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APPLICATION NUMBER:

206143Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM to CLINICAL PHARMACOLOGY REVIEW

Brand Name	Corlanor (proposed)
INN Name	Ivabradine
NDA Number and Type	206,143, Original 505(b)(1)
Applicant Name	Amgen, Inc.
Submission Date	4/6/2015
Serial Number	0075
Indication	Chronic heart failure with systolic dysfunction
Dosage Form & Strengths	Tablets containing 5 and 7.5 mg ivabradine
OCP Division	OCPI, Cardiovascular and renal products
OND Division	ODEI, Division of Cardiovascular and Renal products
Reviewers	Martina Sahre, PhD (Clinical Pharmacology) Sreedharan Sabarinath, PhD (Pharmacometrics)
Team Leader	Rajanikanth Madabushi, PhD (Clinical Pharmacology), Jeffrey Florian, PhD (Pharmacometrics)

Aim

The aim of this addendum is to clarify the effective half-life of ivabradine as well as to serve as an erratum for a mislabeling of half-life in the clinical pharmacology review (date: 11/26/2014, page 16, Section 2.4.1).

Effective Half-Life

Labeling proposed by the applicant states that ivabradine shows an effective half-life of (b) (4). The current EMA label indicates the following: "Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours."¹

The applicant assessed the effective half-life based on a popPK model derived from the following studies: CL2-006, CL2-009, CL2-030, CL2-047, CL3-017, CL3-018, CL3-019, CL3-021, CL3-023. The effective half-life was derived from the following equation:

(b)
(4)

(b) (4)

The sponsor states in the Summary of Clinical Pharmacology³, that ivabradine first half-life was about 2 h, and accounted for 73% of the AUC, while the terminal half-life was approximately (b) (4).

¹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000597/WC500043590.pdf, retrieved 4/7/2015

² 1.11.3 –Response to Labeling Comments – 02 April 2015

³ Summary 2.7.2 (Serial Number 0017), Section 3.1.4.3, page 100

h. The summary document goes on to explain, that terminal half-life was poorly estimated because many plasma samples were close to the LLOQ, thus making the latter half-life not well established.

The applicant suggests that their estimate of effective half-life is more useful as it was obtained from multiple studies and a population PK model. It should be noted that the population PK model used only phase II and III studies with most sparse PK sampling done during 0-12 hours window after ivabradine dose and did not include any of the dedicated repeat dose PK studies with rich PK sampling (e.g. CL1-002, PKH-001). This may have affected the ability of the population PK model to estimate the parameters for the elimination phase more precisely. Moreover, there are issues with internal consistency with the population PK model predicted effective half-life of (b) (4). The expected accumulation for an effective half-life of (b) (4) is approximately 100% (2-fold) with twice daily dosing. The observed accumulation for ivabradine (as well as model predicted accumulation) is only about 30%. The calculated effective half-life of ~6 hours (see equation below) from the dedicated PK studies is in agreement with the observed accumulation of ivabradine (~30%) with twice daily dosing in these studies.

$$\text{Accumulation ratio} = 1/(1-\exp(-(\ln(2)/t_{1/2,\text{eff}})*\tau))$$

In the opinion of the review team, the basic PK characteristics of ivabradine should be derived from dedicated PK studies with rich sampling when available rather than the population PK model. Effective half-life was calculated from such PK studies and includes no model assumptions as in the case of pop-PK analysis. In light of this information, the review team does not agree with the applicant's proposed ivabradine effective half-life as it is not supported by observed data.

Erratum

In the review from 11/26/2014, the effective half-life is referred to as (b) (4) this value should read 6 h. See explanation above.

Further, the elimination half-life was referred to as (b) (4) h, based on study CL1-001, the first in human study. The elimination half-life was highly variable for ivabradine. From study CL2-002 and PKH-001, the elimination half-life was on average 6 and 7 h after multiple dosing. As was mentioned earlier, the estimated terminal half-life of (b) (4) h from population PK analysis is likely an overestimation.

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CLINICAL PHARMACOLOGY REVIEW

Brand Name	Corlanor (proposed)
INN Name	Ivabradine
NDA Number and Type	206,143, Original 505(b)(1)
Applicant Name	Amgen, Inc.
Submission Date	6/27/2014
Indication	Chronic heart failure with systolic dysfunction
Dosage Form & Strengths	Tablets containing 5 and 7.5 mg ivabradine
OCP Division	OCPI, Cardiovascular and renal products
OND Division	ODEI, Division of Cardiovascular and Renal products
Reviewers	Martina Sahre, PhD (Clinical Pharmacology) Sreedharan Sabarinath, PhD (Pharmacometrics)
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1 Executive Summary

Amgen, Inc. is seeking approval for the use of ivabradine to treat chronic heart failure with the intent to reduce (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 bpm. It is proposed to be used (b) (4) that can either include maximally tolerated doses of beta blockers or it can be used when the treatment with beta-blockers is contraindicated (b) (4)

(b) (4) Ivabradine is an inhibitor of the I_f (“funny”) current and it is the first molecular entity of this kind for which approval is sought. Ivabradine is a negative chronotrope. It was developed by Les Laboratoires Servier of France and it has been approved in Europe for the treatment of stable chronic angina and heart failure since 2005 and 2011, respectively. The compound was not developed under an IND and as such, none of the clinical trials were conducted in the United States. Amgen obtained the licensing rights to ivabradine from Servier in 2013 and subsequently submitted this NDA. An indication for treatment of angina pectoris is not sought at this time.

The primary efficacy information supporting this NDA is derived from one randomized, placebo-controlled pivotal efficacy study, SHIFT, in subjects with chronic heart failure (N~6558). Subjects were randomized 1:1 to ivabradine or placebo, on top of guideline recommended standard of care heart failure therapy. Treatment with ivabradine reduced cardiovascular mortality or hospitalization for worsening heart failure, compared to placebo (Hazard Ratio 0.82, 95 % CI 0.75-0.90, $P < 0.0001$).

In addition to SHIFT, two other clinical trials, BEAUTIFUL and SIGNIFY contribute to the understanding of the safety. The trial BEAUTIFUL was in subjects with stable coronary artery disease (CAD) and left ventricular dysfunction (N~10946). The recently concluded SIGNIFY study was in subjects with CAD and not in heart failure. In addition, the applicant provided an extensive *in vitro* and *in vivo* clinical pharmacology package to support the labeling and use of ivabradine for the treatment of chronic heart failure.

The review team agrees with the applicant’s labeling recommendations in general. Labeling language with regard to the use of grapefruit juice and St. John’s Wort extract should be clarified from the current recommendations, which are (b) (4) and (b) (4) respectively. The review team does not recommend the use of ivabradine with St. John’s Wort extract and patients who are on stable doses of ivabradine should be instructed to avoid intake of grapefruit juice.

1.1 Recommendations

Based on the review of the NDA from a clinical pharmacology perspective, the review team finds the information in general supportive of approval and sufficient to provide appropriate dosing instructions for safe and effective use. There are no Phase 4 studies envisioned at this time.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

- The pharmacokinetics of ivabradine and the main active metabolite S18982 are linear in the dose range of 1 to 24 mg.
- The main metabolite S18982 is equipotent to ivabradine.
- The absolute bioavailability of ivabradine after oral administration is 40 %. The first-pass metabolism accounts for most of the loss of exposure following oral administration.
- Ivabradine and S18982 are extensively metabolized by CYP3A4.

- Ivabradine is minimally excreted unchanged. Metabolites are excreted to an equal degree in urine and feces.
- Severe renal impairment did not affect unbound ivabradine concentrations. No differences in the response of the pharmacodynamic marker heart rate were observed compared to normal renal function.
- In subjects with mild or moderate hepatic impairment (by Child-Pugh classification), a slight increase in total, but not in unbound ivabradine concentrations was observed. The impact of severe hepatic impairment has not been studied. No changes in heart rate response were observed compared to patients with normal hepatic function.
- Other intrinsic factors such as age, sex, weight, or race do not affect exposure of ivabradine.
- Subjects with heart failure in the ivabradine treatment arm showed an average ~ 11 bpm reduction in resting heart rate relative to the placebo arm in pivotal efficacy trial.
- Lower baseline heart rate and greater on-treatment heart rate reduction was associated with a lower incidence rate for cardiovascular death or hospitalization for worsening of heart failure for both ivabradine and placebo treatments.
- When ivabradine was administered with strong or moderate CYP3A4 inhibitors, increased peak and total systemic exposures were observed. These inhibitors were excluded comedications in the pivotal trial SHIFT.
- There is also a pharmacodynamic basis for avoiding coadministration with verapamil and diltiazem since both drugs can act as negative chronotropes, like ivabradine.
- After coadministration of ivabradine with the CYP3A4 inducer St. John's Wort (*Hypericum perforatum*) peak and total systemic exposures were reduced ~2-fold.
- Ivabradine is neither an inhibitor, nor an inducer of metabolizing enzymes at clinically relevant concentrations.
- (b) (4) A drug-drug interaction study of ivabradine with metformin in healthy subjects showed no difference in peak or total systemic exposure.

2 Question-Based Review

2.1 General attributes of the drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Ivabradine is a small molecule drug with a molecular mass of 468.6 g/mol. The drug product contains ivabradine in the hydrochloride salt form (Mw: 505.1 g/mol).

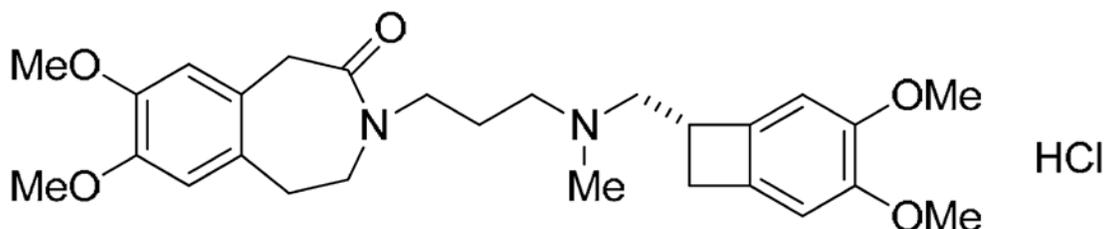


Figure 1. Chemical structure of ivabradine (S16257)

[Source: Figure 1, Module 3.2.S.1.2. - Structure]

Ivabradine is highly soluble over the pH range of the gastrointestinal tract, as shown in Table 1 below.

Table 1. Solubility of ivabradine at different pH

<i>pH</i>	<i>Solubility [mg/mL]</i>
1.1	10.4
7.6	38.9
8.5	7.8

[Source: Module 3, Drug Substance]

The molecule has two basic functions with a pK_{a2} of 2.4 (amide) and pK_{a1} of 8.5 (amine).

The logP of the neutral form is 2.1, the logD at pH 7.4 is 0.95, which suggests that ivabradine should easily distribute between tissues and it could predispose it to good absorption characteristics.

The drug product is a salmon-colored, film-coated immediate-release tablet containing 5 and 7.5 mg ivabradine (5.39 and 8.085 mg ivabradine HCl). The 5 mg tablet is scored, so that a 2.5 mg dose becomes possible. The 7.5 mg tablet is not scored.

2.1.2 What are the proposed mechanism of action and therapeutic indication?

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.

Ivabradine inhibits the I_f current *in vitro* with an IC_{50} of 1.5-3 μ M and the HCN4 channel with an IC_{50} of 2 μ M. 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.

Another current that is predominantly defined for the central nervous system (CNS) is the I_h current, which is maintained through HCN-channels as well. Interaction with the I_h current is could potentially explain a specific adverse event observed with ivabradine treatment that is associated with transient bright spots in the visual field. These visual disturbances are called phosphenes.

Another consideration, particularly for the cardiac safety of ivabradine, is the potential for interactions with other pacemaker tissues in the heart. Such an interaction could be hypothesized to, at least partially, explain the numerically higher overall occurrence of atrial fibrillation observed in patients treated with ivabradine compared to those treated with placebo in the phase III trial. Please see the clinical review by Dr. Dunnmon and the safety review by Dr. Beasley for more information.

The applicant is seeking the following indication for ivabradine: "Reduction of the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) (b) (4) maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated (b) (4)." ."

2.1.3 What are the proposed dosages and routes of administration?

The proposed starting dose is 5 mg twice daily (BID), which can be titrated after two weeks to either 2.5 or 7.5 mg twice daily. Titration is based on observed heart rate. A heart rate persistently below 50 bpm or symptoms related to bradycardia, such as dizziness, fatigue or hypotension should lead to dose reduction to 2.5 mg. A heart rate persistently above 60 bpm during the 2-week period, should lead to an uptitration to 7.5 mg BID. The dose remains at 5 mg BID if the heart rate is between 50 and 60 bpm during the 2-week titration period.

(b) (4)

The drug is to be taken orally twice daily with meals.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The development program included single and multiple ascending dose-studies in healthy subjects with oral and intravenous administration of ivabradine capsules, tablets and aqueous solution. In addition, single and multiple ascending oral and intravenous doses of the major active metabolite S18982 were studied in healthy subjects.

Studies assessing mass balance, effect of food, time of dosing, impact of renal or hepatic impairment on the pharmacokinetics and drug-drug interactions were conducted.

A tabular overview of studies that have been completed as well as some studies that are still ongoing can be found in the electronic submission.¹ After the start of the review clock, a metformin drug-drug interaction study was also submitted by the sponsor.

In total the clinical pharmacology package included 16 *in vitro* studies and 71 *in vivo* studies. Of these the *in vitro* studies and 45 *in vivo* studies were reviewed. Studies that were not reviewed were clinical pharmacology studies in patients with stable angina that were mostly safety related and not dose-ranging and did not add any new information to the understanding of the clinical pharmacology of ivabradine.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The biomarker used for dose selection was heart rate at rest or during exercise (see section 2.1.2 for the mechanism of action). It is not completely clear how the reduction in heart rate translates to outcomes with regard to mortality and hospitalization, but meta-analyses have shown that a high heart rate is a risk factor for mortality and morbidity in patients with heart failure.

The primary clinical endpoint in the pivotal efficacy study was time-to-first occurrence of either cardiovascular death or hospitalization for worsening heart failure. This is a commonly used endpoint in heart failure trials and represents drug effects on mortality and morbidity.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The active moieties that were measured in the clinical pharmacology program are ivabradine and S18982. Please refer to Section 2.8 for details about the methods.

¹ <\\cdsesub1\evsprod\nda206143\0017\m5\52-tab-list\tabular-listing.pdf>

2.3 Exposure-response

2.3.1 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Dose-selection was based on the reduction in heart rate markers at rest and performance of hemodynamic parameters during exercise. It was measured in healthy subjects and in patients with stable angina, as well as in a pilot study (CL2-062) in patients with heart failure.

