Office of Drug Evaluation-I: Decisional Memo

Date	April 15, 2015
From	Ellis F. Unger, MD, Director Office of Drug Evaluation 1, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	206143
Applicant Name	Amgen
Date of Submission	June 27, 2014
PDUFA Goal Date	May 27, 2015 (extended by major amendment)
Proprietary Name/ Established (USAN) Name	Corlanor ivabradine
Dosage Forms/ Strengths	5-mg and 7.5-mg film-coated tablets
Indication	Ivabradine is indicated for the treatment of patients with stable, symptomatic (b) (4) chronic heart failure with reduced left ventricular function (≤ 35%), who are in sinus rhythm with resting heart rate ≥ 70 beats per minute on maximally tolerated doses of beta blockers, to reduce the risk of hospitalization for worsening heart failure.
Action:	Approval

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Alexis T Childers, RAC
Medical Officer Clinical Review	Dunnmon, Preston, MD (efficacy) Nhi Beasley, PharmD (safety)
Clinical Pharmacology and Pharmacometrics Review and Addendum	Martina Sahre, PhD, Rajanikanth Madabushi PhD, Sreedharan Sabarinath, PhD, Jeffrey Florian, PhD
Statistical Review	Steve Bai, PhD; James Hung, PhD
Pharmacology Toxicology	Jean Wu, PhD, Al De Felice, PhD
Executive Cancer Assessment Committee	Paul Brown, PhD (acting chair)
Office of New Drug Quality Assessment	Pei-I Chu, PhD, Wendy Wilson, PhD
Biopharmaceutics Review	Sandra Suarez, PhD, Angelica Dorantes PhD
Carcinogenicity Study	Mohammad Rahman, PhD; Karl Lin, PhD
Division of Medication Error Prevention and Analysis	Janine Stewart, PharmD; Alice Tu, PharmD
Risk Management Review	Danny Gonzales, PharmD, MS, Kim Lehrfeld, PharmD
Cross-Discipline Team Leader	Thomas Marciniak, MD
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge, MD, PhD

Regulatory Action:

Amgen is seeking approval of Corlanor (ivabradine) with a proposed indication "…to reduce the risk of (b) (4) hospitalizations for worsening heart failure (HF) in patients with chronic heart failure (b) (4) and in sinus rhythm with heart rate ≥70 beats per minute, (b) (4) maximally tolerated doses of beta blockers, or when beta blocker therapy is contraindicated (b) (4)

With a number of changes to the label, including changes to the indication statement (see Summary/Conclusions), the review team endorses approval, and I agree with their recommendation.

Description/Mechanism of Action:

Ivabradine is a first-in-class hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker intended to act by lowering heart rate. In mammals, 4 different members of the HCN family have been cloned, differing in tissue distribution, activation kinetics, and response to cyclic AMP. Ivabradine reduces heart rate through a selective, dose-dependent decrease in the conductance of the HCN4 I_f, or "funny" current. Ivabradine reduces the slope of spontaneous diastolic depolarization *in vitro*, without affecting the maximal diastolic potential or the threshold potential of activation. Of note, ivabradine also blocks the equivalent I_f in mouse retina rods (where HCN1 is expressed) with similar potency, and probably does so in humans as well, which accounts for visual side effects. The applicant claims that ivabradine is a (b) (4) heart rate (HR) lowering agent, although it is a negative inotrope in animals at high doses. In light of the animal findings, and given that there is no definition of a (b) (4) negative chronotrope, *the applicant should not use the word* (b) (4) *in their promotional materials*.

Disease Background:

About half of all heart failure (HF) can be categorized as HF with reduced ejection fraction, or HF*r*EF, and about half as HF with preserved ejection fraction. HF*r*EF is a substantial and growing medical problem that affects approximately 2.5 million adults in the US. According to the 2013 American College of Cardiology Foundation/American Heart Association "Guideline for the Management of Heart Failure," the lifetime risk of developing HF is 20% for Americans ≥ 40 years of age, with over 650,000 new cases diagnosed annually (*J Am Coll Cardiol* 2013;e147-239). The incidence of HF increases with age: from ~2 per 100 individuals at age 65 to 69 to over 8 per 100 individuals at age 85 and over.

