribution of the central compartment) by population PK analysis was less than 30% for ivabradine. The predicted variability for AUC_T and C_{max} for ivabradine for subjects with heart failure in the SHIFT study receiving 7.5 mg BID dose was approximately 57% and 51%, respectively. The metabolite had a CV of about 30% for both AUC_T and C_{max}. Pediatric patients: In pediatric patients weighing <40 kg (Age 6 months to 18 years), the inter-individual variability (IIV) for $AUC_{0-\infty}$ after a single dose of 0.05 mg/kg was 66% and 79% for 6-12 months old and 1-18 years old, respectively. The corresponding IIV for C_{max} was 55% and 67% for 6-12 months old and 1-18 years old, respectively. For patients weighing >40 kg, after a single 7.5 mg dose, the IIV for $AUC_{0-\infty}$ and C_{max} were 51% and 84%, respectively.
Absorption	
Bioavailability	The absolute bioavailability of ivabradine is on average 40%., which reflects a sizeable first-pass effect.
T_{max}	0.5 to 2 h
Food effect	**$AUC_{0-\infty}$** | **C_{max}** | **T_{max}** 1.42 | 1.45 | ncreased 15-45 min ollowing a high fat, high calorie meal
(Fed/fasted)	
Distribution	
Volume of Distribution	60-70 L after iv dosing; 100 L after oral dosing
Plasma Protein Binding	70%, predominantly albumin
Substrate transporter systems [*in vitro*]	S18982 is a substrate of P-gp, but not BCRP
Elimination	
Terminal Elimination half-life	Median 8.3 h
Effective Elimination half-life	6 h
Metabolism	
Fraction metabolized (% dose)	~82%
Primary metabolic pathway(s) [*in vitro*]	The major metabolizing enzyme for the generation of S18982 and other metabolites is CYP3A4.
Excretion	
Primary excretion pathways (% dose)	--Feces: 49% (4% unchanged ivabradine) --Urine: 41% (4% unchanged ivabradine)
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	Inhibition only at concentrations exceeding the clinically relevant range.
Inhibition/Induction of transporter systems	) P-gp IC50 is 5.3 µM, higher than clinically relevant concentrations) OCT2 [I]/IC50 >0.1, a DDI study with metformin was performed and did not show changes in metformin exposure

a= Pharmacokinetic parameters are presented as mean ±standard deviation (SD) or median (minimum to maximum) unless otherwise noted; b= Approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Ivabradine (tradename Corlanor) was approved by the U.S. FDA in 2015 for the reduction of risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or less, who are also in sinus rhythm with resting heart rate of 70 beats per minute or greater and on maximally tolerated doses of beta-blockers or who have a contraindication to beta-blockers.

The drug was originally developed by Les Laboratoires Servier and has been approved in Europe for the treatment of stable chronic angina and heart failure since 2005 and 2011, respectively. As part of the requirements to study drugs in the pediatric population, the European Medicines Agency (EMA) agreed on a pediatric investigation plan (PIP) with Servier, and the study that is part of this submission for pediatric heart failure, CL2-090, was conducted under this PIP by Servier. The study was conducted between December 2011 and February 2014. The Agency had issued a Written Request in 2015, and subsequent revisions, mostly to delay the timeline in 2016, 2017, and 2018. The WR was based on the assessment of effect of ivabradine in pediatric patients based on heart rate reduction.

The sponsor submitted an NDA in December 2016; however, the Agency found the application not sufficiently complete in order to permit substantive review. The reason was lack of validated processes for manufacturing and sterilization of the product, which is a sterile, aqueous, non-preserved oral solution. With the current resubmission, that issue is considered addressed.

3.2 Clinical Pharmacology Review Questions

3.2.1 Does the clinical pharmacology information provide supportive evidence of effectiveness for the proposed indication?

Mechanistic basis

Ivabradine works by selectively blocking the activation of the hyperpolarization-activated cyclic-nucleotide-gated ion channel (HCN) present in cardiac muscles. These cyclic-nucleotide-voltage gated cation channels help to generate rhythmic activity of the cardiac cells that leads to rhythmic heart beats. Under normal physiological conditions the channels are activated by hyperpolarization of cardiac cell membranes at voltages of ~ – 50 mV. At these negative (hyperpolarization) voltages, cyclic Adenosine-Monophosphate (cAMP) or cyclic Guanosine-Monophosphate (cGMP) directly bind and activate the HCN channels causing depolarization of the membrane to positive voltages thereby enhance the activity of the channels. Depolarization of the cardiac cell membranes generates currents which are responsible for generation and modulation of the rhythmic heart-beat. Such currents are commonly referred to as pacemaker currents (e.g. I_f, I_h). Blocking of HCN channels by ivabradine leads to decrease in pacemaker I_f currents and thereby reduction in heart rate.

Pediatric dilated cardiomyopathy is characterized by tachycardia which is one of the etiologies of left ventricular dysfunction and consequent heart failure. Both observation and interventional clinical studies have demonstrated association between tachycardia and cardiovascular complication in adult patients with heart-failure. Pediatric patients with dilated cardiomyopathy (DCM) have high resting heart rate compared to age-matched healthy subjects. Therefore, it may be reasonable to expect that reduction of heart rate with ivabradine treatment can help to avert adverse cardiovascular complications associated with DCM.

Dose-response in adults

Data from ivabradine dose-response studies in patients (phase 2 and 3 clinical studies) indicated decrease in heart rate with increasing ivabradine dose. However, the increment of heart rate reduction became increasingly smaller at higher doses indicating that heart rate reductions reaches a plateau at high doses (maximum effect dose-response relationship). Figure 2 shows the dose-versus-heart rate reduction for ivabradine in adult patients. This dose-response relationship is consistent with the mechanism of action of ivabradine, whereby even at complete blockage of I_f currents pacemaker activity is not abolished as it is maintained by other currents (e.g. I_h) involved in the generation of cardiac pacemaker activity.

The magnitude of heart rate reduction by ivabradine is proportional to baseline heart rate. Subjects with high baseline heart rate experience higher heart rate reduction compared to subjects with low heart rate. Substantial heart rate reduction is apparent within 24 hours of treatment and steady state is reached at the third day. No pharmacological tolerance has been observed in long term studies. Upon stopping treatment, heart rate returns rapidly to baseline values without rebound phenomenon.

Population pharmacokinetic/pharmacodynamic (PK/PD) modeling of heart rate versus plasma concentration of ivabradine and its active metabolite provide supportive evidence of effectiveness of ivabradine for reduction of heart rate. The population PK/PD analysis estimated the maximum effect exposure-response relationship between active moieties (ivabradine and N-demethylated metabolite) and magnitude of heart rate reduction. The model estimated maximum heart rate reduction for a typical patient was 42%. Concentrations of ivabradine and its metabolite at which half of maximum heart rate reduction is achieved for a typical patient (EC50) were estimated to be 41 ng/mL and 29 ng/mL, respectively. The model estimated interindividual variability in E_{max} (IIV) was 26%. Equation 1 shows the PK/PD model. Other pharmacodynamic model parameters are given in Figure 3.

Equation 1. Exposure-versus-heart rate relationship for ivabradine and its active metabolite

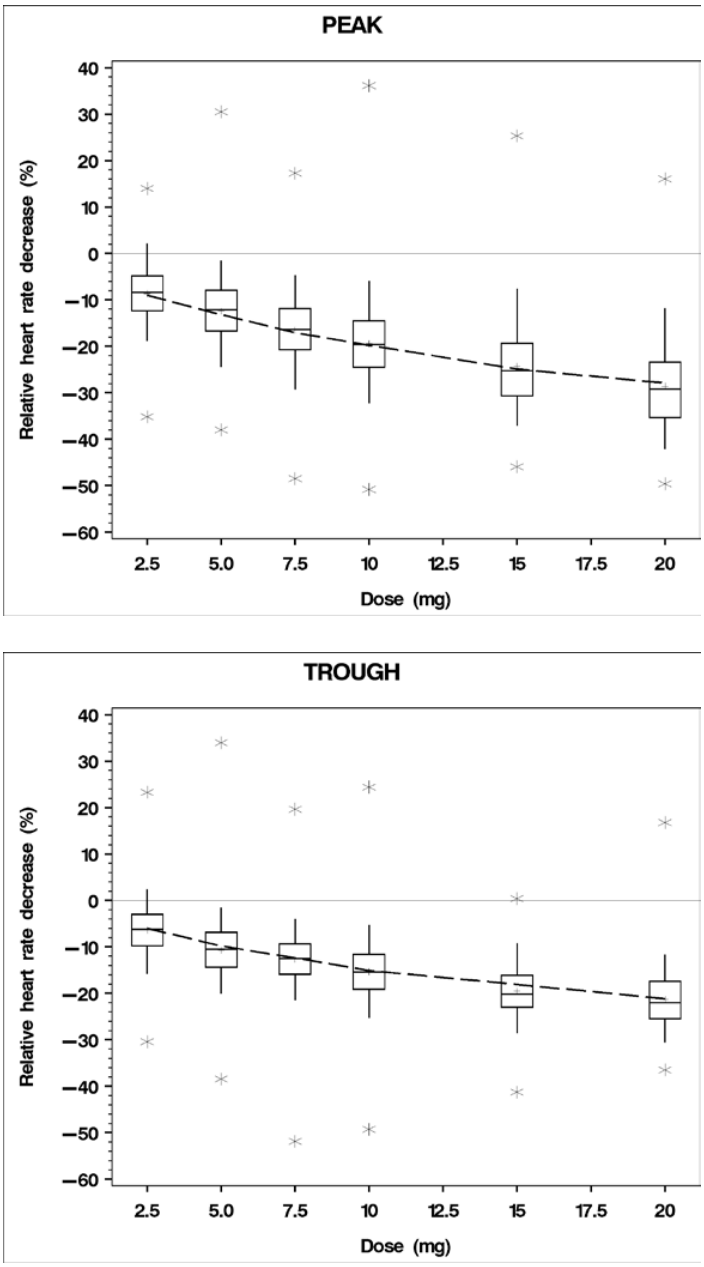
$$NUM = \frac{ivabradine}{EC50D} + \frac{metabolite}{EC50M}$$