In study CL2-16257-062, patients with heart failure were dosed for 6 weeks, starting with 2.5 mg BID, then titration every two weeks to 5 mg and eventually to 7.5 mg BID. Over the 6-week treatment period, heart rate was reduced by a mean of 10 bpm. The mean heart rate reduction over the dose and time range are shown in Figure 2. There is a trend for less than proportional increase in the HR effect with increasing doses. This is consistent with the titration design and the effect of ivabradine being dependent on the baseline heart rate.

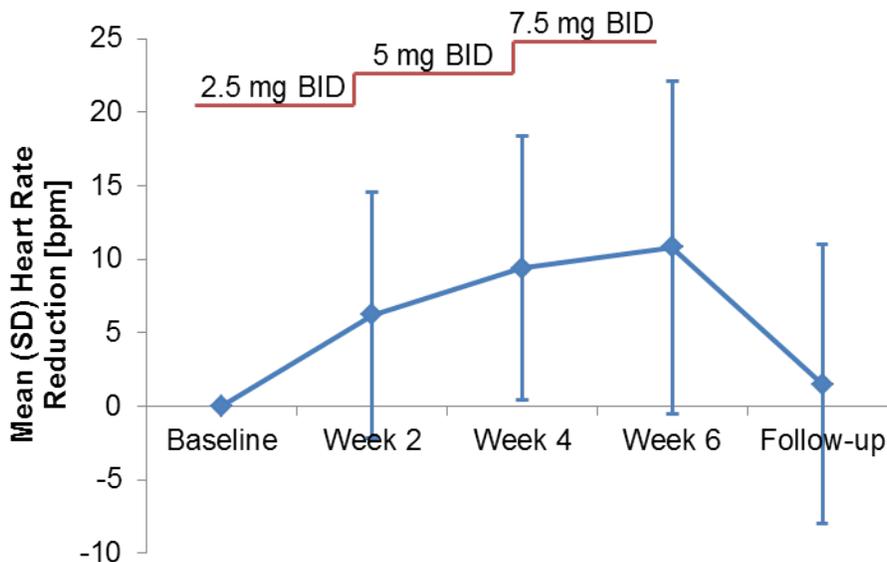


Figure 2. Heart rate reduction in CL2-062, an open-label pilot study in patients with heart failure

[Source: Prepared by FDA reviewer from CSR for study CL2-16257-009]

A meta-analysis of several studies in patients and healthy subjects over a wider dose range (2.5 – 30 mg BID) suggests that higher doses could result in greater reductions in exercise induced heart rate (Figure 3).

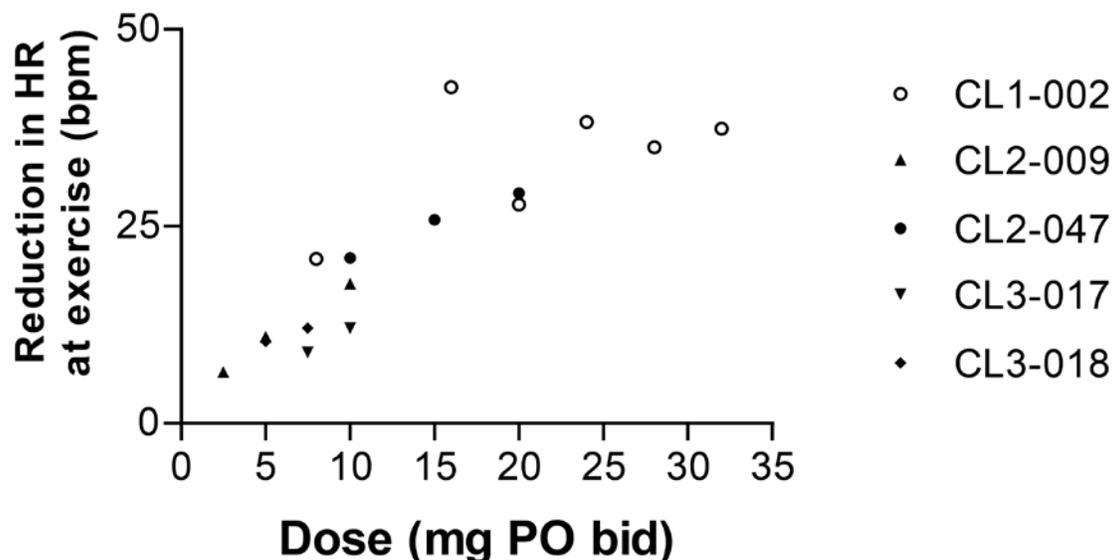


Figure 3. Mean heart rate reduction [bpm] during exercise²

[Source: Summary of Clinical Pharmacology Module 2.7.2, Figure 20]

One dose limitation for ivabradine was the occurrence of visual effects (phosphenes). In study CL2-009, the rate of phosphenes reported was 1.1% (n=1) of patients for 2.5 and 5 mg BID, respectively, and 14.8% (n=13) for 10 mg BID ivabradine dosing. These visual effects resolved after the end of treatment and were generally short in duration (up to 20 min). Phosphenes were also observed in study CL1-002 (MAD study), where almost all subjects at doses of 24 mg and above showed this adverse event (AE). In this study, the duration of visual disturbances was between 15 min to 3 h, while more permanent episodes could last up to 3 days. Hence, it appears that a limitation of dose at 7.5 mg BID is reasonable.

Based on the effects on HR reduction and the dose limiting nature of the visual AEs, a titration-based approach was considered for evaluating the efficacy of ivabradine in the phase III study SHIFT.

2.3.2 What are the key features of the Phase III trial for ivabradine in heart failure patients?

The applicant conducted a single, multi-center, randomized, double-blind, placebo-controlled, event driven Phase III outcome study (SHIFT study) in adult patients with symptomatic systolic heart failure NYHA class II-IV (N~ 6505 randomized). The patients needed to be in sinus rhythm at selection with a resting heart rate (HR) of ≥ 70 bpm, a documented hospitalization for worsening heart failure within the prior 12 months, a documented left ventricular ejection fraction (LEVF) ≤ 35 % within prior 3 months, to be

² CL1-002 (Multiple ascending dose study), CL2-009, CL3-017, CL3-018 (Patients with stable angina pectoris), CL2-047 (Patients with proven coronary artery disease)

considered in stable condition, and to be on an optimal heart failure medication regimen for \pm 4 weeks. The primary composite endpoint (PCE) for SHIFT study was time to first event of cardiovascular death (including death from unknown cause) or hospitalization for worsening heart failure. The study was initiated in 2006 and completed in 2010. There were 625 centers in 37 countries, which did not include the United States.

A schematic of the study design is shown in Figure 4. At inclusion, subjects were required to be receiving stable background heart failure therapy considered optimal by the investigator, usually including a beta blocker, a diuretic, an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). All subjects receiving beta blockers were expected to be receiving maximally tolerated doses for the respective beta blockers.

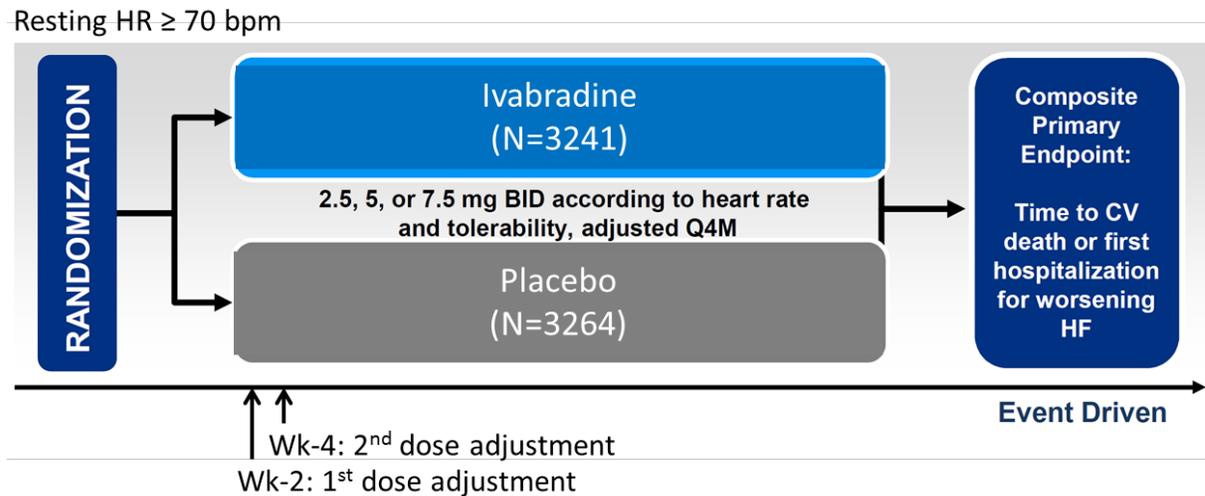


Figure 4. Design of SHIFT study in patients with heart failure. Scheduled dose titration visits were at week-2 and week-4. Further dose adjustments were allowed every 4 months (Q4M) during scheduled study visits. Median follow up was about 22.9 months.

[Source: Prepared by FDA reviewer based on Clinical Study Report CL3-16257-063 SHIFT.]

The study was divided into two periods, a run-in period of 2 weeks to confirm eligibility of subjects, followed by a post-randomization period. Subjects were randomized 1:1 to receive placebo or ivabradine treatments. Randomization was stratified by beta-blocker intake (Yes/No at baseline) and center. The post-randomization period included a titration phase with scheduled visits on week-2 and week-4 followed by a follow-up phase. There were study visits every 4 months thereafter. Subjects received an initial dose of 5 mg twice daily (BID), then were up-titrated to 7.5 mg BID, maintained at 5 mg BID or down titrated to 2.5 mg BID depending on resting HR and tolerability. The dose could be titrated upward if resting HR was $>$ 60 bpm or downward if $<$ 50 bpm or the subject is experiencing signs or symptoms related to bradycardia. Dose titration was mostly performed during the first 4 weeks (titration phase) but was allowed at any of the study visits based on the criteria mentioned above. A small subset of patients provided a

single pharmacokinetic sample each at the month-8 study visit (N~236 evaluable samples).

2.3.3 What are the characteristics of the exposure-response relationships for efficacy?

The SHIFT study employed an individual dose titration scheme, based on subject's HR and tolerability as described in section 2.3.2. Treatment was initialized at 5 mg BID with a target dose of 7.5 mg BID. The three available dose steps were 2.5, 5 and 7.5 mg BID with most patients maintaining the target dose of 7.5 mg BID (~ 60 % in ivabradine and 91 % in placebo arms). The number of evaluable PK samples from the SHIFT sub-study was limited (N~236) and were collected 8 months after randomization (~ 521/6505 subjects were censored including ~ 364 deaths by month 8 visit). Because of these reasons (dose titration and limited PK data) neither dose-response or exposure-response analyses were feasible with the available SHIFT data.

Consideration was given to exploring the ivabradine exposure-response relationships based on available data from two other Phase III trials: BEAUTIFUL and SIGNIFY. However, as no useable pharmacokinetic sampling was conducted during these studies and as the study populations were not similar from the population enrolled in SHIFT, the review team similarly concluded that exposure-response analyses would not be feasible based on data from these studies.

An exploratory analysis was performed for SHIFT to understand the association, if any, between pharmacodynamics effect (HR reduction), and efficacy outcomes.

2.3.4 Is there an association between baseline and on-treatment heart rate with PCE event rate?

Resting HR of ≥ 70 bpm was one of the inclusion criteria for SHIFT study. Approximately 52 % of the patients in the randomized set had a resting HR ≥ 77 bpm at baseline. A pre-specified subgroup analysis showed a hazard ratio of 0.93 (95 % CI 0.80-1.08) for subjects with HR < 77 bpm and 0.75 (95 % CI 0.67-0.85) for subjects with HR ≥ 77 bpm at baseline respectively for the primary composite efficacy endpoint (PCE). There was an absolute difference of 4.5 % (12.3 vs 16.8 %) and 9.1 % (13.2 vs 22.3 %) in annualized event rates within ivabradine and placebo groups respectively, favoring the patient group with higher resting HR (≥ 77 bpm). The mean reduction in HR from baseline to Day 28 was 15.4 ± 10.7 bpm in the ivabradine arm versus 4.6 ± 10.6 bpm in the placebo arm, with a between treatment arm difference of 10.9 bpm.

Based on these observations exploratory analyses were conducted evaluating the relationship between PCE incidence rates and 1) baseline HR, 2) HR observed on Day 28, and 3) percentage change in HR from baseline.

Results exploring the relationship between number of PCE events (incidence rates) and baseline HR are shown graphically in Figure 5 for the ivabradine and placebo treatment arms based on increments of 10 bpm for baseline HR. There were fewer subjects with baseline HR above 106 bpm in either treatment arms. Nevertheless, incidence rates for

PCE showed an increasing trend in subjects with higher resting HR at baseline for both the treatment arms. In agreement with the pre-specified subgroup analysis described above, the results show that improvement of ivabradine over placebo was predominantly in those subjects with higher baseline HR.

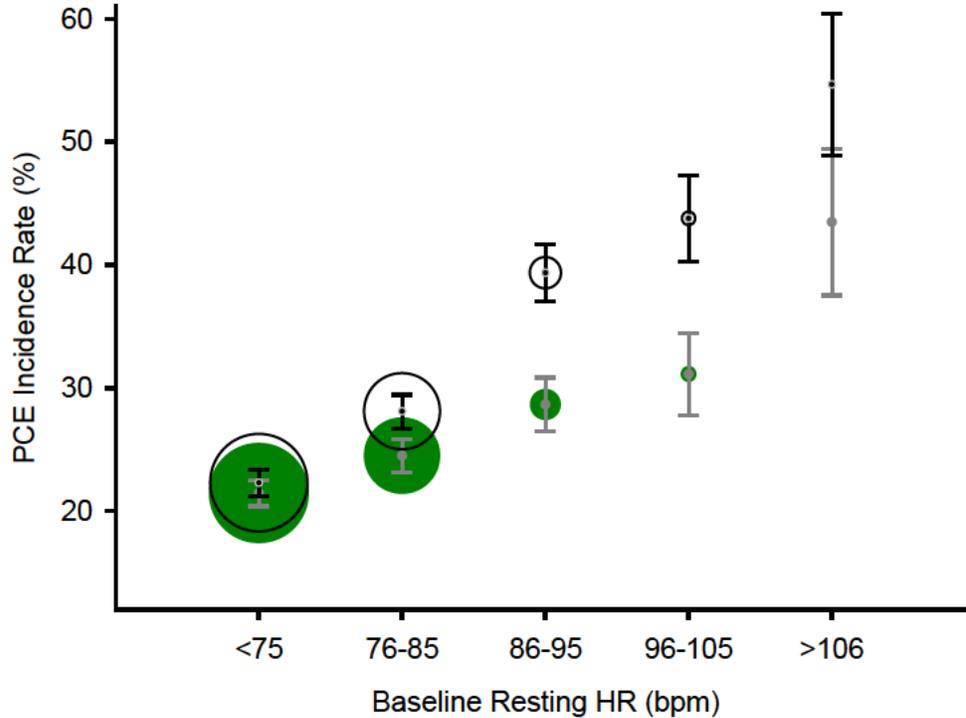


Figure 5. Association between baseline HR and observed PCE incidence rates for ivabradine (green bubbles) and placebo (white bubbles) treatment arms. The size of the bubbles indicates the number of subjects in each group. The error bars represent standard errors for the incidence rates. There were fewer subjects in both treatment arms with baseline HR above 106 bpm.