As life expectancy increases in the US, the prevalence of HF is anticipated to rise. Despite improvements in the management of patients with HF, survival rates within 5 years of diagnosis are still only ~50%.

The therapy of heart failure is well described in Dr. Dunnmon's review, and includes:

- Angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs) if ACE inhibitors are not tolerated
- Beta-blockers (carvedilol, or controlled release/extended release metoprolol succinate)
- Diuretics, if there is evidence of fluid retention

- Spironolactone (provided estimated creatinine clearance is > 30 mL/min and K^+ is < 5.0 mEq/dL)
- Hydralazine/isosorbide dinitrate (for self-identified African Americans with persistently symptomatic NYHA class III-IV heart failure) receiving optimal therapy with ACE inhibitors and beta-blockers

Digoxin carries a Class IIa recommendation to decrease hospitalizations for HF.

Indication statements of some drugs for HF:

Isosorbide dinitrate and hydralazine hydrochloride is indicated "for the treatment of heart failure as an adjunct to standard therapy in self-identified Black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status."

Lisinopril "is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis."

Enalapril "is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients enalapril improves symptoms, increases survival, and decreases the frequency of hospitalization (see clinical pharmacology, heart failure, mortality trials for details and limitations of survival trials)."

Carvedilol "is indicated for the treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization…."

Metoprolol succinate "is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, metoprolol succinate decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure."

In addition to these pharmacotherapies for HF*r*EF, devices now play a major role in the treatment of HF*r*EF. There are Class I recommendations for implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT), as follows:

- ICD therapy for primary prevention of sudden cardiac death (SCD) to reduce mortality in selected patients with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI with left ventricular ejection fraction (LVEF) ≤ 35% and NYHA class II or III symptoms on chronic guideline-directed medical therapy, who have a reasonable expectation of ≥ 1-year survival.
- ICD therapy for primary prevention of SCD to reduce total mortality in selected patients ≥ 40 days post-MI with LVEF ≤ 30%, and NYHA class I symptoms while receiving guideline-directed medical therapy, who have a reasonable expectation of meaningful survival for ≥ 1 year.
- CRT for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of ≥ 150 ms, and NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy.

These drugs and devices play an important role in decreasing morbidity and mortality in HF. Nevertheless, the burden of the disease on the health care system remains high: the death rate remains high, and HF continues to be the leading cause of hospitalization and re-hospitalization in the US. In short, there is a profound need for new treatment options for HF.

Regulatory History:

Ivabradine is a new molecular entity that has not been approved in the U.S., although the drug is approved and marketed in the EU. (Ivabradine is approved in the EU for angina and heart failure.) The drug was not developed under an IND. Significant milestones and agreements are summarized below:

(b) (4) .

A pre-NDA meeting was held on December 6, 2013 to discuss chemistry, manufacturing and controls (CMC) data only. A pre-NDA meeting was held on January 22-23, 2014, where the sponsor presented the top-line results of SHIFT, and the content and format of the NDA were discussed. In these meetings, there were no disagreements between the FDA and Amgen.

On April 8, 2014, the FDA granted Amgen's request for Fast Track designation for ivabradine and also agreed to conduct a rolling review of the planned NDA. Amgen previously submitted complete non-clinical and CMC modules on April 30, 2014, which included the complete nonclinical and CMC modules.