$$DEN = 1 + NUM$$

$$DRUG\ EFFECT = EMAX \times \frac{NUM}{DEN}$$

$$Heart\ rate = Baseline\ Heart\ rate\ \times (1 - DRUG\ EFFECT)$$

Among the investigated demographic, clinical and laboratory characteristics, none of the covariates was identified to have major influence on the population pharmacodynamic (PD) parameters. The investigated covariates included: sex, age, body weight, body mass index, body surface area, serum creatinine level, creatinine clearance, diabetes status, or concomitant treatments.



HR decrease was calculated from observed HR data after treatment administration compared to HR data without treatment at the same time (obtained as an individual prediction from the model) and was expressed as a percentage. Stars represent minimum and maximum HR decrease observed at each dose. "Plus" symbols refer to the mean HR decrease observed at each dose. The dashed line joins mean HR decrease calculated from the individual predictions of the model. Doses refer to single dose in the CL2-16257-006 study and multiple doses (b.i.d., steady-state) in the other studies.

Figure 2. Dose-heart rate reduction for ivabradine in adult heart failure patients.

SOURCE: Clinical study report NP32761 (Page 110), submitted in 0017(22) section 5.3.3.5. File name: np32761.pdf
Link: \\cdsesub1\evsprod\nda206143\0017\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\np32761\np32761.pdf

Model parameter (unit)			Estimate	SE estimate	RSE (%)	95 % CI	
						Lower	Upper
Base*	**(bpm)**	**Male**	71	0.38	0.53	70	71
		Female	76	0.95	1.3	74	78
Age on Base**			- 0.0024	0.00053	22	0.0013	0.0034
Shift***		**Bicycle**	1.04	0.0039	0.38	1.03	1.05
		Treadmill	1.14	0.010	0.89	1.12	1.16
Bicycle Slope	**(bpm/watt)**	**Male**	0.48	0.0052	1.1	0.47	0.49
		Female	0.67	0.022	3.3	0.62	0.71
Treadmill Slope	**(bpm/step)**		11	0.20	1.7	11	12
k_{e0}D	**(1/h)**		0.24	0.037	15	0.17	0.32
k_{e0}M	**(1/h)**		0.048	0.014	30	0.019	0.076
E_{max}	**(%)**		42	3.2	7.6	35	48
EC_{50}D	**(ng/mL)**		41	7.4	18	26	55
EC_{50}M	**(ng/mL**		29	7.0	24	15	43

	Magnitude of interindividual variability					
	Estimate	SE estimate	RSE (%)	Interindividual variability	95 % CI	
					Lower	Upper
Base*	0.017	0.0008	4.8	13	12	13
Shift***	0.0077	0.0005	6.5	8.8	8.2	9.3
Slope	0.068	0.0035	5.1	26	25	27
E_{max}	0.070	0.014	21	26	20	31
k_{e0}D	2.1	0.41	19	146	115	171

	Magnitude of interoccasion variability					
	Estimate	SE estimate	RSE (%)	Interindividual variability	95 % CI	
					Lower	Upper
Base*	0.0070	0.00030	4.3	8.3	8.0	8.7
Slope	0.011	0.00074	6.6	11	9.9	11

	Magnitude of residual variability				
	Estimate	SE estimate	RSE (%)	95 % CI	
				Lower	Upper

Figure 3. Parameter estimates of the population PK/PD model from adult phase 2/3 clinical studies

SOURCE: Clinical study report NP32761 (page 90), submitted in 0017(22) section 5.3.3.5. File name: np32761.pdf Link: \\cdsesub1\evsprod\nda206143\0017\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\np32761\np32761.pdf

Efficacy of ivabradine in pediatric patients

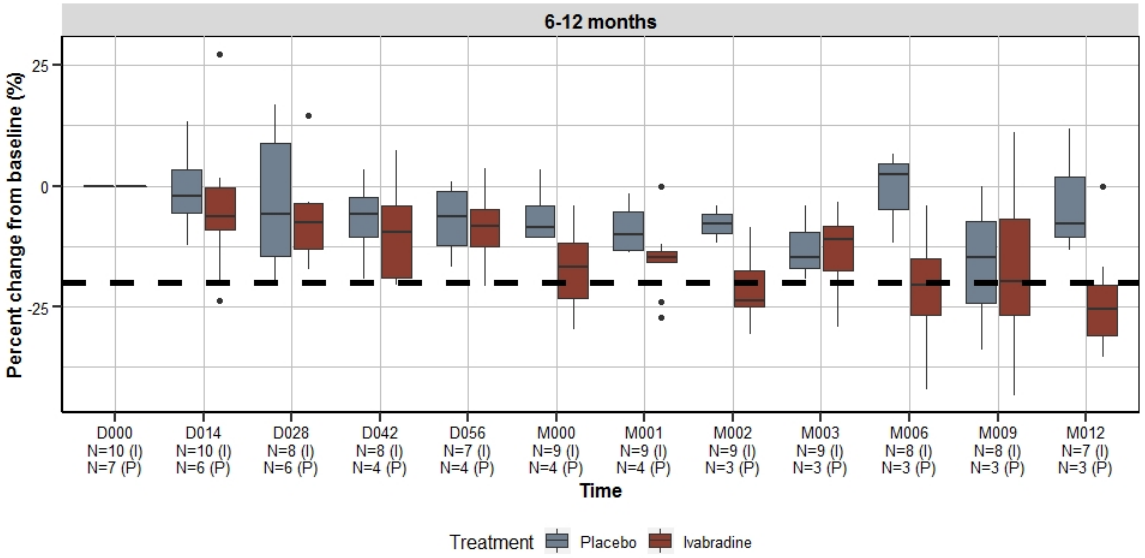
Pivotal evidence of effectiveness of ivabradine in reducing heart rate was provided by a placebo controlled clinical trial in pediatric (6 months to 18 years) patients with heart failure due to dilated cardiomyopathy. In this randomized clinical trial, patients randomized to ivabradine treatment received ivabradine in addition to optimal treatment for chronic heart failure. Patients randomized to placebo received optimal treatment alone. Ivabradine dosing was based on age and body weight as indicated in Table 2.

Table 2. Twice Daily Dosing of Ivabradine or Matching Placebo in Pediatric Subjects in Study CL2-090

Class	Age	Initial Dose	Titration 1	Titration 2	Titration 3	Titration 4
1	6 to 12 months	0.02 mg/kg	0.05 mg/kg	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg
2	1 to <3 years	0.05 mg/kg	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	0.30 mg/kg
3	3 to <18 years; <40 kg	0.05 mg/kg	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	0.30 mg/kg
4	3 to <18 years; ≥40 kg	2.5 mg	5 mg	7.5 mg	10 mg	15 mg

[a] After 2 weeks of treatment, the dose was adapted (up-titrated, maintained, or down-titrated) based on the goal of 20% HRR versus baseline HR. If the lowest dose was not tolerated because of reduction of HR below the predefined threshold and/or symptoms and signs related to bradycardia, the medication was stopped. Note: All subjects received an oral liquid formulation except those in Group 4 who were able to swallow tablets and older than 6 years.
Source: Table (9.4.1) 1 from CL2-090 CSR (NP33304).

The study demonstrated significant heart rate reduction over-time among patients randomized to ivabradine treatment compared to placebo. Figure 4 shows heart rate reduction over-time in ivabradine and placebo treatment groups.