[Source: Prepared by FDA reviewer, dataset: endpoint.xpt, visig.xpt, pksublev.xpt]

An additional analysis also suggests an association between number of PCE events and HR reduction observed on Day 28 (range of 22-40 days), after the initial dose titration period (Figure 6). This relationship between PCE and observed HR reduction did not appear to be dependent on treatment, though the percentage of subjects with observed on-treatment resting HR <70 bpm or <60 bpm on Day 28 was greater in the ivabradine arm than in the placebo arm, as would be anticipated based on ivabradine's pharmacologic effect. In addition, the relationship between PCE incidence rates and observed HR suggests a plateauing of the relationship if the patient reached a HR reduction of 15-20 bpm by Day 28 (Figure 6).

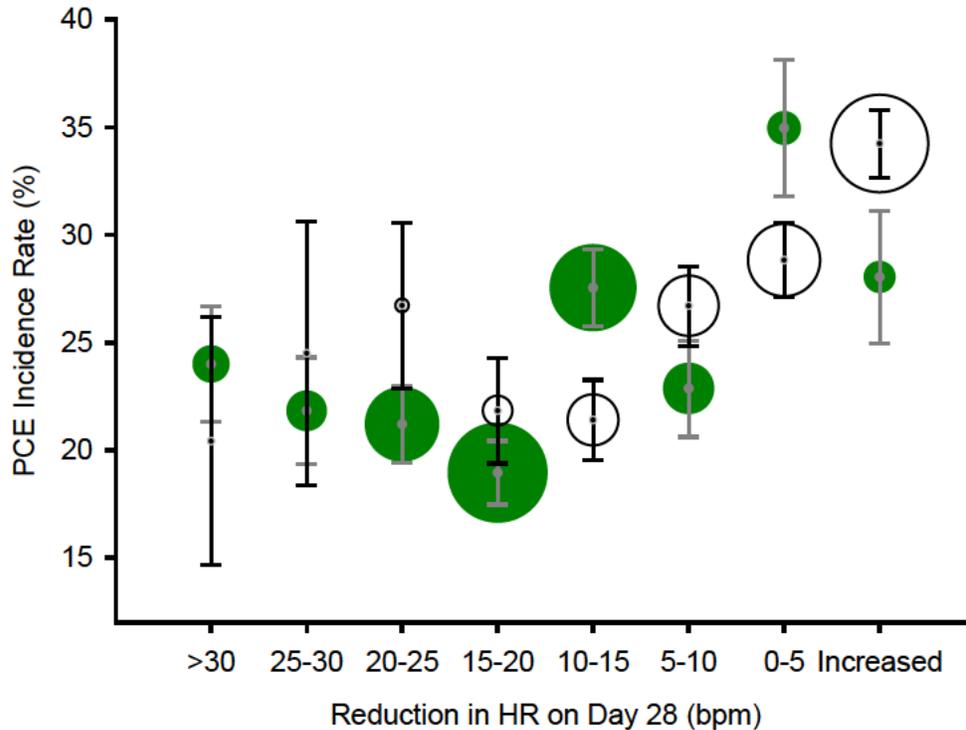


Figure 6. Observed reduction in resting heart rate (bpm) and PCE incidence rates (%) for ivabradine (Green bubbles) and placebo (White bubbles) treatment arms. The size of the bubbles indicates the number of subjects in each group. The error bars represent standard errors for the incidence rates. Subjects with missing values at baseline or Day 28 were excluded. Subjects with ≥ 30 bpm reductions in HR and those with an increase in resting HR from baseline showed the highest incidence rates for PCE.

[Source: Prepared by FDA reviewer, dataset: data files endpoint.xpt, visig.xpt, pksublev xpt]

Another exploratory analysis was conducted evaluating the relationship between PCE incidence rates and percent reduction in HR from baseline around Day 28 (range of 22-40 days) for ivabradine and placebo (Table 2). The observed incidence rates for PCE events were relatively lower for the groups with > 20 % reduction in resting HR from baseline for ivabradine (Figure 7) with the exception of group with $> 40\%$ reduction. Patients with either an increase in HR or a percentage reduction > 40 showed a trend towards increased incidence of PCE events. Similar to the analyses shown above for PCE events and observed HR, the overall trend between PCE events and percent reduction in HR was also similar for the ivabradine and placebo treatment arms, though the percentage of subjects achieving larger reductions in HR (> 15 %) was greater for the ivabradine treatment arm.

Table 2. Association between percentage reduction in HR on day 28 from baseline and PCE incidence rates for ivabradine and placebo treatment arms.

% HR Reduction	Ivabradine		Placebo	
	n/N	% Incidence Rate	n/N	% Incidence Rate
>40	24/92	26.1	2/10	20.0
30-40	87/452	19.3	12/64	18.8
25-30	102/495	20.6	29/120	24.2
20-25	114/570	20.0	42/203	20.7
15-20	128/521	24.6	68/341	19.9
10-15	109/358	30.5	113/438	25.8
5-10	55/259	21.2	127/498	25.5
0-5	71/186	38.2	181/584	31.0
HR increased	60/215	27.9	316/922	34.3

N – Number of subjects, n – Subjects with PCE events, Subjects with missing values were excluded

[Source: Prepared by FDA reviewer, dataset: endpoint.xpt, visig.xpt, pksublev.xpt]

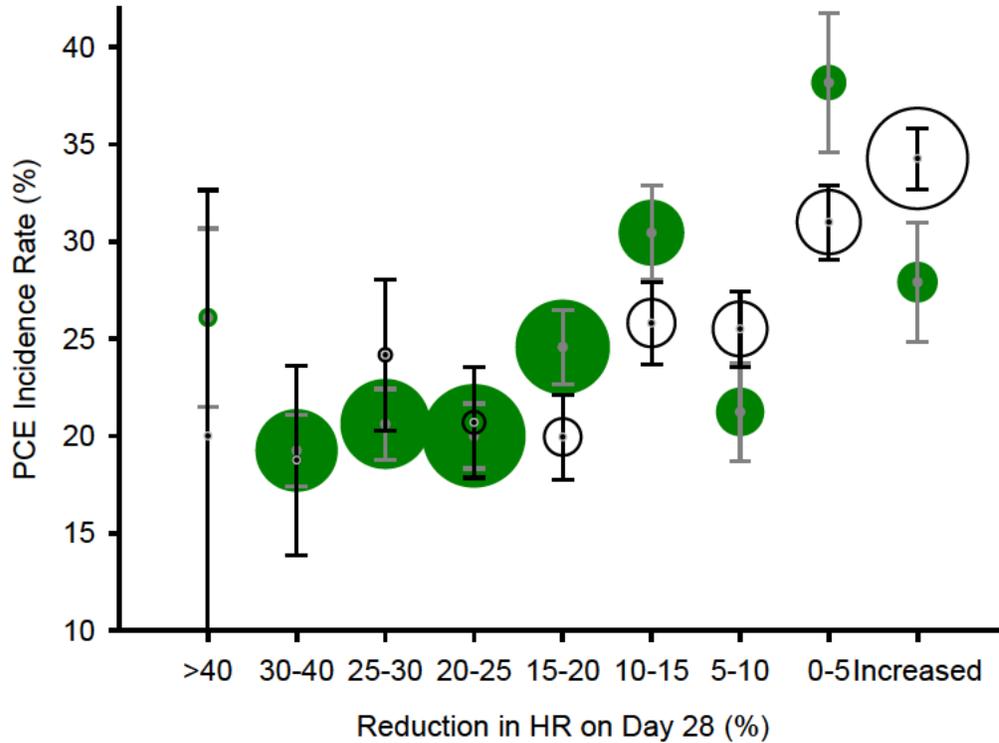


Figure 7. Percentage reduction in resting heart rate (%) and PCE incidence rates (%) for ivabradine (Green bubbles) and placebo (White bubbles) treatment arms. The size of the bubbles indicates the number of subjects in each group. Subjects with missing values at baseline or Day 28 were excluded. More subjects in the placebo arm had minimal to no change or an increase in HR compared to ivabradine treatment arm. The error bars represent standard errors for the incidence rates.

[Source: Prepared by FDA reviewer, dataset: endpoint.xpt, visig.xpt, pksublev.xpt]

2.3.5 Is there a difference in efficacy for ivabradine in subjects with ischemic and non-ischemic origin heart failure?

The primary cause of heart failure was ischemic for approximately 68 % of subjects in the SHIFT study. A pre-specified sub group analysis showed a hazard ratios of 0.72 (95 % CI 0.6-0.85) and 0.87 (95 % CI 0.78-0.97) for the non-ischemic and ischemic subsets respectively. (b) (4)

(b) (4)

(b) (4)

. In adult patients (7.5 mg BID group) with non-ischemic origin of heart failure, a body weight normalized ivabradine doses of 0.094 mg/kg (IQR: 0.08 to 0.11 mg/kg) were associated with an average percentage HR reduction of about 20 % from baseline. As this corresponds to approximately where the PCE event rate is at lower

levels in the overall and non-ischemic population (b) (4)

2.3.6 Is there an association between dose and treatment emergent adverse events?

Adverse events that were relatively more frequent in the ivabradine arm than in the placebo arm included atrial fibrillation, inadequate blood pressure control, bradycardia and phosphenes. Sitting diastolic and systolic blood pressures increased from baseline in both treatment arms (Table 3).

Table 3. More frequent treatment emergent adverse events in the ivabradine arm compared to placebo arm.

<i>Treatment Emergent Adverse Event (%)</i>	<i>Ivabradine</i>	<i>Placebo</i>
Atrial fibrillation	8.3	6.7
Inadequate BP control	7.1	6.1
Symptomatic bradycardia	4.6	0.9
Phosphenes	2.8	0.5
Mean change in sitting DBP (mmHg, SD)	0.4 ± 10.2	0.7 ± 10.3
Mean change in sitting SBP (mmHg, SD)	4.1 ± 16.0	2.0 ± 16.2

[Source: Prepared by FDA reviewer based on safety analysis, SHIFT clinical study report NP29800-01]

A greater number of treatment emergent adverse events were reported in subjects receiving the target dose of 7.5 mg BID, which represented approximately 60 % and 91 % of the SHIFT study population in ivabradine and placebo treatment arms respectively. As described in section 2.3.3, it was not feasible to further evaluate these relationships in dose-response or exposure-response analyses with the available data. Please refer to the clinical safety review for details on adverse event profile of ivabradine.

2.3.7 Does this drug prolong the QT or QTc interval?

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). (b) (4)

2.4 Pharmacokinetic Characteristics

2.4.1 What are the single dose and multiple dose PK parameters?

When ivabradine was administered as a single intravenous bolus to healthy subjects, the total ivabradine exposure (AUC_{inf}) was approximately linear over the dose range of 1 to 24 mg. Renal clearances after intravenous doses were about 90-130 mL/min and total plasma clearance was on average 475 to 594 mL/min with no discernable trend across doses. This indicates the role of non-renal and renal pathways of elimination. The fraction excreted unchanged in urine was on average 20%. Renal clearance for S18982 was also in the order of 90-140 mL/min. Renal clearances measured in this study had coefficients of variance in the order of 30-50% associated with them. Taking into account that ivabradine is 70% protein bound and that renal clearances based on total exposure approach or slightly exceed glomerular filtration rate on average, it appears that glomerular filtration is the predominant pathway for renal elimination.

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 C_{max} were dose-linear up to 24 mg. Peak and total systemic exposures at higher doses were less than dose proportional. Peak exposures are reached within a range of 0.5 to 2 h and this does not appear to be influenced by dose. Following a single dose, the mean terminal half-life was ~2 - 3 h. The fraction of ivabradine dose excreted unchanged in urine ranged from 4.2 to 7.0% across doses, with no discernable trend. The calculated renal clearance was between 84 and 136 mL/min, which as mentioned above suggests that glomerular filtration was the predominant pathway for renal elimination.

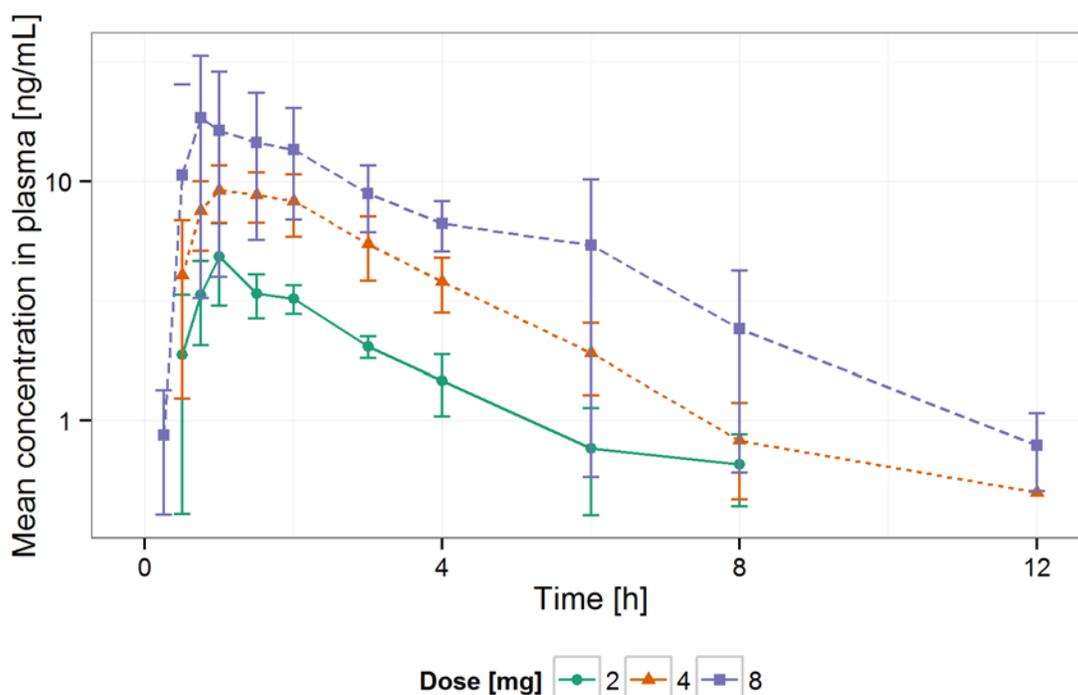


Figure 8. Mean (SD) plasma concentrations of ivabradine in the SAD study (log-linear)

[Source: CSR for study CL1-16257-001, dataset: bkinet.xpt]

Following repeat administration the accumulation was in the range of 40-60%. Variability in the observed accumulation is likely due to small sample size. Renal clearances after multiple oral doses were approximately 62-74 mL/min when ivabradine 8 and 16 mg were given BID. Renal clearances were slightly higher, 90-120 mL/min, at higher doses (20-32 mg BID). Half-lives were longer compared to single dose studies with an average around 6 and 8 h, but the range of half-lives observed was also markedly wider (1.8-18 h, with a median of 8.3 h). This may in part have been affected by values being close to the lower limit of quantitation beginning 12 h after the last drug intake. Figures 9 and 10 show that the majority of the drug has been eliminated within 12 h post-dose, similar to what is observed after single and intravenous dosing. The effective PK half-life of ivabradine is in the range of ^{(b) (4)} h. The time-course for ivabradine and S18982 are shown in Figures 9 and 10.