Chemistry Manufacturing and Controls:

Ivabradine is intended to be marketed in 5-mg and 7.5-mg strengths. The 5-mg strength is an oval-shaped, film-coated tablet, scored on both edges and bisected on the other face. The tablet can be broken in half to provide a 2.5-mg strength. The 7.5-mg strength is a triangularly-shaped, film-coated tablet. The CMC reviewers, Drs. Pei-I Chu and Wendy Wilson, determined that the chemistry manufacturing and controls (CMC) information provided for the drug substance and drug product are adequate and recommend approval with no pending issues. The stability data support shelf-lives of 36 and 24 months for the blister and bottle packages, respectively.

Pharmacology/Toxicology:

Jean Q. Wu, Ph.D. provided the pharmacology-toxicology review. The major findings in the nonclinical safety assessment of ivabradine were observed in the eyes, and in the heart (both fetal and adult), at or close to human exposures.

The heart is the primary organ of toxicity. In rats, but not dogs, there were numerous findings at all dosages including atrial and ventricular hypertrophy, mucification and metaplasia in the chordae tendinae, cardiomyocyte vacuolation, contraction bands, necrosis, and fibrosis. The no-observed-adverse-effect level (NOAEL) was not established. The findings were thought to be similar to those previously reported for beta blockers. Dogs did not exhibit these effects.

ECG findings in dogs included bradycardia, sinoatrial (SA) block or arrest, and 1st and 2nd degree atrioventricular block at almost all doses. ECGs normalized after drug withdrawal.

One dog, receiving approximately 40 times the human $AUC_{0\text{-}24h}$ at the maximum recommended human dose (MRHD), was found dead on Day 341 without antecedent clinical signs. Ivabradine could not be excluded as the cause of death.

The eye is another target organ of toxicity. Ivabradine inhibits I_h of isolated mouse rods. Visual symptoms reported in the clinical trials triggered ophthalmologic assessments in the 52-week dog study. There were no changes detected by ophthalmoscopy or transmission electron microscopy, but abnormalities were detected in the cone system by electroretinography (decreased b-wave amplitude; delay in dark adaptation). These findings normalized after a 1-week recovery period.

Based on the weight of all of the evidence submitted, the genotoxic risk for ivabradine is considered minimal at the proposed dose.

Ivabradine had no effects on fertility in rats. Fetal interventricular septal defects and anomalies of the great arteries were observed, however, when gravid rats were exposed to 3X human $AUC_{0\text{-}24h}$ at their MRHD.

Increased post-implantation loss was observed in pregnant rabbits exposed to ivabradine during organogenesis at $\geq$ 5X the human $AUC_{0\text{-}24h}$ at MRHD. Reduced fetal and placental weights and a small number of fetuses with ectrodactylia were observed at ~34X the human $AUC_{0\text{-}24h}$ at their MRHD. In the rat pre-postnatal study, reduced neonatal survival associated with interventricular septal defects and abnormal cardiac shape were observed in the F1 pups delivered by dams that received ~15X the human $AUC_{0\text{-}24h}$ at MRHD. Enlargement of the heart was observed in adult F1 rats at dosages $\geq$ ~4X the human $AUC_{0\text{-}24h}$ at MRHD.

Ivabradine is present in breast milk and transferred to placenta in rats.

In light of these findings, the pharmacology-toxicology review team recommended a contraindication in pregnant women, particularly during cardiac organogenesis, and, in view of the presence of the drug in rat milk as well as enhanced postnatal mortality in rats, avoidance of the drug in lactating women.

The pharmacology-toxicology review staff concluded that an appropriate pharmacologic class for ivabradine would be “hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker.” This would be a new Established Pharmacologic Class.

Carcinogenicity:

The applicant submitted 2-year carcinogenicity studies in rats and mice, where ivabradine was administered daily through food admixture. There were no ivabradine-related neoplastic findings in either species at up to the maximum tolerated dosage.

The Executive Carcinogenicity Assessment Committee found the 2-year studies acceptable and negative in both species.