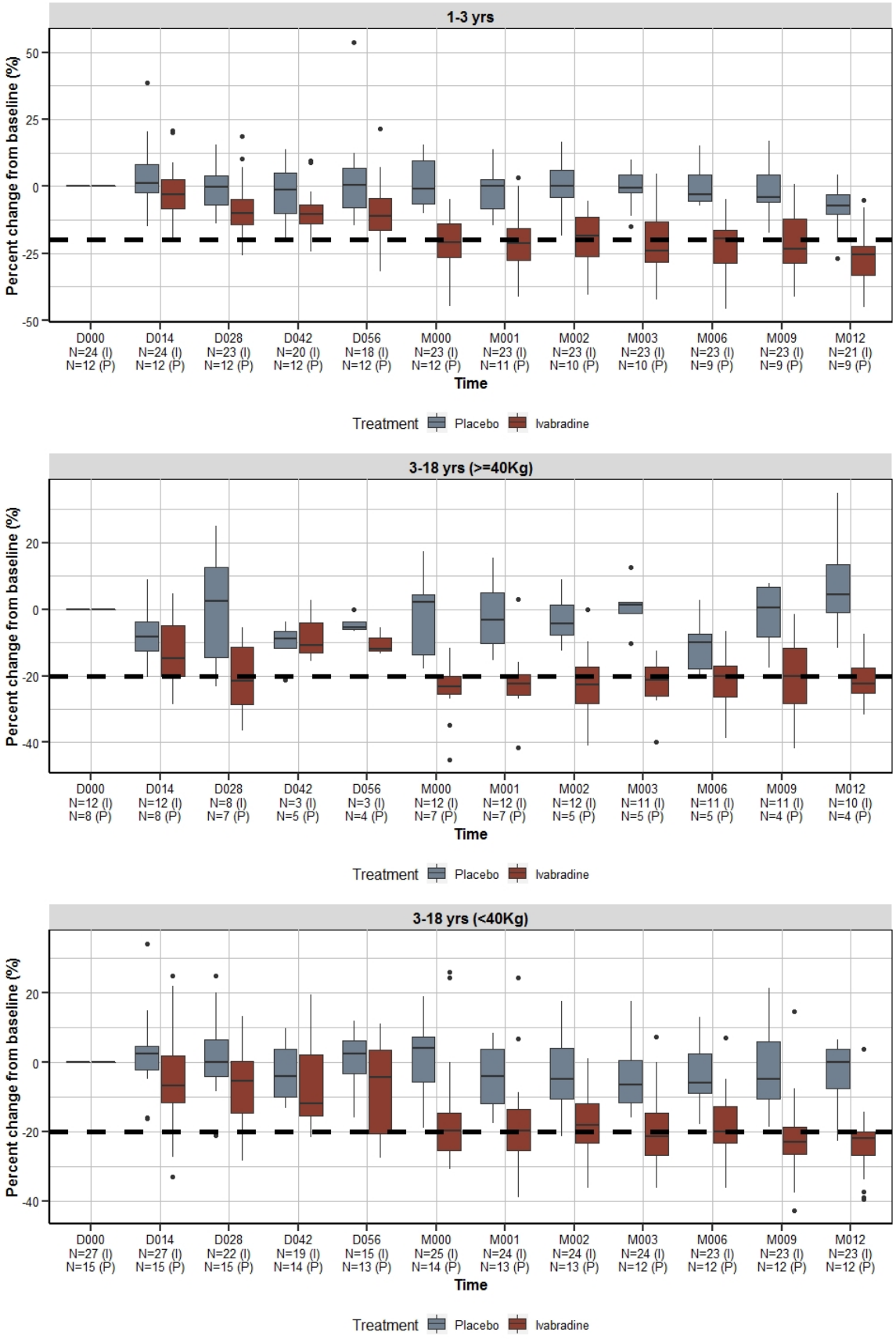
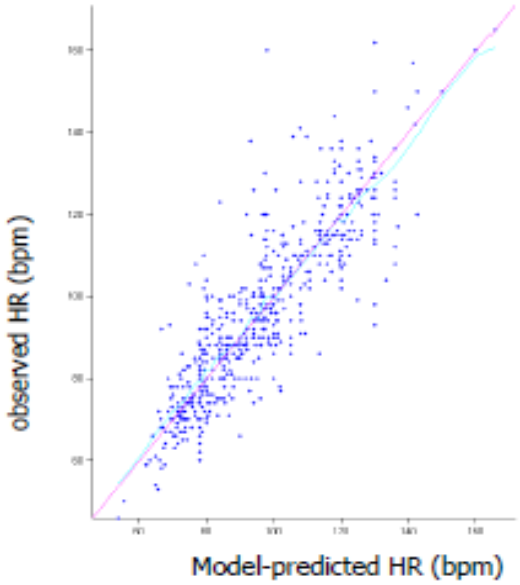


Figure 4. Percent heart rate reduction over-time in ivabradine and placebo treatment groups. DXXX = Day of treatment e.g. D000 = Day 0. M000 = 70 days after treatment. MXXX = Months after the last scheduled titration day (day 56), e.g. M001 = One month after day 56. Source: Reviewer's independent analysis.

Exposure-response in pediatric patients

The applicant conducted a population pharmacokinetic/pharmacodynamic analysis using the population pharmacodynamic model developed in adult patient population. Data for the PK/PD analysis were plasma and blood concentration of ivabradine and its N-demethylated metabolite and the corresponding heart rate data obtained prior to each blood sampling. Up to 5 PK samples were collected from each pediatric subject; 2 samples (1 hour and 2 hours post-dose) on day 13, 2 samples on day 14 (pre-dose and 4 hours post-dose), and 1 sample 2 to 8 weeks after day 14 (7 hours post-dose). The resting HR measurements were performed at baseline and systematically measured just before each PK sampling (i.e., up to 5 measurements per subject).

The population pharmacodynamic parameters estimated using adult data were able to predict adequately the heart rate data observed in pediatric subjects. For this reason, the applicant did not perform any further PD parameter estimation using pediatric data. This implies that the exposure response for heart rate reduction is similar between adult and pediatric patient population. Figure 5 shows the goodness of fit between the predicted and observed heart rate data in pediatric subjects.



Bpm = beats per minute; DCM = dilated cardiomyopa hy; HR = heart rate; PD = pharmacodynamics; PK = pharmacokine ic.
Source: Modified from Figure 48 from Study CL2-090.

Figure 5. Predicted versus observed heart rate in pediatric subjects with DCM

Source: Summary of clinical pharmacology studies. Submitted in 0012(14)
Link: \\cdsesub1\evsprod\nda209964\0012\m2\27-clin-sum\summary-clin-pharm.pdf

3.2.2 Is the proposed general dosing regimen appropriate?

No. The applicant's proposed dosing is complex and difficult to implement. This conclusion is supported by results from a human factor study that was conducted to assess if the applicant's proposed dosing as presented in the product label could support safe and correct dosing of ivabradine in the context of intended use by the intended user groups. In general, results from the study showed that physicians did not always prescribe the correct dose, the pharmacists did not always dispense the correct dose and caregivers did not always implement the dosing instructions correctly. The following sections describe the applicant's proposed dosing scheme and an alternative dosing scheme recommended by the reviewer team.

Applicant's Proposal

(b) (4)

Review Team's proposal

Because the applicant proposed dosing was not supported by the human factor study, the review team considered the dosing scheme in 'mg/kg' implemented in trial CL2-090 as a starting point for safe and effective labeling. For pediatric patients > 1 y of age and weighing < 40 kg, the review team recommends labeling as studied in the clinical trial. These patients were adequately represented in the clinical trial and their heart rate response to the dosing algorithm implemented in the clinical trial seem

acceptable as shown in Table 4. Starting dose for this age and weight group is 0.05 mg/kg. Based on heart rate dose can be increased by 0.05 mg/kg increments every 2 weeks until target heart rate reduction of 20% is achieved. The maximum dose in this age group is 0.3 mg/kg. (b) (4) However, in the very young patients i.e., 6 to 12 months of age, the heart rate response following the starting/initial dose(s), as observed in the clinical trial, is low (Table 4). Therefore, the starting dose in the youngest age group has been revised to 0.05 mg/kg. This starting dose is also supported by modeling and simulation as it eliminates a potentially subtherapeutic dose and help patients achieve the target sooner. It also shows that there is no additional risk incurred with increasing the starting dose than studied. In this age group dose can be increased by 0.05 mg/kg based on heart rate reduction until a maximum dose of 0.2 mg/kg is reached.

Table 4. Number of patients in the ivabradine group reaching target heart rate reduction for each titration step (PPS dataset)

Age groups	No. of responders					Cumulative responders n (%)
6-12 mon (n=8)	0.02 mg/kg	0.05 mg/kg	0.1 mg/kg	0.15 mg/kg	0.2 mg/kg	
	1	0	0	1	2	4 (50%)
	0.05 mg/kg	0.1 mg/kg	0.15 mg/kg	0.2 mg/kg	0.3 mg/kg	
1-3 y (n=20)	1	3	1	1	8	14 (70%)
3-18 y, <40 kg (n=24)	4	3	3	5	2	17 (71%)
3-18 y, >40 kg (n=12)	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	
	4	5	0	0	2	11 (92%)

Details of the proposed dosing by the reviewing team is provided in Appendix 4.2. Results from modeling and simulations that supports this dosing scheme are provided in Appendix 4.3.