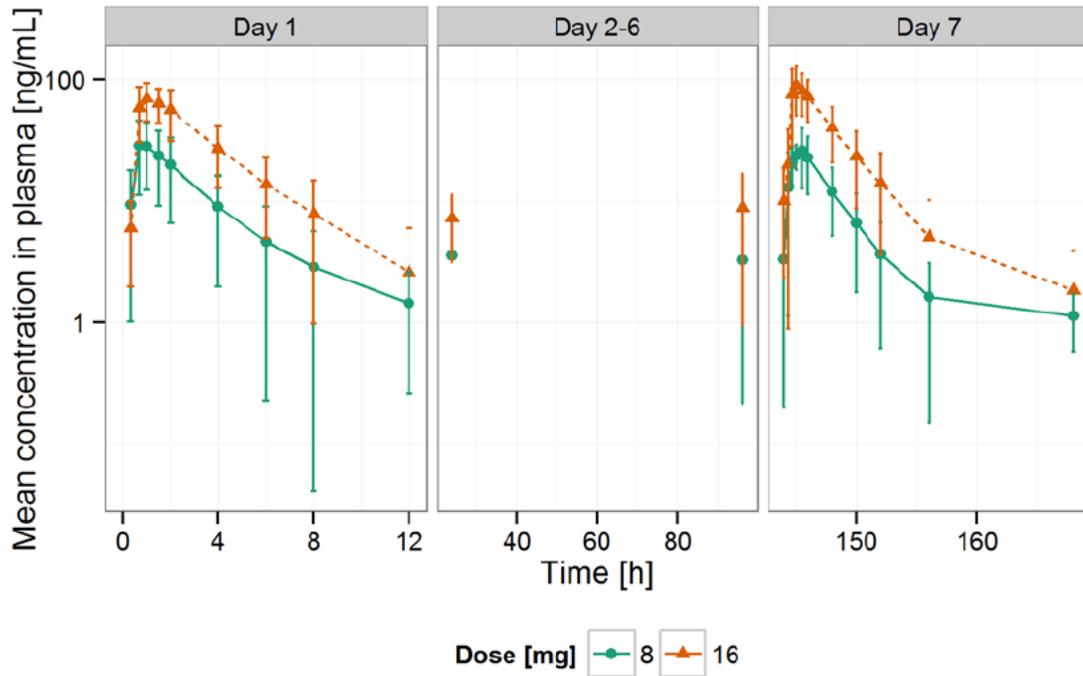


Figure 9. Mean (SD) plasma concentrations of ivabradine in the multiple ascending dose study

[Source: CSR for study CL1-16257-002, dataset: bkinet.xpt]

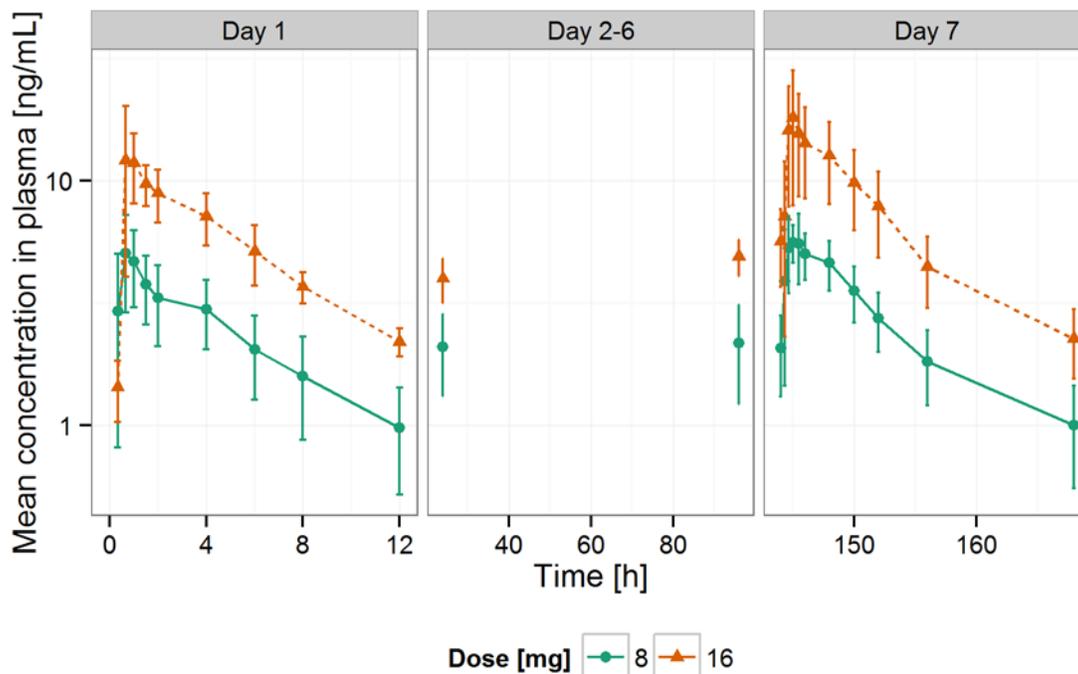


Figure 10. Mean (SD) plasma concentration of S18982 in the multiple ascending dose study

[Source: CSR for study CL1-16257-002, dataset: bkinet.xpt]

2.4.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK parameters of ivabradine and S18982 are reasonably similar between healthy subjects and heart failure patients. Table 4 below lists 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.

Table 4. Comparison of PK parameters between healthy subjects and heart failure patients

Analyte	Parameter	Healthy Subjects* (8 mg BID Capsules)	Heart Failure Patients** (7.5 mg BID tablets)
Ivabradine	AUC _T	111 ± 56	176 ± 101
	C _{max}	31 ± 12	35 ± 18
	C _{min}	3.3 ± 3.1	6.1 ± 5.3
S18982	AUC _T	43 ± 10	54 ± 17
	C _{max}	6.8 ± 2.0	7.5 ± 2.2
	C _{min}	2.2 ± 0.9	1.7 ± 1.0

*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 substudy report NP30429]

2.4.3 What are the characteristics of drug absorption?

After oral administrations, ivabradine is absorbed quickly, with a T_{max} around 0.5-2 h, which is very similar across doses and dosing regimens. The absolute bioavailability of ivabradine is on average 40%, which reflects a sizeable first-pass effect. In a mass balance study, only about 4% of radioactivity in feces was recovered as unchanged ivabradine and only one (of 4) subjects in the study showed any radioactivity in fecal samples in the first 24 h post-dose. It is likely, that the overall absorption from the gut is greater than 40%, and that most of the loss of the absorbed drug stems from the first-pass effect.

When the pharmacokinetics of ivabradine were assessed after single intravenous bolus doses ranging from 1 to 24 mg, slight elevations in concentrations were observed around 1 – 2 h post dose. These could be due to enterohepatic circulation. Since they occur around the T_{max} after an oral dose, it might be difficult to observe this effect after oral dosing.

2.4.4 What are the characteristics of drug distribution?

Ivabradine shows a mean protein binding of 70%, which indicates that small changes in protein binding are unlikely to result in major changes in pharmacokinetics. The predominant binding protein is albumin. After intravenous dosing, the volume of distribution was in the range of 60 to 70 L. Following oral administration, volume of distribution was about 100 L, which was also observed in clinical studies in patients. This indicates that ivabradine is easily distributed into tissues.

2.4.5 Based on the mass balance study, what is the major route of elimination?

About 4% of unchanged drug was recovered either in urine or in feces, suggesting hepatic metabolism as the major route of elimination. Radioactivity associated with metabolites was excreted to a similar degree in feces (around 45%) and urine (around 37%). Please see Figure 11 for a graphical representation of recovery of radioactive dose. Most of the drug was recovered in urine in the first 24 h after administration and very little radioactivity was recovered in feces during that time. The urinary excretion of radioactivity was effectively complete after 24 h, while fecal elimination of radioactivity took between 48 and 72 h to complete. Ivabradine accounted only for a third of the circulating radioactivity in plasma (Figure 12).

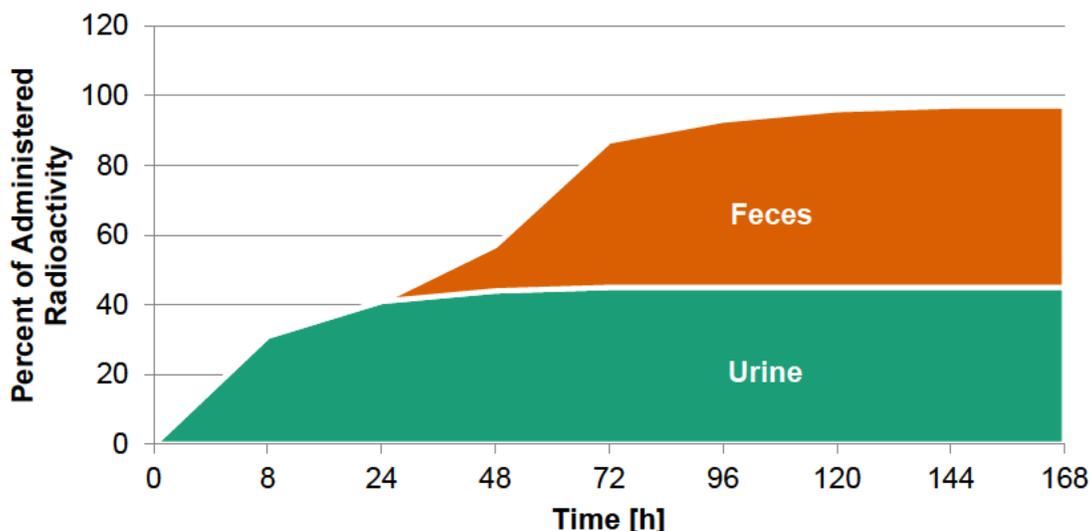


Figure 11. Excretion balance after a 20 mg oral dose of ¹⁴C-ivabradine

[Source: CSR for Study PKH-16257-002-NLD, page 40/62, Table 8]

2.4.6 What are the characteristics of drug metabolism?

Ivabradine is extensively metabolized, as can be observed from the fact that only about 4% of ivabradine dose is recovered unchanged in urine or feces. The major metabolizing enzyme for the generation of S18982 and other metabolites is CYP3A4. Figure 12 below shows the plasma concentration time profile of ivabradine and S18982 as well as the equivalent concentration for overall radioactivity. At T_{max} , ivabradine concentration accounts for only about one third of the overall radioactivity, suggesting that other metabolites are present.

In the pooled samples, the predominant metabolite was M3, which is a fragment containing the cyclobutan ring accounting for about 29 and 14% of radioactivity in the chromatogram in the 1 and 5 h samples, respectively. Other metabolites circulating at higher concentrations, about 11-14%, were M5, M6/7, M10, and M28. Ivabradine itself accounted for 27 and 15% of total radioactivity on the chromatogram of the 1 and 5 h samples, respectively. S18982 (M29) was not found in the pooled plasma samples. A schematic of the metabolic tree for ivabradine can be found in the Written Summary on Pharmacokinetics.³

³ [\\cdsesub1\evsprod\nda206143\0014\m2\26-nonclin-sum\pharmkin-written-summary.pdf](#) (Page 25 of 33)

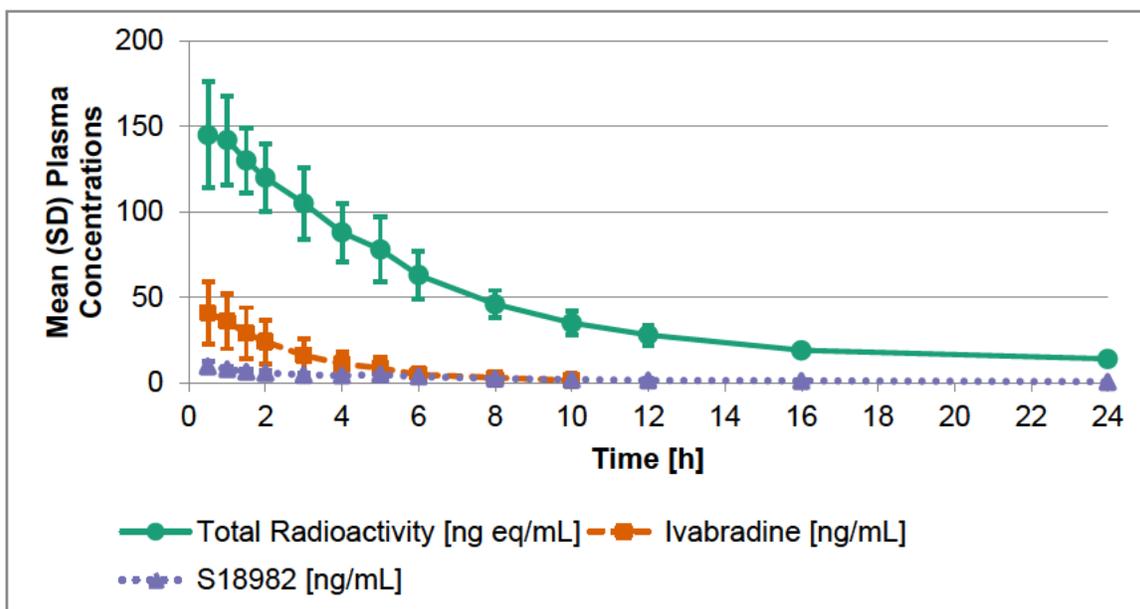


Figure 12. Mean (SD) plasma concentration of ivabradine, S18982, and total radioactivity
 [Source: Prepared by FDA from CSR for study PKH-16257-002]

2.4.7 What are the characteristics of drug excretion?

In the mass balance study, unchanged drug accounted for ~4% in the urine or feces. The metabolites of ivabradine accounted for about 37 and 47% of radioactive dose in urine and feces, respectively. This shows that the hepatic route is the major elimination pathway for ivabradine, while both hepatic and the renal route are equally participatory in the excretion of the metabolites.