Site Inspections:

The Office of Scientific Investigation (OSI) inspected 5 foreign clinical sites in SHIFT. No regulatory violations were found at 2 sites, and minor regulatory violations were found at 3 sites for failure to follow the investigational plan. OSI deemed all 5 sites acceptable for support of the NDA, and considered the violations unlikely to affect the quality or the integrity of the data.

OC/OMPQ provided an overall recommendation of acceptable for all facilities listed for ivabradine tablets.

Biopharmaceutics:

The biopharmaceutics team (Drs. Sandra Sharp and Angelica Dorantes) recommends approval. They focused on use of disintegration in lieu of dissolution testing, the disintegration acceptance criterion, (b) (4), and adequacy of bridging throughout the phases of the drug product's development. Given the (b) (4) solubility, a disintegration acceptance criterion of <10 minutes was agreed upon with the applicant in lieu of dissolution testing per International Conference on Harmonisation (ICH) Guideline Q6A. The classification of ivabradine (b) (4) drug substance/drug product is currently pending. As approvability of the NDA is not affected by the BCS designation of the product, (b) (4) recommendation can be conveyed to the applicant at any time.

Testing methods and criteria were agreed, and there are no unresolved biopharmaceutics issues.

Pharmacokinetics:

Drs. Martina Sahre, Sreedharan Sabarinath, Rajanikanth Madabushi, and Jeffry Florian conducted the clinical pharmacology review.

The pharmacokinetics of ivabradine and its main active metabolite (S18982) are linear in the range of 1 to 24 mg. Ivabradine and its main metabolite are equipotent, and both are extensively metabolized by CYP3A4. The absolute bioavailability of ivabradine after oral administration is approximately 40%. First pass metabolism accounts for most of the loss of exposure following oral administration, primarily by CYP3A4. Peak levels of ivabradine appear within 1 hour. The effective half-life, based on dedicated pharmacokinetics studies with rich sampling, is approximately 11 hours. The volume of distribution is about 100 L; about 70% is protein-bound, mostly to albumin. Various metabolites are excreted in urine and feces. Severe renal impairment does not affect unbound ivabradine concentrations. Moderate hepatic impairment has little effect on PK, and severe hepatic impairment has not been studied. Age, sex, weight, and race do not affect ivabradine exposure.

Use of strong and moderate 3A4 inhibitors and other negative chronotropes, e.g., verapamil and diltiazem, was not allowed in the clinical studies.

- Coadministration with strong or moderate CYP3A4 inhibitors increases ivabradine and S18982 exposure. Concomitant use of strong inhibitors (ketoconazole) will be contraindicated. Use of moderate inhibitors should be avoided.

- Both verapamil and diltiazem are moderate CYP3A4 inhibitors that increase ivabradine exposure. In addition, both drugs are negative chronotropes; therefore, use of ivabradine with either drug has the potential to cause severe bradycardia.
- After coadministration of ivabradine with the CYP3A4 inducer St. John's Wort, peak and total systemic exposures were reduced ~2-fold, thus co-administration of St. John's Wort should be avoided.
- Ivabradine is neither an inhibitor nor an inducer of metabolizing enzymes at clinically relevant concentrations.
- (b) (4)
  Because OCT2 mediates renal secretory clearance of metformin, a drug-drug interaction study of ivabradine with metformin was conducted. The study, in healthy subjects, showed no effect of ivabradine on metformin exposure. The reason for the absence of an interaction is unknown.

Pharmacodynamics:

Ivabradine causes a dose-dependent reduction in heart rate, and decreased resting heart rate by an average ~ 11 bpm in subjects with heart failure. At clinically relevant doses, ivabradine is not a negative inotrope, although, as noted above, the company should not promote their drug as a (b) (4) negative chronotrope.

Abuse Potential:

At the 1/23/14 pre-NDA meeting, the Division noted that the pharmacology and toxicology studies did not raise significant concerns with respect to abuse, but requested clinical data on abuse, withdrawal symptoms, and rebound behavior.