3.2.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes. Population pharmacokinetic analysis of ivabradine and its active metabolite identified age and body weight to be clinically meaningful covariates. Age was identified as a covariate on ivabradine metabolic clearance while body weight was a covariate on clearance (total clearance and inter-compartment clearance) and volume (central and peripheral volume of distribution) parameters. As described in Section 3.2.2. ivabradine should be dosed based on age and body weight. No other intrinsic factor was identified to guide further dose individualization. Details of pharmacokinetic model development and validation by the applicant is given in Appendix 4.4

3.2.4 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The applicant conducted a two-period, two-sequence, cross-over study comparing the relative bioavailability of a 7.5 mg tablet to 7.5 mL of a 1 mg/mL oral solution. The study population consisted of 24 (12 per group) healthy males, aged 18 to 53 years old.

Tablets were administered with 150 mL of non-carbonated water, and oral solution was administered in 150 mL of non-carbonated water and drunk.

The bioanalytical method was validated prior to sample analysis and performed within limits required by guidance.

The results are shown in Table 5.

Table 5. Mean (SD, or range) pharmacokinetic results from Study PKH-086 (Relative BA Tablets to Oral Solution)

PK Parameter	Tablet		Oral Solution	
	Ivabradine	S18982	Ivabradine	S18982
Cmax (ng/mL)	23 (7.1)	3.9 (0.91)	20 (7.6)	3.3 (0.99)
AUClast (ng*h/mL)	83 (29)	26 (7.8)	85 (37)	25 (10)
AUCinf (ng*h/mL)	86 (30)	35 (7.8)	88 (38)	37 (15)
Tmax (h)	1.5 [0.5-2.5]	1.5 [1.0-3.0]	1.8 [1.0-3.0]	2.0 [0.5-3.0]
Tlag (h)	0.13 [0-0.5]	0.25 [0-0.5]	0 [0-0.25]	0 [0-0.25]
Tlast (h)	12 [12-24]	24 [12-24]	12 [12-24]	24 [12-24]
t1/2,z (h)	2.8 (0.72)	9.3 [2.4]	2.6 (0.68)	9.1 (2.8)

The applicant calculated the relative bioavailability as follows:

$$F_{rel} = \frac{AUC_{test} * Dose_{ref}}{AUC_{ref} * Dose_{test}} * 100$$

The calculated Frel [%] is 101 (18.3), with a range from 62.6-145%. It is unclear whether values were log-transformed for analysis. The values were recalculated according to typical analysis standards for relative BA studies. Results are depicted in Figure 7.

The oral solution meets BE criteria for AUC, but not for Cmax. Given that a tablet formulation was compared to an oral solution, it is not surprising that Cmax is higher for the oral solution. However, given that the point estimate remains within the 80-125% range and that the upper 90% CI was about 1.3, together with the fact that the exposure-response relationship does not suggest steep heart rate response that this Cmax would lead to drastically more heart rate reduction, this finding is likely not clinically significant.

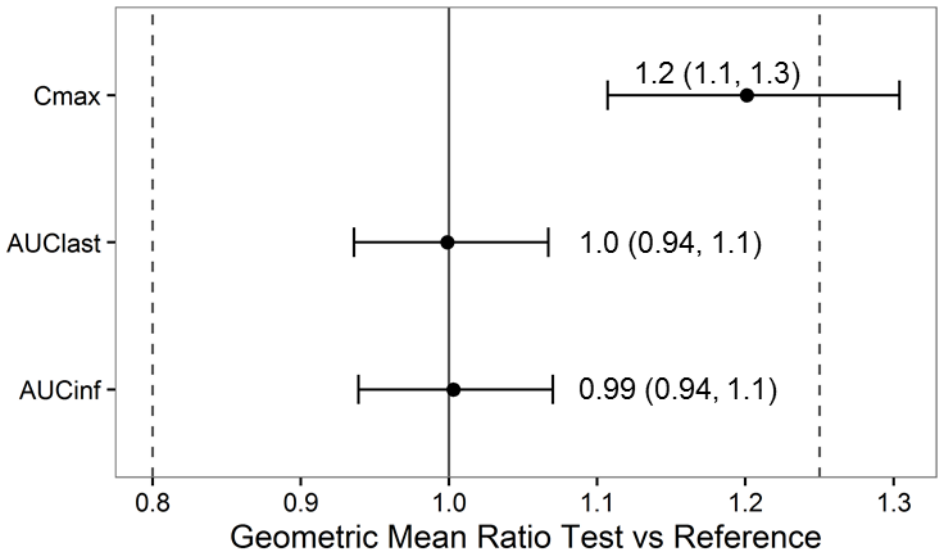


Figure 6. Forest plot of geometric mean ratios and 90% CI [Source: Reviewer's analysis CSR PKH-086]

4 APPENDICES

4.1 Applicant's proposed dosing scheme for pediatric patients

Corlanor is supplied for use as an oral solution or as tablets to be taken twice daily with meals. Tablets are administered to patients weighing 40 kg and greater and who are able to swallow tablets; otherwise they should receive the oral solution.

Pediatric patients are titrated to achieve a heart rate reduction of at least 20% from baseline and based on tolerability. (b) (4)

(b) (4)

Oral Solution

Corlanor oral solution is provided in single-use, 5 mL ampules (b) (4)

(b) (4)

Corlanor 5 mg/5 mL (1 mg/mL)

(b) (4)

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Oral Solution Preparation and Administration

To administer Corlanor oral solution, empty the entire contents of the ampule(s) into a medication cup. [redacted] Do not store or reuse any solution left in either the medication cup or the ampul [redacted]

Tablets for Pediatric Use

[redacted] 2.5 mg twice daily. Assess patient [redacted] and adjust dose by 2.5 mg [redacted] to target a heart rate (HR) reduction of at least 20% based on tolerability. The maximum dose is 7.5 mg twice daily. [redacted]

4.2 Review Team proposed dosing scheme for pediatric patients

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 (b) (4)

Oral Solution Preparation and Administration.

To administer Corlanor oral solution, empty the entire contents of the ampule(s) into a medication cup. With a calibrated oral syringe, measure the prescribed dose of Corlanor from the medication cup. (b) (4) Do not store or reuse any oral solution left in either the medication cup or the ampule (b) (4)

Dose Reduction for Bradycardia

If bradycardia develops, reduce the dose to the previous titration step. In patients who develop bradycardia at the recommended initial dosage, consider reducing the dosage to 0.02 mg/kg twice daily.

4.3 Optimization of Ivabradine Pediatric Dose Titration Scheme

4.3.1 Introduction

Ivabradine dosing-scheme implemented during the pediatric clinical trial offers a good benchmark on which pediatric dosing of ivabradine can be optimized. The pediatric clinical trial dosing of ivabradine was based on body-weight (Table 2). In general, the pediatric clinical-trial titration scheme resulted in greater reduction of heart rate over-time in the ivabradine group compared to placebo group. However, in the ivabradine group, only one subject of the subgroup with age younger than 1 year had showed response at the initial dose (0.02 mg/kg) and all other responders in that subgroup did not show response until reaching the highest dose level (0.2 mg/kg) This delay in achieving target indicates the needing for a higher but safe starting dose in the younger subjects compared to the starting dose utilized in the clinical trial.

After reviewing the applicant's suggested dosing scheme and the entailed difficulties it presented to prescribers, dispensers and caregivers the reviewers decided to conduct a dosing scheme optimization. Optimization aimed to obtain a dosing scheme that: (1) is easy to implement (prescribe, dispense and administer) (2) Provide early treatment success with low risk for bradycardia (3) and can be implemented using the available drug formulation.

4.3.2 Methods

Heart rate reduction was simulated for different starting doses with the aim of choosing a scheme that improved heart rate response but at an in acceptable frequency/probability of bradycardia over-time. The following steps were followed: (1) First, the ability of the population PK/PD model to regenerate heart rate data observed in the pediatric clinical trial was checked; (2) Second, for each tested dosing scheme, heart rate data was simulated as would be observed in a sample of patients. This simulation was repeated 200 times to generate heart rate data for 200 population samples. For each population sample, proportions of treatment success (20% hear-rate reduction by 70^{th} day of treatment) and number of bradycardia events (frequencies/probability) throughout the treatment period were determined. The median probability and 95% prediction intervals for treatment success and bradycardia were determined from the results of the 200 samples.

4.3.3 Results

4.3.3.1 Validity of the simulation model

The ivabradine population PKPD model was able to simulate heart rate data that were reasonably similar to those observed in the clinical trial. Figure 7 shows the observed and simulated percent heart rate reduction over-time.