2.4.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

PK parameters from single and multiple dose studies suggest that ivabradine PK is approximately dose linear in the range from 0.5 to 24 mg.

2.4.9 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-individual variability (% CV) for ivabradine was about 20 % and 55 %, respectively, for AUC and C_{max} after 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} .

2.5 Intrinsic Factors

2.5.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The population PK and PK/PD analyses were carried out mainly in healthy subjects. The covariates tested in the population PK model included sex, age, body weight and BMI. None of the covariates tested were significant, partly because of the homogenous demographics of the analysis population.

2.5.2 Are there any recommended dose adjustments based on extrinsic or intrinsic factors?

No dose adjustments are recommended based on sex or weight. (b) (4)

Please see Section 2.5.3.

2.5.3 Elderly

(b) (4)

2.5.4 Pediatric patients

(b) (4)

2.5.5 Gender

No effect of gender on exposure or response has been observed.

2.5.6 Race

During the development program, many studies were conducted in Caucasians, therefore, the ability to assess effects of race on exposure or response was limited.

2.5.7 Renal impairment

The impact of severe renal impairment on the exposure of ivabradine and S18982 has been studied. The fraction of ivabradine exposure not bound to plasma proteins was on average 38%, while in healthy subjects the mean fraction unbound was 31%. For S18982 mean protein binding in healthy subjects was 22%, while it was 24% in severe renal impairment.

The sponsor used a previously developed model to estimate pharmacokinetic parameters observed in patients with severe renal impairment and to contrast them with controls with normal renal function. This comparison showed that ivabradine AUC_{inf} and C_{max} were found to be on average 30% lower in the renal impairment group. S18982 exposure was not affected. Since the fraction of unbound ivabradine increases slightly in severe renal impairment, the unbound concentrations of AUC_{inf} and C_{max} for ivabradine and S18982 are not significantly different. The PK in patients with mild or moderate renal impairment was not characterized. However, given the lack of significant interaction in patients with severe renal impairment, no significant effect of mild/moderate impairment in renal function on the PK of ivabradine and its metabolite are expected.

Table 5. Mean (CV%) PK parameters in patients with severe renal impairment

<i>Analyte</i>	<i>Parameter</i>	<i>Mean (CV%)</i>
Ivabradine	AUC_{inf}	168 ng*h/mL (50%)
	C_{max}	16 ng/mL (50%)
S18982	AUC_{inf}	105 ng*h/mL (32%)
	C_{max}	10 ng/mL (33%)

[Source: CSR for study PKH-16257-008-FRA, dataset metapat4-cor-dm-io.v.xpt]

2.5.8 Hepatic impairment

The impact of mild and moderate hepatic impairment on pharmacokinetics of ivabradine and S18982 was assessed in a single arm study, and the results were compared to those of healthy matched controls from a previous study. In subjects with hepatic impairment, the mean fraction of ivabradine and S18982 that was not bound to plasma proteins was 38.6 (26% increase) and 53.5% (2.4-fold increase), respectively. In healthy subjects, the mean fraction unbound is 30.7 and 22% for ivabradine and S18982, respectively. Figure 13 shows the time profiles of ivabradine after i.v. and oral dose in by Child-Pugh status of patients. The sponsor concluded that most of the changes in exposure were due to protein binding changes, which were more pronounced for S18982. The heart rate reduction caused by ivabradine was similar in patients with hepatic impairment and patients without hepatic impairment.

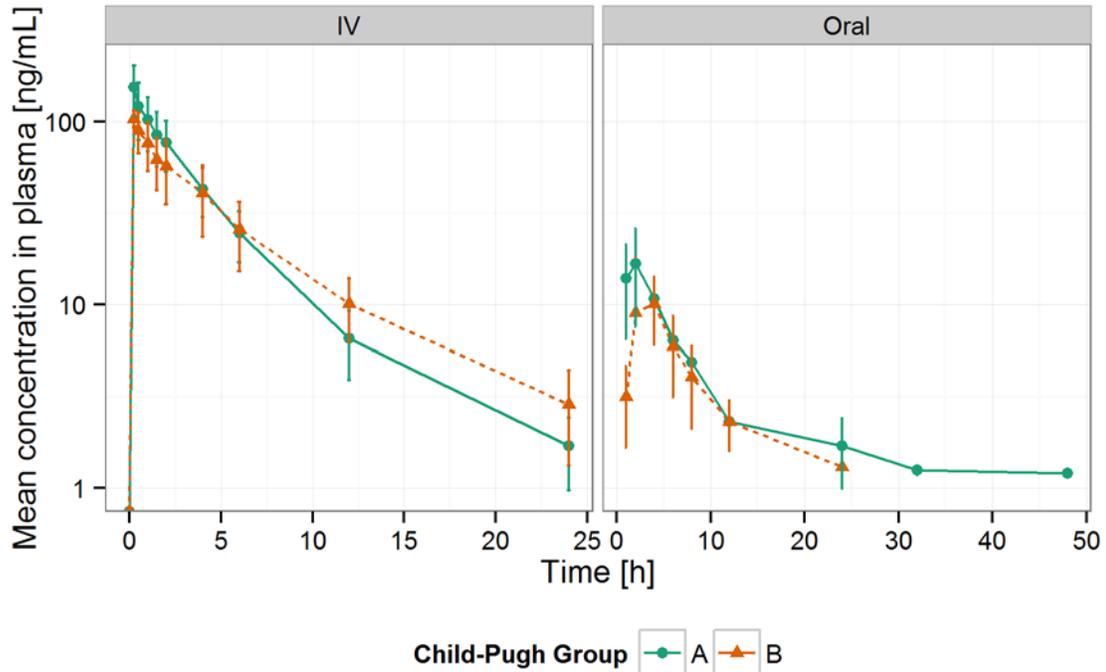


Figure 13. Mean (SD) plasma concentrations of ivabradine in patients with mild and moderate hepatic impairment

[Source: Prepared by FDA from CSR for study PKH-6257-008-FRA]

2.5.9 What pharmacogenetics information is there in the application and is it important or not

There is no pharmacogenomics information submitted with this NDA.

2.5.10 What pregnancy and lactation use information is there in the application?

In animal studies, ivabradine was found to interfere with normal heart development and in rabbits, embryo-fetal survival was reduced. The label recommends that women not become pregnant while being treated with ivabradine, (b) (4)

(b) (4) The applicant proposes labeling with (b) (4) in Europe, where use of ivabradine is contraindicated for women who are pregnant or who a looking to become pregnant. Please refer to the Pharmacology/Toxicology Review by Dr. Jean Wu for more detail into observations from animal assessments.

Since ivabradine may be secreted with milk, the proposed label suggests not to use ivabradine while nursing.

2.6 Extrinsic Factors

2.6.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Since ivabradine is extensively metabolized, there is potential for drug-drug and drug-food interactions. The sponsor has studied the impact of CYP3A4 inhibitors (including grapefruit juice) and one inducer (Hypericum perforatum extract) on the exposure of ivabradine and S18982. Further, drug interactions with commonly coadministered drugs were also assessed.

As expected, coadministration with CYP3A4 inhibitors resulted in increases in ivabradine and S18982 exposure. The co-administration with strong CYP3A4 inhibitors is proposed to be contraindicated. Coadministration with the moderate CYP3A4 inhibitors verapamil and diltiazem led to slightly lower increases in exposure compared to strong inhibitors, however, the concern is that both drugs are also inhibitors of heart rate at the sino-atrial node. Therefore, the coadministration is not recommended.

2.6.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Ivabradine and S18982 are found *in vitro* to be substrates of CYP3A4, therefore, the potential for drug-drug interactions exists.

2.6.3 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Ivabradine and S18982 are substrates for CYP3A4 and *in vitro* studies suggest that it may be the only relevant drug metabolizing enzyme for both compounds. The influence of genetic polymorphism on metabolism has not been assessed. *In vitro* metabolism in human liver microsomes showed an intrinsic clearance of 16.3 and 10.1 mL/min/g protein and an extrapolated hepatic clearance of approximately 55 mL/min for ivabradine and 400 mL/min for S18982. These numbers are in relative agreement with values observed *in vivo*.

2.6.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Ivabradine and S18982 were found to inhibit cytochrome P450 enzymes only at concentrations significantly greater than what is observed at clinically relevant doses.

2.6.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

S18982 is transported by P-gp, but not BCRP. The IC₅₀ for inhibition of P-gp is 5.3 μM, which corresponds to a concentration of 2,400 ng/mL, which is at least two orders of magnitude higher than observed total plasma concentrations for this compound. As such, the capacity to inhibit P-gp at relevant systemic concentrations is small. However, the concentration of ivabradine in a 7.5 mg dose is similar to the IC₅₀ determined *in vitro*, but it is lower than the guidance recommended threshold of 10 times the ratio of molar

dose to IC_{50} for the decision of conducting a study. A drug-drug interaction with digoxin in healthy volunteers did not lead to changes in PK parameters.

2.6.6 Are there other metabolic/transporter pathways that may be important?

(b) (4)
This was the basis for a drug-drug interaction study with metformin.

2.6.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Ivabradine can be used either alone or in combination with beta-blockers, if the maximally tolerated dose of beta-blockers does not yield sufficient results. A DDI study with atenolol did not indicate a PK or PD interaction.

2.6.8 What other co-medications are likely to be administered to the target patient population?

Patients with chronic heart failure may also be treated with beta-receptor antagonists, angiotensin-converting enzyme (ACE)-inhibitors, or angiotensin receptor blockers (ARBs), aldosterone antagonists, diuretics, nitrates, statins, and digoxin.

2.6.9 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Drug-drug interaction studies that were done with CYP3A4 inhibitors and one inducer did yield actionable recommendations. Please see the forest plots in Figures 14 and 15 for reference.

Ketoconazole and Josamycin – Strong CYP3A4 Inhibitors

When ivabradine was coadministered with ketoconazole, AUC_{inf} increased on average 7.7-fold, while C_{max} was increased 3.6-fold. S18982 AUC_{inf} increased on average 1.3-fold and C_{max} decreased about 2-fold. Substantially similar results were observed with Josamycin.

Heart rate changes were observed for both studies (ketoconazole and josamycin), where heart rate was lower at 4 and 8 h time points compared to administration of ivabradine alone. Since the studies enrolled healthy subjects, in the HR effects associated with the high exposures may not be applicable to a patient with intrinsic conduction system disorder.

The proposed labeling language recommends a contraindication for the use of ivabradine with strong CYP3A4 inhibitors. Since a dosage form that could be made useful for a dose adjustment is not available and there may be increased risk to patients associated with almost 8-fold increase in exposures, the contraindication is reasonable.

Verapamil and Diltiazem – Moderate CYP3A4 Inhibitors with Negative Chronotropic Activity

Coadministration with verapamil or diltiazem resulted in 2- and 3-fold increase in ivabradine AUC_{inf}, respectively. C_{max} was increased 1.9- and 2.5-fold. S18982 exposures were affected slightly less, AUC_{inf} increased 1.5- and 1.2- fold and C_{max} was increased 1.5- and 1.6-fold, respectively. The coadministration with diltiazem was well tolerated and none of the healthy subjects in the study showed major adverse events related to extensive lowering of heart rate or other conduction problems. In the verapamil study in healthy subjects, Holter and cardiac monitoring showed an increase in ventricular extrasystoles and one subject showed a junctional escape rhythm for part of an overnight period when verapamil was coadministered with ivabradine.

Based on the potential for interactions due to a potentially combined negative chronotropic effect, the proposed labeling language issues a negative recommendation for the concomitant use of ivabradine with either drug.

St. John's Wort – CYP3A4 Inducers

After coadministration with St. John's Wort extract 300 mg three times per day, both C_{max} and AUC of ivabradine were decreased on average by half. [REDACTED] (b) (4)

[REDACTED] exposures (C_{max} and AUC) were less affected by coadministration than those of ivabradine and heart rate reductions at rest were slightly lower.

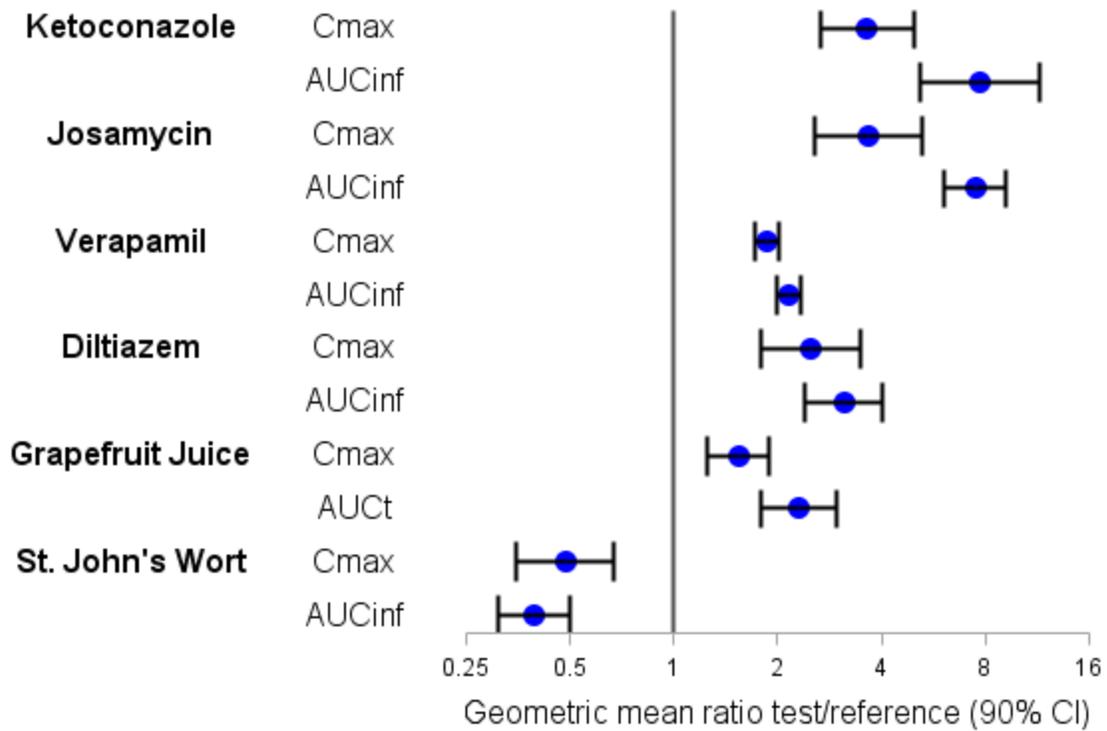


Figure 14. Geometric mean ratios obtained from DDI studies for Ivabradine

[Source: FDA reviewer's analysis]

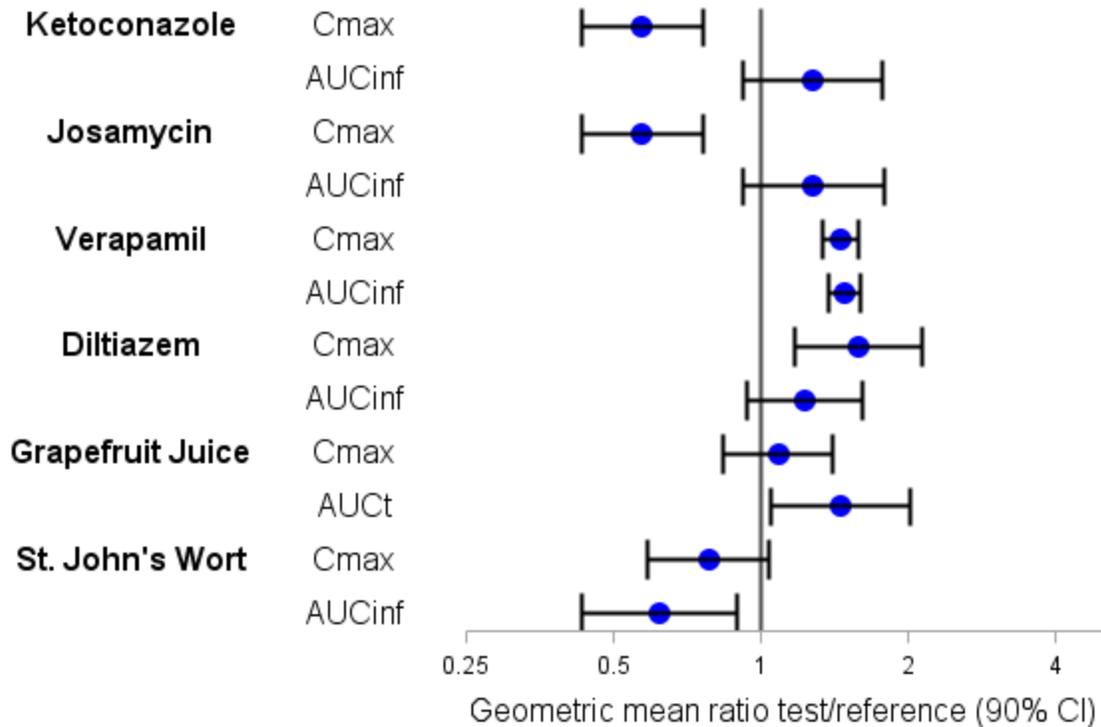


Figure 15. Geometric mean ratios of S18982 exposures obtained from DDI studies for ivabradine

[Source: FDA reviewer's analysis]

Digoxin

Digoxin or ivabradine exposures were not altered when both were coadministered. Further, the reduction of heart rate when ivabradine was added to digoxin was similar to that observed in healthy subjects receiving ivabradine alone. However, healthy subjects may not be the appropriate population to compare pharmacodynamic effects, as digoxin can lead to larger reductions in heart rate in heart failure compared to what was observed in healthy subjects. Therefore, patients who receive both digoxin and ivabradine should be monitored carefully.

2.6.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Please see Section 2.6.9 for potential interactions based on chronotropic actions with verapamil and diltiazem.

The SHIFT study allowed guideline recommended heart failure therapy, including beta blockers. A pre-specified subgroup analysis showed that ivabradine treatment is more favorable in subjects with no beta blocker intake at randomization compared to those subjects using beta blockers (hazard ratio 0.68, 95 % CI 0.52-0.99 vs. 0.85, 95 % CI

0.76-0.94). The treatment effect seemed to be minimal for subjects using beta blockers at or above their target daily dose (Table 1).

Table 6. Estimates of the effect of randomized treatment by baseline beta blocker usage category

Beta blocker use at baseline*	Number of PCE events		Hazard Ratio (95 % CI)
	Ivabradine	Placebo	
No beta blocker	101	134	0.71 (0.55-0.93)
< 25 %	148	171	0.74 (0.59-0.92)
25 to < 50 %	204	260	0.81 (0.68-0.98)
50 to < 100 %	181	212	0.88 (0.72-1.07)
≥ 100 %	149	150	0.99 (0.79-1.24)

*Beta blocker use as % of target daily dose

[Source: Section 2.7.3 Summary of Clinical Efficacy-SHIFT, Page 113]

2.7 General Biopharmaceutics

2.7.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

(b) (4)

Ivabradine shows an absolute bioavailability of 40%. In the mass balance study about 97% of the administered radioactivity was recovered, approximately 4% as unchanged drug in urine and feces, respectively, suggesting that the remaining radioactivity underwent some form of metabolism; however, whether this is due to intestinal or hepatic first pass mechanisms cannot be verified. The oral and intravenous single and multiple ascending dose studies suggest that both C_{max} and AUC are linear in the range from 1 to 24 mg, with T_{max} in oral studies occurring around 1 to 2 hours

In summary, the available information (mass balance results, dose linearity, fast T_{max} , small fraction of dose excreted unchanged) suggests that ivabradine can cross intestinal membranes freely. It is a substrate and potentially an inhibitor for P-gp and the degree to which this impacts absorption is not entirely clear. The low absolute bioavailability is likely due to an extensive first-pass phenomenon, with contributions from intestinal and hepatic metabolism.

2.7.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food increased the AUC_{inf} for ivabradine by 1.42-fold and for S18982, the AUC_t was increased 1.24-fold. C_{max} for ivabradine and S18982 was increased 1.45- and 1.14-fold, respectively. Ivabradine C_{max} occurred about 15 to 45 min later compared to fasted administration, S18982 T_{max} was increased by 45 min to 2 h. The applicant recommends administering ivabradine tablets with meals. Ivabradine was administered with meals in most clinical studies, including the pivotal clinical trial SHIFT.

2.8 Analytical section

The total concentrations of analytes ivabradine and S18982 were identified in plasma and urine by a number of methods.

The bioanalysis method utilizes high-performance liquid chromatography (HPLC) followed by fluorescence detection at 283 and 328 nm. It was first developed to detect ivabradine only, and then extended to detect S18982 as well. This method was used in all studies that were conducted prior to 2005, i.e. most of the clinical pharmacology studies. The method was cross validated by (b) (4) with an extended linear range for studies conducted after 2005. Both methods met validation criteria. Their performance throughout the individual studies is detailed in the individual study reports and was found to be acceptable.

The method used after 2005 was an LC/MS/MS method and also performed according to applicable standards (FDA Guidance for Bioanalytical Method Validation). It was linear in the range from 0.250 to 250 ng/mL for both ivabradine and S18982. No interferences were observed with ivabradine or S18982 eluting peaks. Spiked plasma samples of ivabradine and S18982 were found to be stable after a period of 26 months stored at -20 °C.

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MARTINA D SAHRE
11/26/2014

SREEDHARAN N SABARINATH
11/26/2014

JEFFRY FLORIAN
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RAJANIKANTH MADABUSHI
11/26/2014

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 206-143 (000)	Reviewer: Sandra Suarez Sharp, Ph.D.	
Division:	DCRP		
Applicant:	AMGEN, INC.	Team Leader: Angelica Dorantes, Ph.D.	
Trade Name:	Corlanor (ivabradine) Tablets	Acting Supervisor: Paul Seo, Ph.D.	
Generic Name:	Ivabradine IR film-coated tablets	Date Assigned:	March 31, 2014
Indication:	Treatment of chronic heart failure	Date of Review:	Nov 19, 2014
Formulation/strength	IR Tablets 5 mg and 7.5 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates		Date of Informal/ Formal Consult	Primary Review Due Date in Panorama
04/30/14 08/18/14 10/03/14 11/18/14		March 31, 2014	
Type of Submission:	Original NDA (Priority Review)/Fast Track Designation		
Key review points	<ol style="list-style-type: none"> 1. Use of disintegration in lieu of dissolution testing 2. Disintegration acceptance criterion 3. (b) (4) 4. Bridging throughout the phases of drug product's development 		

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Amgen, Inc. seeks approval of Ivabradine Tablets for the treatment of chronic heart failure. Ivabradine was originally developed by Les Laboratoires Servier and this drug product has been already approved outside the United States (U.S.A.) in several countries for the treatment of chronic heart failure and for the treatment of angina. The efficacy and safety of ivabradine for the proposed indication is supported primarily by the results of a single large, randomized, placebo-controlled study with support from 5, phase 2 heart failure studies conducted outside the US (foreign clinical data).

Ivabradine hydrochloride is formulated as an immediate release oral solid dosage form in strengths of 5 mg and 7.5 mg of Ivabradine as the free base equivalent. The two strengths are considered (b) (4) and the Applicant states that the PK is approximately dose proportional over the 2.5 to 7.5 mg dose range. The 5 mg tablet is scored. CMC and dissolution data were provided to justify the bridging between split and non-split tablets.

There are two manufacturing sites for the drug product under review; (b) (4) which are the proposed and previous manufacturing sites, respectively. Dissolution data were submitted to support the bridging.

The Biopharmaceutics review is focused on the evaluation and acceptability of the data supporting: 1) The use of disintegration in lieu of dissolution testing; 2) Disintegration acceptance criterion; 3) (b) (4) and 4) Bridging throughout the phases of drug product development.

1) Disintegration in Lieu of Dissolution Testing:

Disintegration is being proposed in lieu of dissolution testing based on the recommendations described in the ICH 6QA guidance:

1. Drug substance solubility is (b) (4)
2. Rapid dissolution (> (b) (4)% in 15 min) of the formulation throughout the same pH range,
3. There is a correlation between dissolution and disintegration testing or disintegration is more sensitive than dissolution to manufacturing changes.

The data submitted demonstrated that the drug substance has (b) (4) and the drug product dissolves (b) (4) (> (b) (4)% in 15 min) across the physiologically relevant range of pH. In addition, the data included show that disintegration is likely to be more sensitive to changes in (b) (4). The results from the long-term stability data also showed no change in the dissolution/disintegration performance under the conditions studied.

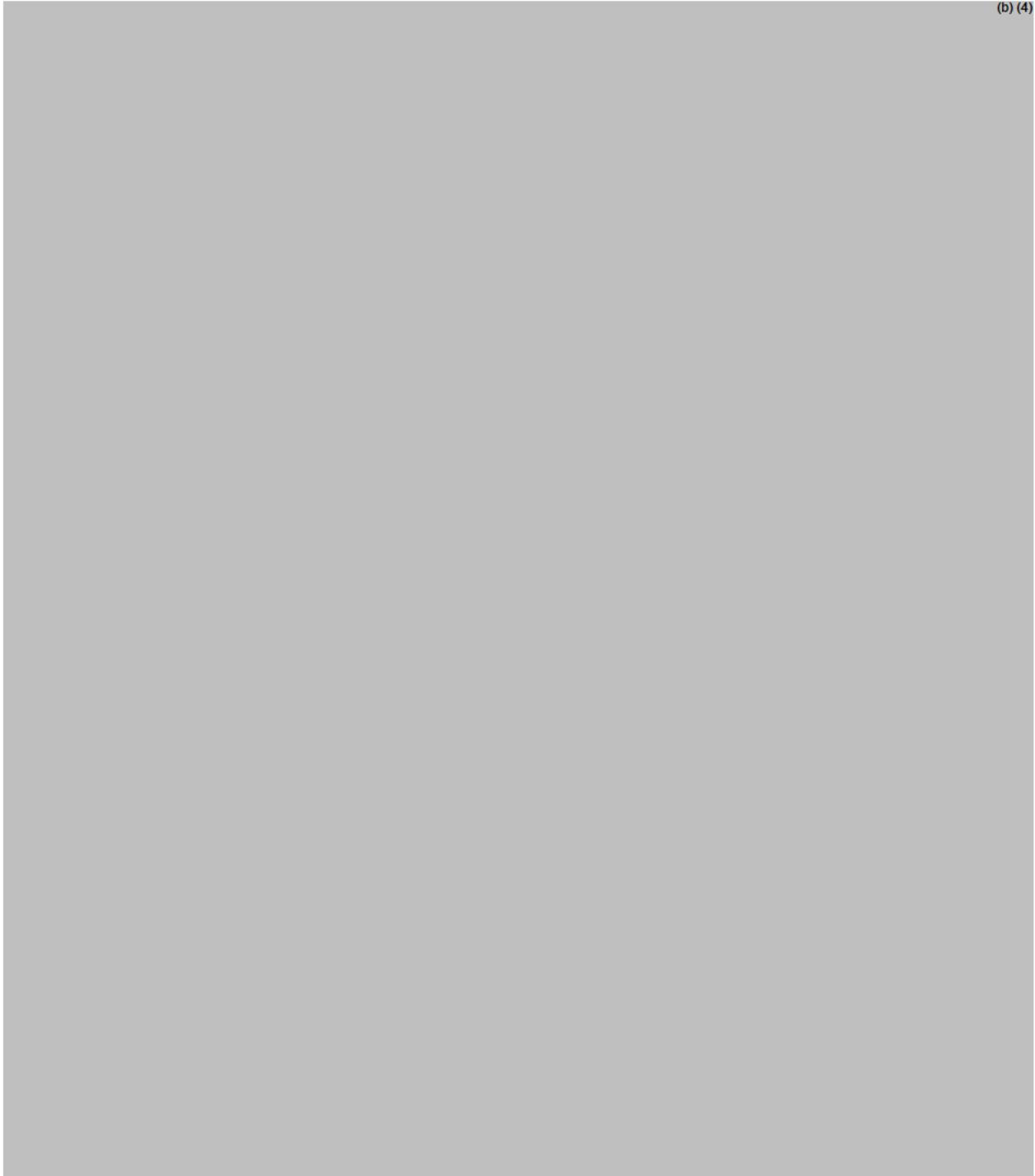
Since this drug product meets the criteria listed under ICH guidance Q6A for using disintegration testing, dissolution is not included in the QC tests of the drug product.

2) Disintegration Acceptance Criterion

The following disintegration acceptance criterion was agreed upon with the Applicant (refer to submission dated Nov 18, 2014) for both strength of the proposed product:

Proposed Disintegration Acceptance criterion
≤ 10 minutes

(b) (4)





Reviewer's Evaluation – (b) (4)

The classification of Corlanor (ivabradine Tablets, 5 mg and 7.5 mg as (b) (4) drug substance/drug product is currently PENDING, because the review of the (b) (4) (b) (4) has not been completed by OCP's Clinical Pharmacology team as of November 21, 2014.

After the Clinical Pharmacology team, complete their review on whether ivabradine is a (b) (4) (b) (4) t (e.g. mass balance, oral BA, linear PK), (b) (4) (b) (4)

(b) (4)

It is noted that the approvability of this NDA is not affected by the BCS designation of Ivabradine Tablets and therefore, the FDA's (b) (4) recommendation can be conveyed to the Applicant at any time once a decision is made.