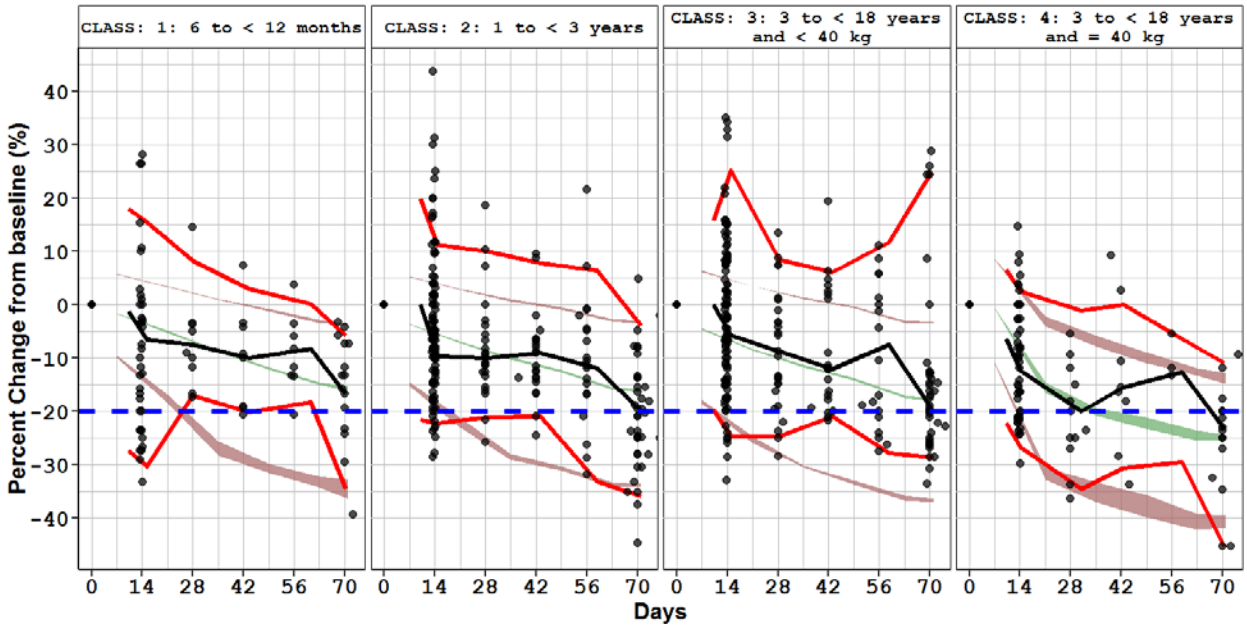

Figure 7. Observed and predicted percent heart rate change from baseline over-time.

Black points = observed data, black solid line = median of the observed data, red solid lines = 5th and 95th percentiles of the observed data. Green shaded area = Prediction interval of the median for simulated data. Brown shaded areas = prediction interval for 5th and 95th percentiles of the simulated data.

4.3.3.2 Ivabradine titration scheme for pediatrics 6 – 12 months old

The probability of treatment success (20% heart rate reduction by day 70) and bradycardia (any heart rate below bradycardia threshold over-time) for selected ivabradine dose titration schemes for pediatric patients 6-12 months old are shown in Table 9. All the dosing schemes had the maximum dose of 0.2 mg/kg and therefore the probability of treatment success was same for all the tested dosing schemes on Day 70. The probability of bradycardia for the titration schemes in Table 9 was very small (around 1.5%) and comparable between them. The titration scheme with starting dose at 0.05 mg/kg, dose increments of 0.05 mg/kg every 14 days, and maximum dose of 0.2 mg/kg was selected to provide a balance between achieving treatment response earlier without increasing the risk for bradycardia for highly sensitive subjects. It should be noted that the model does not account for potential inter-individual variability in ivabradine treatment response i.e., heart rate reduction.

Table 9. Probability of treatment success and bradycardia for different dose titration schemes

TITRATION SCHEMES	CANDIDATE DOSING SCHEMES				SUCCESSFUL SUBJECTS	
	START DOSE	END DOSE	INCREMENTS	NUMBER OF STEPS	SUCCESS PROBABILITY (95% CI)	BRADYCARDIA PROBABILITY (95% CI)
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)

Figure 8 shows progressive reduction of heart rate overtime for the selected dosing schemes in pediatrics 6-12 months old. The figure shows that for the responder subjects, alternative dosing schemes provide earlier treatment success compared to clinical trial dose titration protocol.

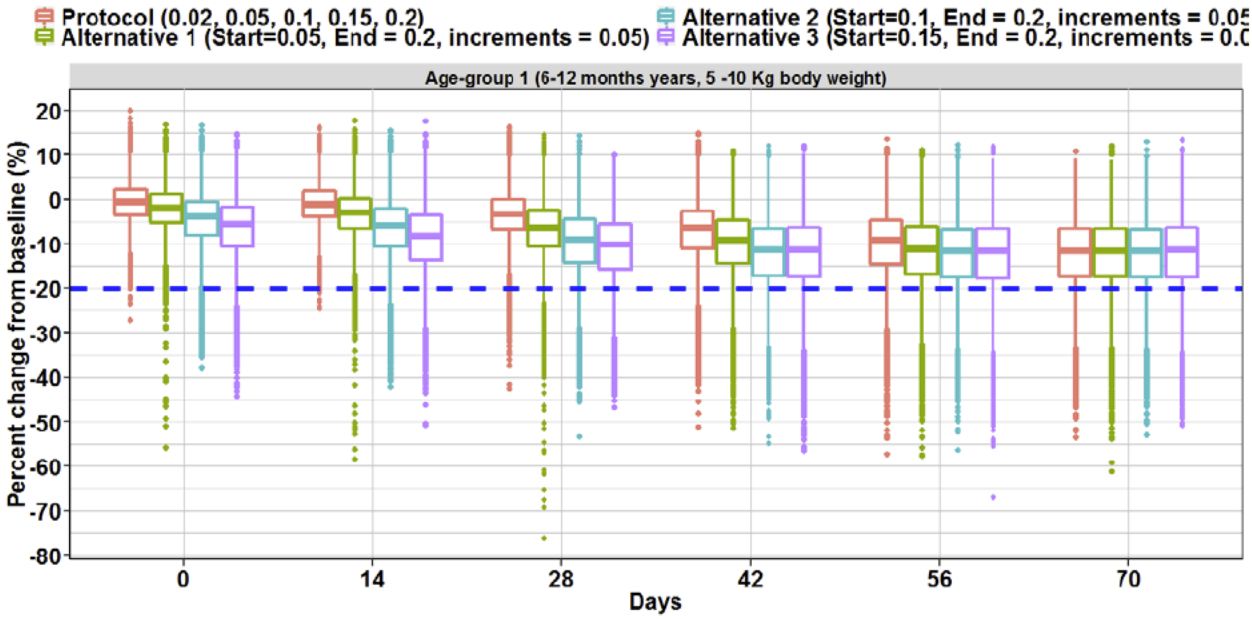

Figure 8. Simulated percent heart rate change from baseline over-time after ivabradine treatment using selected ivabradine dose titration schemes.

Blue-dashed line = 20% reduction in heart rate (Cut-off for response)

4.3.3.3 Monitoring window for bradycardia after each dose titration step

Initiation of ivabradine treatment and upward dose titrations could result in bradycardia due to accumulation of ivabradine at the effect site. This is of concern for subjects with greater accumulation factor and longer effective half-life of ivabradine. Tables 10 and 11 show the accumulation factors and effective half-life for subjects who participated in the clinical trial and the simulated subjects, respectively. Tables 10 and 11 show that some subjects may have up to 2-fold accumulation of ivabradine exposure at steady state compared to exposure after single dose. For these subjects the maximum exposure will be reached after a minimum of 2 – 3 days. Therefore, subjects undergoing initiation of ivabradine treatment or upward dose titration should be observed for bradycardia for a minimum period of 3 days.

Table 10. Accumulation factor and effective half-life for trial subjects based on post-hoc pharmacokinetic parameters (Empirical Bayes Estimates)

BASED ON POSTHOC PK PARAMETERS												
PARAMETERS	MEAN	SD	CV	GEO MEAN	GEO CV	MEDIAN	QT5	LIQR	UIQR	QT95	MIN	MAX
Effective half-life	5.3	3.5	66.0	-	-	4.6	0.0	3.5	6.4	11.2	0.0	21.4
Accumulation factor	1.3	0.4	27.1	1.3	21.6	1.2	1.0	1.1	1.4	1.9	1.0	3.1

Table 11. Accumulation factor and effective half-life for trial subjects based on stochastic simulation of pharmacokinetic parameters

BASED ON SIMULATED PK PARAMETERS												
PARAMETERS	MEAN	SD	CV	GEO MEAN	GEO CV	MEDIAN	QT5	LIQR	UIQR	QT95	MIN	MAX
Effective half-life	5.8	4.2	73.1	-	-	4.6	3.5	3.5	6.6	13.7	0.0	28.9
Accumulation factor	1.3	0.5	33.8	1.3	25.5	1.2	1.1	1.1	1.4	2.2	1.0	4.0

4.4 Population pharmacokinetic model development and validation

4.4.1 Methods

4.4.1.1 Data

Data for pharmacokinetic modeling were obtained from the pivotal study in pediatric subjects that aimed to determine efficacious and safe dose of ivabradine. In this study 73 and 43 subjects were randomly assigned to ivabradine and placebo treatments respectively. All subjects receive optimal background treatment for heart failure. Ivabradine or placebo dosing scheme is provided in Table 1.

For each patient, 5 sparse pharmacokinetic samples were collected in the following manner:

Table 12. Pharmacokinetic sampling scheme

SN	Day after starting treatment	Time after Dose	Remarks
1	13	1 hour	Dried blood spot (DBS) sample collected one hour after evening drug intake
2	13	2 hours	DBS sample collected 2 hours after evening drug intake
3	14	11 hours	DBS sample taken within 1 hour before drug intake
4	14	4 hours	DBS sample collected 4 hours after drug intake
5	28 – 70	7±1 hour	Plasma and DBS sample collected 7±1 hour after morning drug intake.