4) Appropriate Bridging Throughout Phases of Drug Development

During the clinical development of ivabradine, several oral formulations and a solution for injection were manufactured and administered to subjects and patients. The Applicant is proposing to change the drug product's current manufacturing site, (b) (4)

To support this change, in vitro dissolution comparisons in 3 media were performed. The data showed that more than (b) (4) % of the label amount is dissolved in 15 min for both strengths in all 3 media. Therefore, the proposed change in manufacturing site is acceptable from biopharmaceutics perspective.

In addition, the in vitro dissolution profiles of the definitive tablet over-encapsulated in hard-gelatin capsule vs. not encapsulated, were compared at physiological pH of (b) (4). The definitive tablet and the over-encapsulated definitive tablet for three of the dose strengths used in clinical studies (5, 7.5, and 10 mg) comply with the definition of a rapidly dissolving across the media/pH tested.

The majority of PK studies and all phase III trials were conducted with the final formulation. Specifically, there is PK information on the final commercial formulation. These data along with the dissolution profiles comparisons for the manufacturing sites are providing an acceptable bridging throughout the phases of development.

5) Risk Assessment Evaluation:

(b) (4)

(b) (4) from the Biopharmaceutics perspective, Ivabradine IR tablets is considered a low risk drug product. Refer to the CMC review for the overall quality risk assessment table of this product.

Risk Assessment for Corlanor (ivabradine) Tablets

Initial Biopharmaceutics Risk Assessment			Final Biopharmaceutics Risk Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Disintegration	None identified	L	<ul style="list-style-type: none"> Disintegration testing is more sensitive than dissolution to changes in hardness. The drug substance is (b) (4) and the product dissolves within 15 min. 	Acceptable	(b) (4)

II) RECOMMENDATION

From the Biopharmaceutics perspective, NDA 206-143 for Corlanor (ivabradine) IR film-coated Tablets, 5 mg and 7.5 mg, is recommended for **APPROVAL**.

**Sandra
Suarez -A**

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Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Angelica
Dorantes -S**

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Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

A) GENERAL ATTRIBUTES

Drug Substance

The physical and chemical properties of ivabradine hydrochloride are summarized in Table 1.

Table 1. Physicochemical properties of Ivabradine

Physical and Chemical Properties	Results
Appearance	white to slightly yellow powder
Solubilities according to European Pharmacopoeia 1.4 ^{a, b}	(b) (4)
purified water	
acetone	
dimethylsulfoxide (DMSO)	
ethanol	
methanol	
methylene chloride	
Solubilities at saturation in aqueous medium after 2 hours ^a :	
purified water	
glucose solution (5 %)	
saline solution (NaCl 0.9 %)	
Solubilities in 0.15 M KCl as a function of the pH ^{a, d}	
pH=1.1	
pH=4.5	
pH=6.8	
pH=7.6	
pH=8.0	
pH=8.5	
pH=9.1	
pH=9.5	
pH=10.1	
pH=12.0	

Physical and Chemical Properties	Results
Solubility for the neutral form (B) in 0.15 M KCl ^a	(b) (4)
Dissociation constant (pKa ₁ of couple BH ⁺ /B)	
Dissociation constant (pKa ₂ of couple BH ₂ ²⁺ /BH ⁺)	
logP octanol/0.1 M KNO ₃ (neutral form B)	
logP octanol/0.1 M KNO ₃ (ionised form BH ⁺)	
logP octanol/0.1 M KNO ₃ (ionised form BH ₂ ²⁺)	
logD octanol/0.1 M KNO ₃ (pH 7.4)	
pH in aqueous solution at 10 mg/mL (23°C)	
Specific optical rotation (10 g/l, dimethylsulfoxide)	
Melting point (determined by DSC at 5°C/minute)	
Ultraviolet spectrum	
Hygroscopicity	

The solubility of S 16257-2 is high between pH 1 and pH 8. According to the Applicant, because of the (b) (4) solubility, particle size distribution and (b) (4) are not expected to affect drug product performance. The (b) (4) of S 16257-2 is ensured by the manufacturing process and by conformance of the IR spectrum required in the drug substance specification. The pH solubility profile is presented in Figure 1.

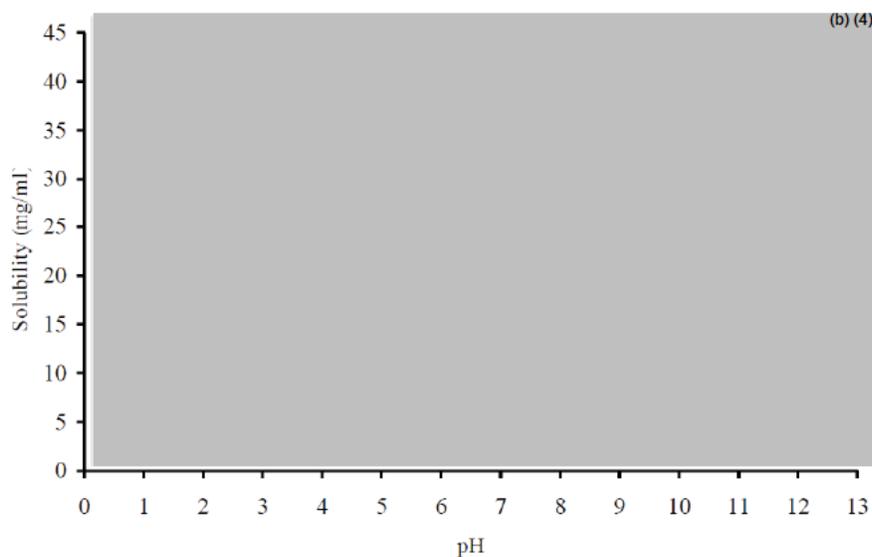


Figure 1. Solubility Profile of Ivabradine Hydrochloride in 0.15 M KCl as a Function of pH

The following information request was submitted to the Applicant in regards to the potential for solid state transformation:

- *Provide data on the physicochemical properties (eg, solubility profile, melting point, hygroscopicity, and intrinsic dissolution) for all of the potential solid state forms of ivabradine hydrochloride drug substance. If there are clear differences in these physicochemical properties (eg, low solubility at the physiologically relevant pH), then you should provide justification for the lack of impact of any observed differences on the bioavailability of the drug product.*

The Applicant response received on Aug 18, 2014, can be summarized as follows:

According to the Applicant (b) (4)

(b) (4)

Dissolution profiles of tablets containing (b) (4) release greater than (b) (4) of the drug content in 15 minutes. These results strongly support that tablets containing different levels of (b) (4) will have a similar rapid dissolution behavior (for more details refer to:

<\\CDSESUB1\evsprod\NDA206143\0035\m1\us>.

Drug Product

The 5 mg strength is presented as salmon colored, oval shaped, film-coated tablet, scored on both edges, debossed with “5” on one face and bisect on the other face. The 7.5 mg strength is presented as salmon colored, triangular shaped, film-coated tablet, debossed with “7.5” on one face and plain on the other face. The components and composition of the tablets are summarized in Tables 2 and 3.

Table 2. Composition of Ivabradine 5 mg and 7.5 mg Tablets

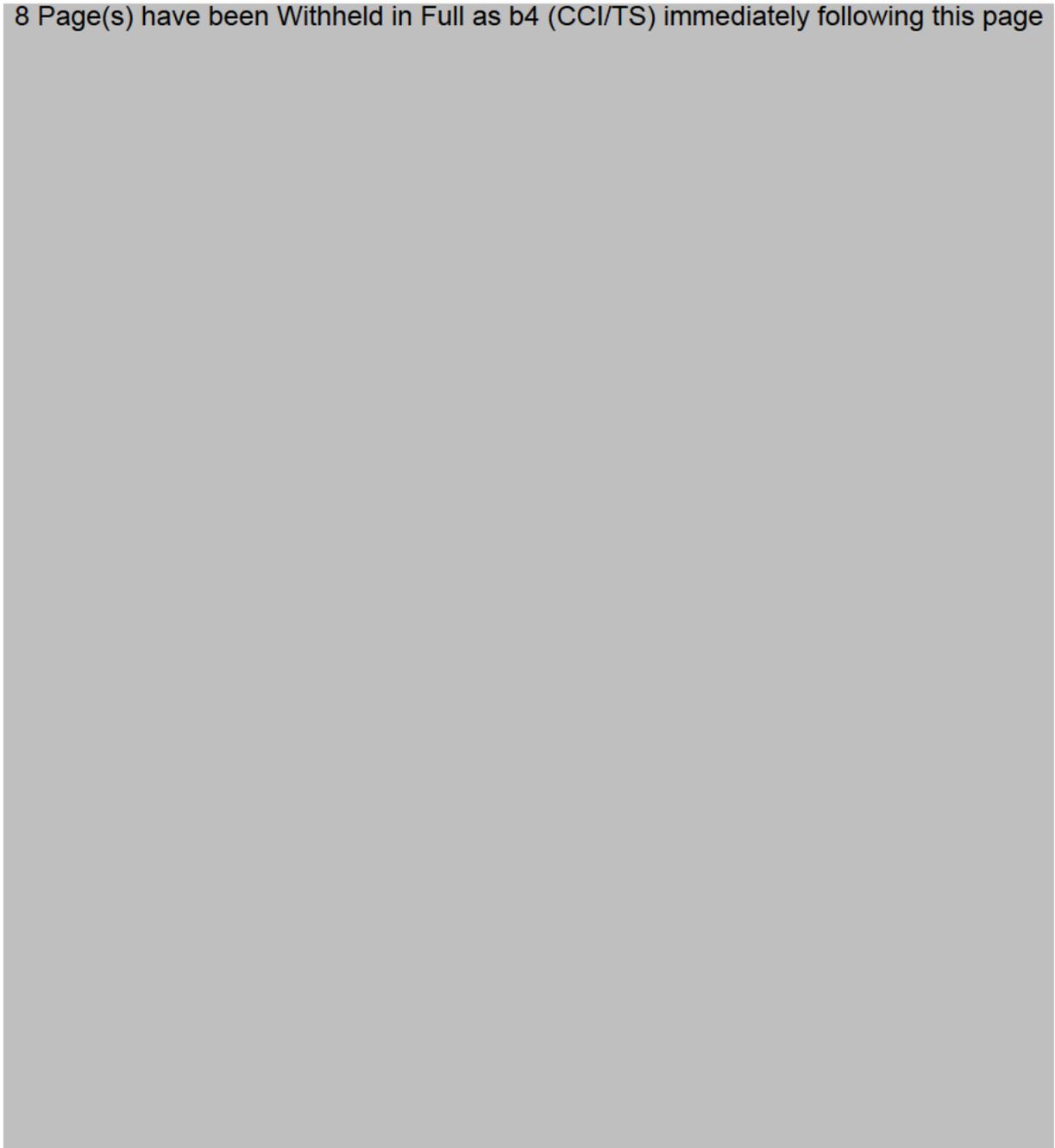
Component	5 mg		7.5 mg		Function	Reference to specifications
	Percentage (% w/w)	Quantity (mg/tablet)	Percentage (% w/w)	Quantity (mg/tablet)		
Tablet						
Ivabradine hydrochloride ^a (free base equivalent)	5.39 (5.00)	5.390 (5.000)	8.085 (7.50)	8.085 (7.500)	Drug substance	In-house
Lactose monohydrate	(b) (4)				(b) (4)	USP/NF, PhEur.
Maize starch	(b) (4)				(b) (4)	USP/NF
Maltodextrin	(b) (4)				(b) (4)	USP/NF, PhEur
Magnesium stearate	(b) (4)				(b) (4)	USP/NF, PhEur
Colloidal silicon dioxide (b) (4)	(b) (4)				(b) (4)	USP/NF, PhEur
	(b) (4)				(b) (4)	USP
Core Tablet Total	(b) (4)				(b) (4)	(b) (4)
Film-Coating						
(b) (4) salmon ^c	(b) (4)				(b) (4)	See 3.2.P.4.1
Polyethylene glycol 6000 (b) (4)	(b) (4)				(b) (4)	USP/NF, PhEur
	(b) (4)				(b) (4)	USP
Total	102.0	102.0	102.0	102.0		(b) (4)

^a The molecular weights of Ivabradine hydrochloride anhydrous and ivabradine free base are 505.1 g/mol and 468.6 g/mol, respectively. (b) (4)

Table 3. Qualitative and Quantitative Composition of (b) (4) Salmon

Ingredients	% w/w (b) (4)	Compendial References
Hypromellose	(b) (4)	USP/NF
Titanium dioxide (b) (4)	(b) (4)	USP/NF
Glycerol	(b) (4)	PhEur
Magnesium stearate	(b) (4)	USP/NF
Polyethylene glycol 6000	(b) (4)	USP/NF
Iron oxide (b) (4) yellow	(b) (4)	USP/NF
Iron oxide (b) (4) red	(b) (4)	USP/NF

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C. DISSOLUTION INFORMATION

The Applicant is proposing the use of disintegration in lieu of dissolution testing based on the recommendations described in the ICH 6QA guidance:

4. Drug substance solubility is (b) (4)
5. (b) (4) dissolution (> (b) (4) % in 15 min) of the formulation throughout the same pH range,
6. There is a correlation between dissolution and disintegration testing.

Data demonstrating (b) (4) and (b) (4) dissolution were presented above. However, to justify the use of disintegration, no data were presented showing that the drug substance does not exhibit polymorphism or that there is a control implemented for it. Also, there were no data showing a correlation between dissolution and disintegration or that disintegration testing is more sensitive than dissolution towards formulation/manufacturing changes. Therefore, during the review cycle, several comments were conveyed to the Applicant as follows:

In a response dated Aug 18, 2014 the Applicant stated that (b) (4)
(b) (4)
Also, see Applicant's response above under drug substance.

- A. ***We acknowledge your proposal to use disintegration is lieu of dissolution testing. Note that if no data are provided to support the superior discriminating ability of disintegration over dissolution testing (see also comment C), you need to provide data supporting an adequate (discriminating) dissolution method for your proposed product.***

In a submission received on Aug 18, 2014, the Applicant stated that attempts to develop a discriminating dissolution media were investigated by; **a)** maintaining a low paddle speed (50 rpm), **b)** decreasing the dissolution volume to minimize sink ratio (500 mL), and **c)** varying the pH of the dissolution media within the physiological pH range (b) (4). Under all these conditions, dissolution rates of the drug product have been fast, practically superimposable, with > (b) (4) % released in 15 minutes.

- B. ***Provide data showing the superior discriminating capability of disintegration testing. The testing conducted to demonstrate the discriminating ability of this test should compare the dissolution profile and disintegration time of the drug product manufactured under target conditions vs. aberrant products intentionally manufactured with meaningful variations (i.e., +/-10-20% outside established specification ranges) for the most critical formulation and manufacturing parameters.***

On Aug 18, 2014 the Applicant stated that disintegration rate of the drug product was evaluated and, as expected, has also been consistently fast (< 10 minutes) and added that a direct relationship between fast disintegration and fast dissolution is consistent with the requirement that tablet disintegration into smaller particles should precede drug dissolution from the dispersed granules.

According to the Applicant, a 23-run DOE study for each strength was conducted to investigate the influence of variations in process parameters (all greater than 10%) on final tablet properties, including dissolution and disintegration. Table 7 shows most relevant inputs and variations for the experiment design.

Table 7. Parameters of the Optimization Study

(b) (4)

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(b) (4)

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C. Provide disintegration values of all the batches tested in pivotal phase 3 clinical trials.

The requested data are summarized on the Table 9 below submitted on Aug 18, 2014.

E. To ensure that disintegration testing is able to pick up possible changes in the dissolution rate of your product that may occur during stability, provide disintegration and multipoint dissolution profile data for the registration batches throughout the stability time-period supporting the shelf-life of your product.

The Applicant provided the requested information in a submission dated Oct 3, 2014. An example is provided on Table 11.

Table 11. Stability Data for Drug Product Batch AB2394D 5 mg Tablets in Bottles x 180 at 30°C/65%RH

Test	Time (Months)			
	Initial	3	6	9
Disintegration Time (minutes)				(b) (4)
Dissolution (% released)				
10 minutes (individual)				
10 minutes (average)				
15 minutes (individual)				
15 minutes (average)				
30 minutes (individual)				
30 minutes (average)				
45 minutes (individual)				
45 minutes (average)				
60 minutes (individual)				
60 minutes (average)				

Reviewer’s Comments

Tablets 5 and 6 show that disintegration is likely to be more sensitive than dissolution to manufacturing changes. Specifically, Table 6 shows that disintegration varies from (b) (4). In addition, Table 8 shows that disintegration is likely to be more sensitive to changes in (b) (4). These data along with the fact that the solubility of the drug substance (b) (4) is high, Applicant’s proposal of using disintegration in lieu of dissolution testing is acceptable.

B.2. ACCEPTANCE CRITERION

Disintegration is being proposed in lieu of dissolution testing. Since this drug product meets the criteria listed under ICH guidance Q6A for using disintegration testing, dissolution criterion is not being considered. The following disintegration acceptance criterion was originally proposed by the Applicant as a QC for Ivabradine IR tablet:

Proposed Disintegration Acceptance criterion
Less than (b) (4) min

Reviewer's Comments

The proposed disintegration acceptance criterion is permissive and not supported by the data. The results of the clinical batches are shown in the tablet below:

Batch Number	Strength	Reported Disintegration Time (min)
L0008910		(b) (4)
L0008911		(b) (4)
L0011230		(b) (4)
L0011281		(b) (4)
L0012452		(b) (4)
L0012453		(b) (4)
L0013975		(b) (4)
L0013977		(b) (4)
L0017120		(b) (4)
L0017875		(b) (4)
L0018137		(b) (4)
L0018142		(b) (4)
L0020219		(b) (4)
L0020220		(b) (4)
L0022040		(b) (4)
L0022041		(b) (4)

Based on these data, the following acceptance criteria for disintegration were recommended on an IR letter dated Nov 14, 2014:

Proposed Disintegration Acceptance criterion
5 mg Tablets: \leq (b) (4) minutes
7.5 mg Tablets: \leq (b) (4) minutes

In a submission dated Nov 18, 2014, the Applicant proposed a common criterion for disintegration of ≤ 10 min for both strengths. This proposal was found acceptable given that the product is (b) (4) dissolving and the drug substance in (b) (4).

APPROPRIATE BRIDGING ACROSS PHASES OF DEVELOPMENT

During clinical development of ivabradine, several oral formulations and a solution for injection have been manufactured and administered to subjects and patients, as summarized below and in Table 12.

Type A formulation: a hard gelatin capsule at doses ranging between (b) (4) mg was the first pharmaceutical formulation developed and used in the early phase I studies or in the first study conducted in patients (CL2 006).

Type B formulation: a solution for injection (b) (4) used in the context of some clinical pharmacology and pharmacokinetic studies.

Type C formulation: a film-coated tablet formulation was manufactured at doses ranging between 2.5 mg and 10 mg with a final tablet weight of (b) (4) mg. This experimental tablet was used for two phase II studies including the pivotal dose-ranging study in patients, CL2 009, and one PKH study.

Type D formulation: this definitive formulation was manufactured at doses of 5 mg, 7.5 mg, and 10 mg with a (b) (4) weight of (b) (4) mg. This formulation has been used for the Phase III trials and most of the Phase I and Phase II studies, namely CL1, CL2 and PKH studies.

Type E formulation: the type D tablets were over-encapsulated to maintain blinding conditions for clinical studies involving comparators or to achieve the targeted dose with tablet halves.

Table 12. Ivabradine - Oral Pharmaceutical Formulations and Clinical Studies

Pharmaceutical oral formulations	Protocol number			
	CL1	CL2	CL3	PKH
Hard-gelatin capsule formulation)	001, 002, 005, 007, 008	006		001, 003 (type A
Experimental tablet: coated tablet with a finished mass of 130 mg (type C formulation)		009, 013		004 film-
Definitive tablet: coated tablet with a finished mass of 102 mg	024, 027, 029, 033, 036, 038, 041, 042, 043, 049, 055	026, 030, 050, 052, 054, 062	018, 021, 022, 044, 056, (b) (4)	005, 006, 007, film-coated tablet with a finished mass of 102 mg, 008, 009, 010, 012, 013, 015, (type D formulation)
Encapsulated definitive (type E formulation)	048	028, 047	017, 019, 023	012 tablet

Data Supporting the Manufacturing Site Change

The drug product manufacturing site will change from the current site, (b) (4). In vitro dissolution comparisons in 3 media were performed. The data showed that more than (b) (4)% of the label amount is dissolved in 15 min for both strengths in all 3 media. Therefore, the change in manufacturing site is acceptable from biopharmaceutics perspective.

In addition, the in vitro dissolution profiles of the definitive tablet over-encapsulated in hard-gelatin capsule or not, were compared at physiological pH of (b) (4). The definitive tablet and the over-encapsulated definitive tablet for three of the dose strengths used in clinical studies (5, 7.5, and 10 mg) comply with the definition of a rapidly dissolving across the media/pH tested (Figure 6 for pH (b) (4) for more details see <\\CDSESUB1\evsprod\NDA206143\0017\m2\27-clin-sum>).

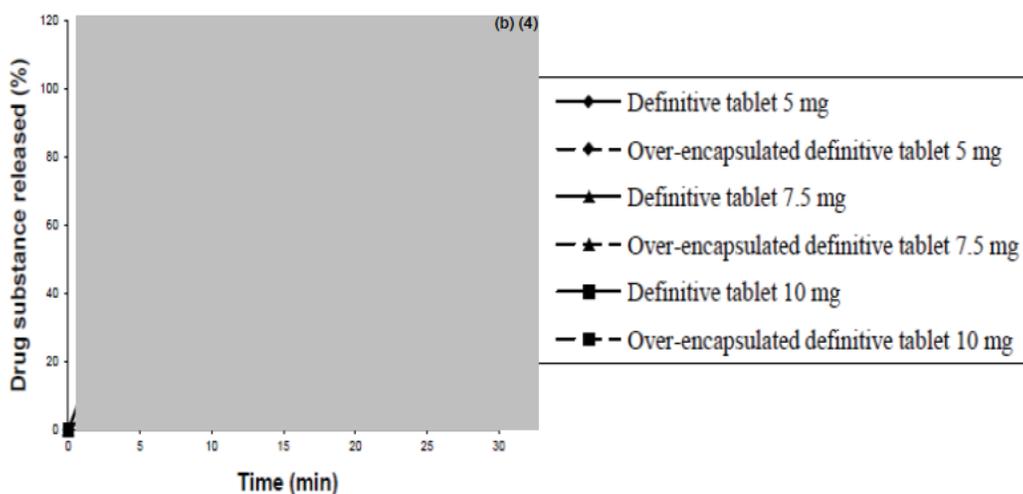


Figure 6. Comparison of the Dissolution Profiles of the Over-encapsulated Definitive Tablet and the Non Over-encapsulated Definitive Tablet.

Reviewer's Comments

As shown above in Table 12, the majority of PK studies and all phase III trials were conducted with the final formulation. Specifically, there is PK information on the final commercial formulation. These data along with the dissolution profiles comparisons across manufacturing site provides a complete bridging throughout the phases of product's development.

**Office of Clinical Pharmacology
New Drug Application Filing and Review Form**

<i>General Information</i>			
<p>Background: Amgen Inc. has submitted NDA 206,143, ivabradine, for the reduction of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4).</p> <p>Ivabradine is approved in several countries outside the US for the treatment of angina pectoris (since 2005), and chronic heart failure (since 2012). The applicant obtained U.S. licensing rights from Les Laboratoires Servier, the original developer of ivabradine. Servier conducted one clinical trial (CL3-063, SHIfT) to support the heart failure indication. This multi-center trial was done entirely outside of the U.S. Servier met with the Agency on November 15, 2011, and Amgen met with the Agency on January 23, 2014 to discuss the steps that would be necessary to submit an NDA for ivabradine.</p>			
	Information		Information
NDA/BLA Number	206,143	Brand Name (proposed)	Corlanor
OCP Division	I	Generic Name	Ivabradine
Medical Division	Cardiovascular and Renal Products	Drug Class	Inhibitor of I_f current
OCP Reviewer	Martina Sahre, PhD	Indication(s)	Chronic heart failure
OCP Team Leader	Rajanikanth Madabushi, PhD	Dosage Form	Tablet
Pharmacometrics Reviewer	Sreedharan Sabarinath, PhD	Dosing Regimen	BID
Pharmacometrics Team Leader	Jeffry Florian, PhD	Route of Administration	Per os
Date of Submission	6/27/2014	Applicant	Amgen Inc.
Estimated Due Date of OCP Review	12/6/2014	Priority Classification	Y
Medical Division Due Date		PDUFA Due Date	2/27/2015

<i>Clinical Pharmacology Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	PKH-002
Isozyme characterization:	X	11	11	NP06900, NP29916, NP16117, NP16173, NP15184, NP07226, NP15218, NP25546, NP08070, NP16016, NP08471
Transporters	X	3	3	NP32566, NP32565, NP31384
Blood/plasma ratio:	X	1	1	NP07530
Plasma protein binding:	X	1	1	NP15217
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	2	CL1-001 (FIH), CL1-039,
multiple dose:	X	3	2	CL1-002, CL1-040
Patients-				
single dose:	X	1	1	CL2-006 (sAP)
multiple dose:	X	s.b.	s.b.	CL3-063
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	PKH-017
fasting / non-fasting multiple dose:	X	1	1	PKH-003 (Timing)
Drug-drug interaction studies -				

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
In-vivo effects on primary drug:	X	21	16	PKH-004 (K), PKH-005 (J), PKH-006 (K), PKH-009 (PPI), PKH-012 (K), PKH-014 (StJW), CL1-027 (D), CL1-029 (V), CL1-033 (W), CL1-036 (Dig), CL1-042 (Sim), CL1-043 (A, H), CL2-050 (Am), CL2-054 (Si, sCAD), CL1-049 (T, I), CL1-041 (H, Plat+Asp)
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Asthmatics	X	1	1	CL1-038
renal impairment:	X	2	2	PKH-15 (severe RI) NP15364 (Dialysis)
hepatic impairment:	X	1	1	PKH-008
PD -				
PK/PD Characterization Healthy	X	3	3	CL1-004, CL1-003, CL1-005 (vision),
Patients	X	9	7	CL2-010, CL2-047 (I vs A PK), CL2-052 (Electrophys), CL2-015 (H), CL2-011 (LVdx), CL2-030 (HF & CAD), CL2-062 (HF, OL)
Phase 2:	X	9	1	CL2-053 (HF),
Phase 3:	X	13	2	CL-3-063 (SHIFT, HF), CL3-056 (Beautiful, sCAD)
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	s.a.	s.a.	CL-3-063 (SHIFT, HF)
Population Analyses -				
Data rich:				

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
Data sparse:	X	s.a.	s.a.	CL3-063 (SHIfT substudy)
II. Biopharmaceutics				
Absolute bioavailability	X	1	1	PKH-001
Relative bioavailability - solution as reference:				
alternate formulation as reference:				
Bioequivalence studies - traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	PKH-007 (GJ)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	X	1	1	NP08378, (b) (4) conversion
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		71 clinical 16 <i>in vitro</i>	45 clinical, 16 <i>in vitro</i>	

s.a. - See above, s.b. - See below

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	NME NDA

	Content Parameter	Yes	No	N/A	Comment
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			Some datasets were not submitted in electronic format.
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	

	Content Parameter	Yes	No	N/A	Comment
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Applicant:

- Your Clinical Pharmacology Summary states that relevant (b) (4) cannot be ruled out at clinically relevant doses of ivabradine. However, neither the Summary, nor the label refers to a potential interaction. Have any studies been done to substantiate this potential drug-drug interaction? If none have been done, how do you plan to address the issue?
- Please submit pharmacokinetics, pharmacodynamics, and laboratory datasets (specifically serum creatinine measurements) in electronic format (not NONMEM files) for the following studies: CL1-001, CL1-002, CL1-003, CL1-004, CL1-029, CL1-039, CL1-040, PKH-001, PKH-003, PKH-004, PKH-005, PKH-006, PKH-010, CL2-006, CL2-009, CL2-030, CL2-047, CL2-062. We have not been able to locate the study electronic datasets in the submission. Please clarify if these have been submitted along with their location in the submission. If they are not part of the existing submission other than as part of NONMEM files, please submit them by 09/01/2014 to facilitate review.
- Please submit a table listing studies and the bioanalytical methods used. If possible crosslink with validation reports and bioanalytical reports from the study.
- The define files for NP27189 datasets ddidm-pl.xpt and mergeable-ddidmpl.xpt do not correctly identify study numbers. Please submit corrected define files and/or datasets.
- Based on report NP08547 studies CL1-16257-001, CL1-16257-002, PKH-16257-001, PKH-16257-003, and CL1-16257-042 were used for the Pop-PK analysis. However, the 'define' file shows variable name STU (study number) 41 for CL1-41. Please clarify whether the nonmem ready dataset provided used study CL1-16257-042 as specified in the report or CL1-41 as mentioned in the 'define' file. For report NP15444, six studies (CL2-16257-006, CL2-16257-009, CL2-16257-047, CL3-16257-017, CL3-16257-018, and CL3-16257-023) were used. The 'define' file did not provide details of variable names 'STUD' or 'STU'. Please confirm the variables for 'STU' in the corresponding dataset.

Martina Sahre	8/13/2014
Reviewing Clinical Pharmacologist	Date
Rajanikanth Madabushi	8/13/2014
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTINA D SAHRE
08/13/2014

RAJANIKANTH MADABUSHI
08/13/2014