DBS samples on day 13 and 14 were collected from finger stick (capillary) or forearm (whole blood) venipuncture. For everyone, the same site of blood collection was used to collect all 4 blood samples. For the fifth PK sample, both plasma and DBS samples were collected at the same time between day 28 – 70. For subjects whose DBS samples were collected from finger stick on day 13 and 14, the fifth PK samples consisted of one plasma and one DBS sample from forearm venipuncture, and one DBS sample from finger stick. For subjects whose DBS samples were from forearm on day 13 and 14, the fifth PK samples were one plasma and one DBS sample from forearm.

The collected plasma and DBS samples were analyzed using validated HPLC methods to quantify plasma and blood concentrations of ivabradine and its active metabolite. Concentrations below the limit of quantification were considered left censored and therefore considered in the population PK analysis.

For each subject, demographic, clinical, laboratory, medication history, and concomitant medication information were collected and analyzed to assess intrinsic and extrinsic factors affecting PK parameters.

4.4.1.2 Population pharmacokinetic analysis

The applicant developed the population pharmacokinetic model using MONOLIX version 4.2.2. Model parameters were estimated using Stochastic Approximation Expectation Maximization Algorithm (SAEM). Objective function values (OFV) computed using importance sampling (IMP) algorithm were used for likelihood ratio test (LRT) comparisons of hierarchical models. Non-nested models were compared using Bayesian Information criteria (BIC) computed from OFV. Model selection was also based on goodness-of-fit (GOF) plots, individual fits and precision of parameter estimates.

The applicant made the following assumptions when developing the population pharmacokinetic model:

1. Assumed equal bioavailability between liquid and tablet formulation in pediatric population. This was based on data from study performed in adult population which demonstrated equal bioavailability between oral and tablet formulation.
2. Assumed ivabradine and its metabolite to have the same molecular weight.
3. Assumed that values of PK parameters estimated using plasma concentration data are comparable to those computed using blood concentration data.
4. Assumed that ivabradine undergoes dual absorption pathways. The first pathway is direct absorption of ivabradine to the systemic circulation. In the second pathway, ivabradine is completely metabolized to its active metabolite (N-des-methylated metabolite) which is subsequently absorbed to the systemic circulation.
5. Assumed that the directly absorbed ivabradine is eliminated by renal and metabolic pathway to its active metabolite.
6. Assumed the same values of bioavailability of both ivabradine and its metabolite in pediatric population as in the adult population.
7. Assumed that the volume of distribution of the metabolite was equal to the sum of central and peripheral volume of distributions of its parent drug (ivabradine).
8. Assumed first order absorption process for both ivabradine and its metabolite, without lag time.

Figure 9 shows the schematic diagram of the final structural model for disposition of ivabradine and its metabolite.

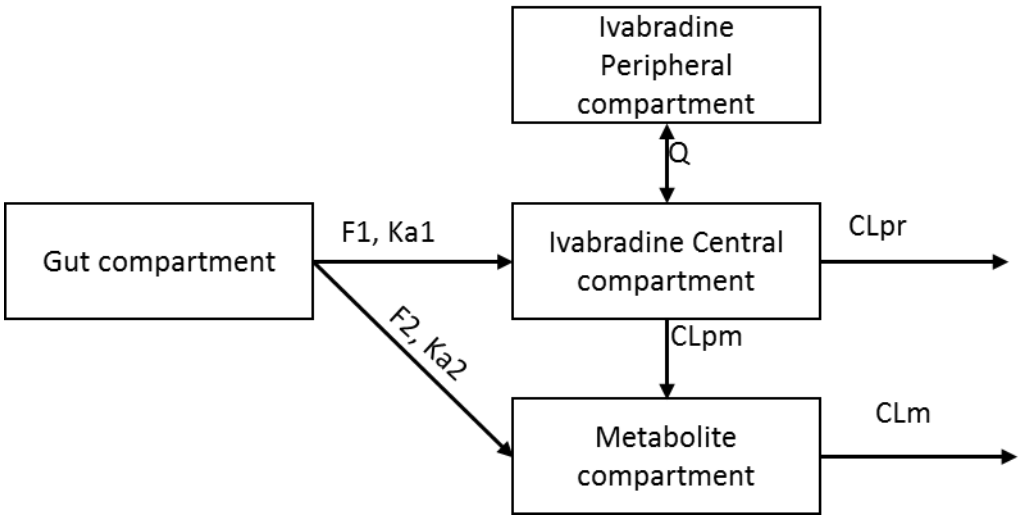

Figure 9. Structural model for ivabradine absorption, distribution and elimination. F1 = bioavailability for ivabradine; Ka1 = absorption rate constant for ivabradine; F2 = bioavailability for metabolite; Ka2 = absorption rate constant for metabolite; CLpm = ivabradine metabolic clearance; CLpr = Ivabradine renal clearance, CLm =metabolite clearance; Q = ivabradine inter-compartment clearance.

Inter-individual variability was investigated on every model parameter and was deleted in case on not acceptable precision (High residual standard error) or if the variance was close to the value of 0. Residual error was considered as a random variable and described discrepancies between model predictions and observed data.

Potential covariates were investigated through exploration of relationships between model empirical Bayes estimates and patients' characteristics. Potential covariates were subsequently incorporated into the model.

4.4.2 Results

The values of parameters estimated from the final population pharmacokinetic model are given in Table 13. The influence of weight on disposition parameters was modeled through allometric scaling based on prior knowledge. Equation 1 shows the relationship between weight and ivabradine disposition parameters. The effect of age on renal and metabolic clearance of ivabradine and renal clearance of metabolite was modelled using a maturation function as shown in Equation 2.

Equation 2. Allometric scaling of disposition parameters by body weight. θ_i=disposition parameter for individual i; θ_{TV}=typical population value of a disposition parameter; θ_{WT}=effect of body weight, fixed to 0.75 for clearance and 1 for volume

$$\theta_i = \theta_{TV} \left(\frac{WT_i}{WT_{TV}}\right)^{\theta_{WT}}$$

Equation 3. Maturation function for renal and metabolic clearance for ivabradine and renal clearance for metabolite. θ_i=disposition parameter for individual i; θ_{TV}=typical population value of a disposition parameter; effect of age was fixed to the value reported in literature of 0.83.

$$\theta_i = \theta_{TV} \times \left(\frac{AGE^{0.83}}{AGE^{0.83} + AGE^{0.83}}\right)$$

Table 13. Final estimates of population pharmacokinetic parameters.

Parameter (Unit)	Estimate (RSE)	IIV (%) (RSE)
ka1 (1/h)	2.14 (28%)	168 (15%)
F1	0.38 fixed	60.3 (9%)
COV	1 fixed	64.6 (13%)
ka2 (1/h)	0.51 fixed	-
F2	0.18 fixed	-
V1 (L)	24.9 (10%)	18.7 (65%)
V3 (L)	82.6 (11%)	54.7 (20%)
Q1 (L/h)	1.85 (19%)	93.9 (20%)
CLpm (L/h)	9.21 (8%)	14.2 (55%)
CLpr (L/h)	1.02 (17%)	27.4 (50%)
CLm (L/h)	48.6 (6%)	22.9 (17%)
Residual errors		
σ S 16257 prop (%)	38.9 (7%)	-
o S 18982 add (ng/mL)	0.122 (17%)	-
σ S 18982 prop (%)	17.7 (15%)	-

Figure 10 shows the goodness of fit plots for the final population PK model. Based on population prediction versus individual observed data plot for ivabradine, the structural model under-predicts high concentrations. In general, despite some misspecification the model was able to describe the observed data.

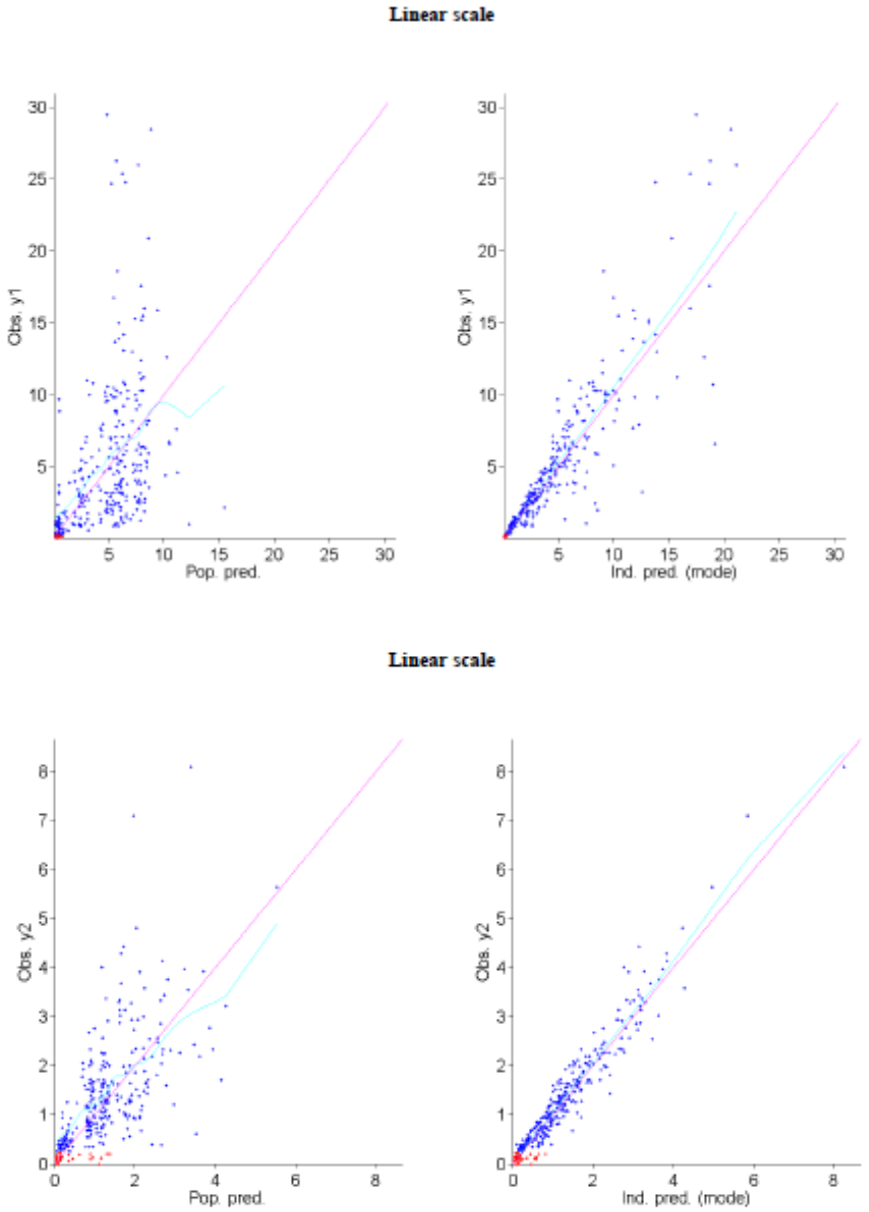

Figure 10. Population and individual predictions versus observed ivabradine and metabolite concentrations

Source: 27-164 associated; submitted in 0012(14); section: study report body.
Link: \\cdsesub1\evsprod\nda209964\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-heart-failure\5351-stud-rep-contr\np33304\27-164-associated.pdf

Reviewer comment:

The Applicant's PK/PD model was acceptable for the content of use i.e., to compare dosing regimens. However, there is a caveat to be noted as outlined below.

The Applicant's PK model estimated PK parameters based on blood concentrations collected from forearm or fingertip using DBS. Due to difference in blood-versus-plasma relationships between the two sampling locations (fingertip vs forearm), the corresponding plasma concentration varied by sampling location. This had a caveat that the simulated heart rate would depend not only on individual PK parameter/dosing history, but also on the DBS sampling location. Such a model is not optimal. A better model would have estimated PK parameters based on plasma rather than blood concentration since plasma exposure is the driver of heart rate response. In addition, the applicant made assumptions which might have increased the unexplained variability of the model parameters including residual variability.

4.5 Summary of Bioanalytical Method Validation and Dried Blood Spot Sampling

The sponsor conducted Study PKE-16257-005 to assess the use of dried blood spot sampling in study CL-090 (pediatric pivotal study).

The study objectives were to compare at first dose (D1) and at steady-state (D5) the plasma PK of S16257 and the metabolite S18982 when measured from plasma, forearm blood by dried blood spot sampling and capillary blood by dried blood spot sampling. Only ivabradine results were described in detail, however, the behavior of ivabradine and the metabolite were similar during analysis.

Design

The study design was as follows: The study was a single-center, open-label, one period study in 6 healthy male participants. Ivabradine 10 mg tablets were dosed every 12 h from Day 1 to Day 4 (twice-daily dosing), and a morning dose on Day 5. Samples were obtained on Days 1 and 5 pre-dose and at pre-determined time points until 12 h post-dose.

Sampling

Venous blood from forearm: once for DBS (0.5 mL blood, added to blood sample for plasma) and once for plasma (3 mL blood), Capillary blood from finger for DBS via lancet incision, collected at the same time

For DBS, at each sampling time point, 4 aliquots of 0.04 mL (two finger, two forearm) were spotted (2 spots of 0.05 mL, each). Cards were then dried at room temperature for at least 2 h, protected from light, then stored in plastic bag with desiccant. Only one card per bag.

Plasma samples frozen, cards at room temperature sent to analytical site (October 2011).

Results

Demographics

All 6 participants completed the study and were part of the PK analysis set. The median age (range) was 33 (26-43) years, and the mean weight (SD) was 77.02 (6.78) kg.

Results are summarized in Tables 14 and 15 and Figures 11 and 12

Table 14. Ivabradine PK comparison between sampling modalities

PK Parameter	D1			D5		
(unit)	Plasma	Venous blood	Capillary blood	Plasma	Venous blood	Capillary blood
C_{max} (ng/mL)	27 ± 12 (47)	20 ± 9.7 (48)	23 ± 9.6 (43)	32 ± 15 (46)	22 ± 11 (49)	24 ± 10 (43)
t_{max} (h)	1.5 (0.50; 2.0)	1.5 (0.50; 4.0)	1.5 (0.50; 4.0)	2.0 (0.50; 4.0)	2.0 (1.0; 4.0)	2.0 (1.0; 4.0)
t_{lag} (h)	0.080 (0.080; 0.080)	0.080 (0.080; 0.080)	0.080 (0.080; 0.080)	-	-	-
AUC_{12} (h*ng/mL)	117 ± 71 (61)	86 ± 51 (60)	88 ± 56 (64)	146 ± 95 (65)	100 ± 67 (67)	97 ± 60 (61)

Mean ±SD (CV%) except for t_{max} and t_{lag} where median (range) presented
'-' Not applicable

[Source: Table 2, Link]

Table 15. S18982 PK comparison between sampling modalities

PK Parameter (unit)	D1			D5		
	Plasma	Venous blood	Capillary blood	Plasma	Venous blood	Capillary blood
C_{max} (ng/mL)	4.3 ± 0.92 (21)	3.6 ± 1.1 (30)	3.8 ± 0.97 (25)	7.5 ± 2.5 (33)	5.4 ± 2.0 (36)	5.7 ± 2.2 (38)
t_{max} (h)	1.5 (0.50; 4.0)	1.5 (0.50; 4.0)	1.5 (0.50; 4.0)	2.0 (0.50; 4.0)	2.0 (1.0; 4.0)	2.0 (1.0; 4.0)
t_{lag} (h)	0.080 (0.080; 0.080)	0.080 (0.080; 0.080)	0.080 (0.080; 0.080)	-	-	-
AUC_{12} (h*ng/mL)	28 ± 6.6 (23)	21 ± 4.8 (23)	21 ± 4.2 (20)	53 ± 16 (30)	36 ± 10 (28)	34 ± 10 (29)

Mean ±SD (CV%) except for t_{max} and t_{lag} where median (range) presented
'-' Not applicable

[Source: Table 3, Link]

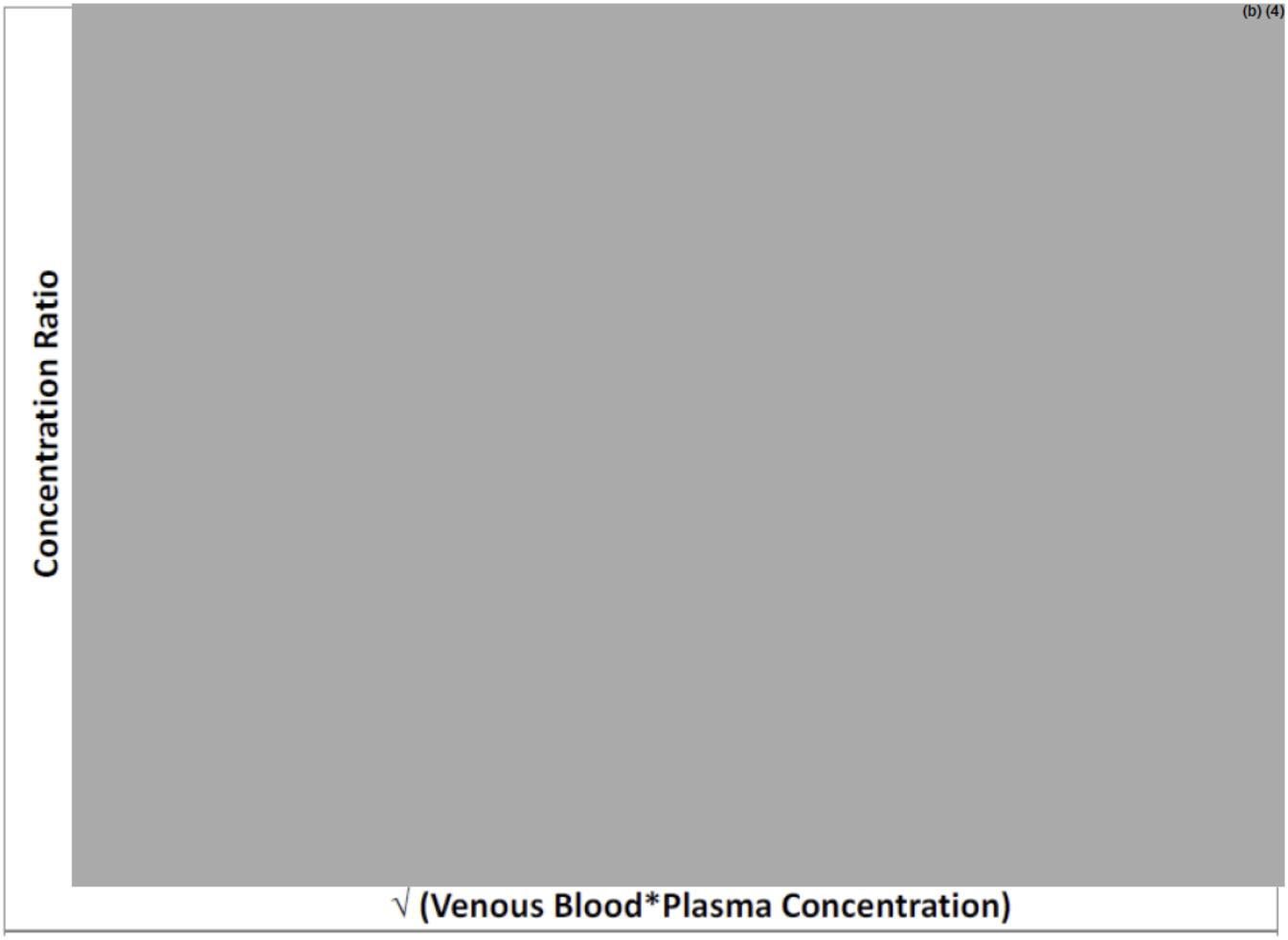

Figure 11. Bland-Altman plot of the ratio of venous blood to plasma concentrations vs the geometric mean of the two numbers for ivabradine (Day 1 samples) [Source: CSR, Figure 6]

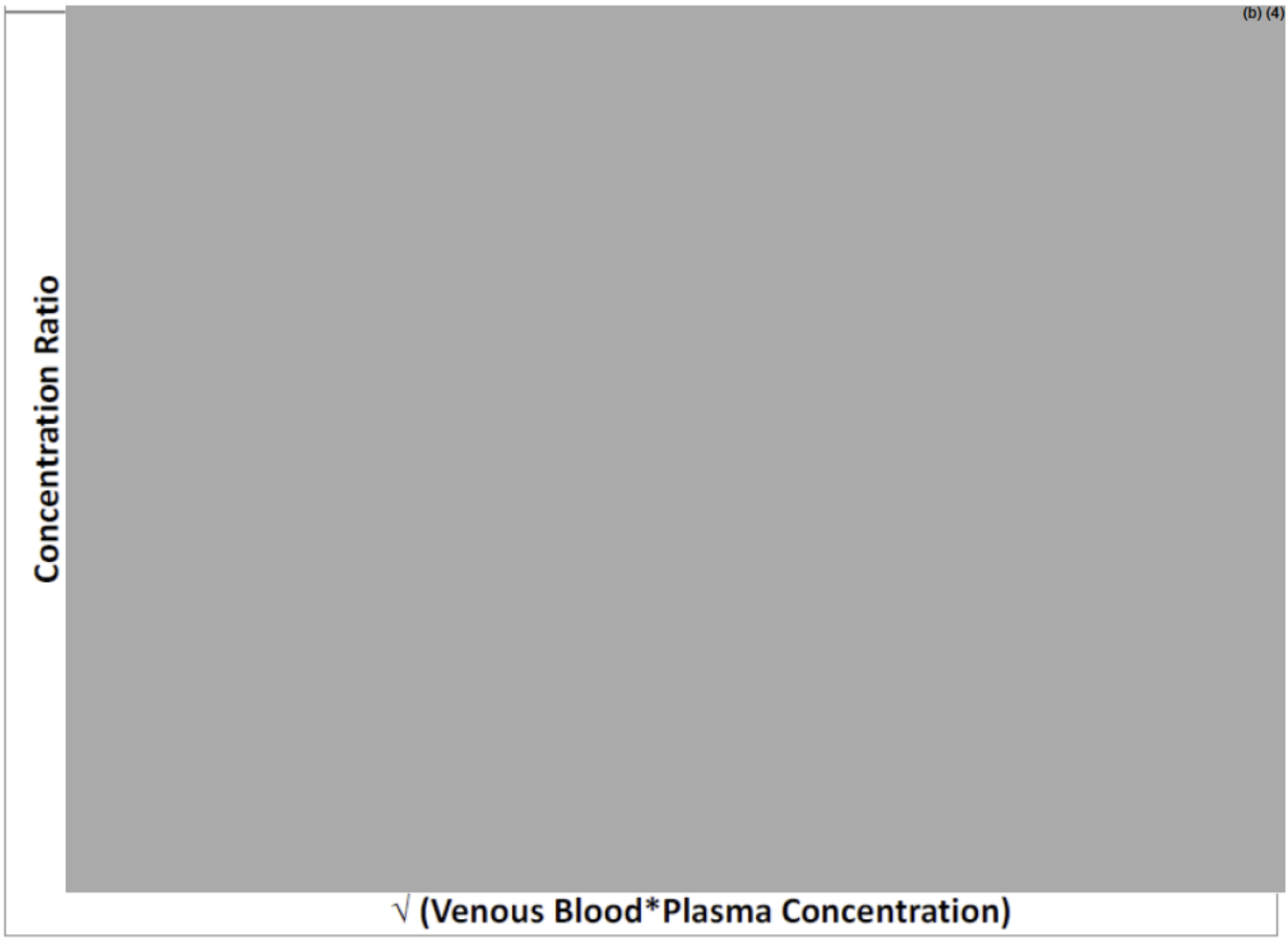

Figure 12. Bland-Altman plot of the ratio of venous blood to plasma concentrations vs the geometric mean of the two numbers for ivabradine (Day 5 samples) [Source: CSR, Figure 6]

Methods Used and Validation

Report Number	Description	Related Method
N-U-BIO-11-116A (Human Plasma)	Bioanalytical Report for ivabradine and metabolite from plasma	MA190 (14Sep2004) and Amendments dated: 11Nov2003, 02-Apr2007, 28May2009
N-U-BIO-11-116B	s.a., whole blood	UA108 (5Oct2010) and MA190 (14Sep2004)
UA108	Validation of LC/MS/MS Method for	

(np30947, np32240 (Amendment 1),)	determination of S16257 (ivabradine) and S18982 in dried blood spots from LI-heparinized whole blood samples	
MA190 (np15954)	LC-MS/MS method for plasma (heparinized)	

Summary Method MA190

Matrix	Plasma (Li-heparinized)	
Separation/Detection	LC-MS/MS	
Linear range		0.250 to 250 ng/mL
Precision	Within	2.2 to 9.8 %
	Between	4.3 to 6.9 %
Accuracy	Within	0 to 9.9 %
	Between	1.1 to 1.7 %
Selectivity		
Extraction recovery	Ivabradine	63%
	S18982	56%
	Internal standard	63%
Dilution	1/100 (25 µL)	CV 7.9 %, Accuracy: -0.8 %
Stability	5 C	7 weeks

Summary Method UA108

Matrix	Plasma (heparinized)	
Separation/Detection	LC-MS/MS	
Linear range		0.250 to 250 ng/mL
Precision	Within	2.3 to 5.8 %
	Between	4.38 to 7.17 %
Accuracy	Within	97.1 to 107 %
	Between	97.7 to 104 %
Selectivity		
Spot Cut Diameter		6 mm
Spot Recovery	Ivabradine	74.6 %
Sample Volume		25 µL (0.025 mL)
Dilution	1/100 (25 µL)	
Stability	5 C	
Note	The report mentions in a footnote, to Table 3.1 that the 6 mm whole punch did not always contain the whole spot.	

Reports 116A, and 116B

The plasma method (MA190 worked within established ranges during the bioanalytical sample analysis.

Method UA108 also worked as defined during bioanalytical sample analysis

Conclusion and Discussion

The report concludes that the methods are adequate to assess ivabradine and S18982 in dried blood spot samples. One point of caution is that the study reports only detailed that 6 mm punches were cut out from cards, there was no mention that the impact of hematocrit had been assessed. While hematocrit was stable on average in the population, there is literature to suggest that even small differences in hematocrit can have a difference, and some of the variability between the plasma and DBS samples could likely stem from the lack of adjustment of samples for hematocrit. Nevertheless, the applicant, for data analysis and exposure-response analysis comparison between adults and pediatrics, used mathematical relationships to describe the observed differences between DBS and plasma samples. The study was conducted, and samples analyzed in 2011, guidance was issued in 2018 that hematocrit was an important factor to consider in the analysis of this data. Therefore, the results are acceptable in the context of use for this program.

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