The applicant did not perform a specific pharmacodependency study. In long-term non-clinical studies, signs of potential dependency were not observed during the off-dose period, and in the phase 2 and 3 clinical trials, there were no cases of drug abuse or drug-seeking behavior. In the post-marketing setting, the applicant found no reports of abuse.

QT Effects:

The development program was designed and completed prior to the issuance of the ICH guideline on the conduct of a thorough QT/QTc study (ICH E14, 2005); therefore, a thorough QT study was not performed. Moreover, the QT-Interdisciplinary Review Team noted that a thorough QT study would not adequately assess ivabradine's proarrhythmic liability because of the drug's negative chronotropic effects.

Evidence of Effectiveness:

The applicant submitted three major outcome trials: BEAUTIFUL, SIGNIFY, and SHIFT. SHIFT provided the evidence of ivabradine's efficacy, and will receive the greatest attention here.

BEAUTIFUL

BEAUTIFUL (*Lancet* 2008;372:807) was a randomized, placebo-controlled, double-blind study in 10,917 subjects with coronary artery disease (CAD), impaired left ventricular systolic function

(left ventricular ejection fraction [LVEF] < 40%), and heart rate ≥ 60 bpm. Subjects were New York Heart Association (NYHA) functional class I to III on the basis of either ischemia or HF. Subjects were randomized 1:1 to ivabradine or matching placebo at an initial dose of 5 mg BID, with the dose up-titrated to 7.5 mg BID depending on resting heart rate and tolerability. The 1° endpoint was time-to-first cardiovascular death, hospital admission for acute MI, or hospital admission for new or worsening HF.

SHIFT was enriched by selecting subjects who had been hospitalized for heart failure within 12 months of study participation, whereas recent hospitalization was not required in BEAUTIFUL. The lack of a requirement for recent hospitalization would be expected to decrease the numbers of events and the magnitude of the treatment effect in BEAUTIFUL relative to SHIFT, but otherwise would not be expected to affect the generalizability or applicability of the findings.

BEAUTIFUL was conducted between 2004 and 2008 at 757 centers in 33 countries, including Canada, Australia, and countries in Western Europe, Eastern Europe, Asia, and South America (no centers in the US). Through a median follow-up of 19 months, the study was neutral on the 1° endpoint (HR: 1.00; *p* = 0.95). Results were confirmed by Dr. Bai.

Table 1: BEAUTIFUL – Primary Composite Endpoint and Components

	Ivabradine (N=5479) n (%)	Placebo (N=5438) n (%)	HR (95% CI)	p-value
Primary Composite Endpoint	844 (15.4)	832 (15.3)	1.00 (0.91, 1.10)	0.945
Secondary Endpoints				
Cardiovascular Death	469 (8.6)	435 (8.0)	1.07 (0.94, 1.22)	0.316
Hospitalization for acute MI	199 (3.6)	226 (4.2)	0.87 (0.72, 1.06)	0.159
Hospitalization for new onset or Worsening Heart Failure	426 (7.8)	427 (7.9)	0.99 (0.86, 1.13)	0.850

In the subgroup of subjects with baseline heart rate ≥ 70 bpm, ivabradine was associated with nominally statistically significant reductions in hospitalization for acute myocardial infarction and coronary revascularization. These findings, along with the belief that elevated heart rate is a marker of cardiovascular risk, led to the hypothesis upon which SIGNIFY was based, i.e., that ivabradine, by lowering heart rate, would reduce morbidity and mortality in patients with CAD.

SIGNIFY

SIGNIFY (*N Engl J Med* 2014;371:1091) was a randomized, double-blind, placebo-controlled trial of ivabradine added to standard background therapy in patients with stable coronary artery disease, the absence of heart failure, and heart rate ≥ 70 bpm. *Given that the absence of clinical HF was a criterion for enrollment, SIGNIFY is notable because its population and the proposed indicated population are mutually exclusive.* The 1° endpoint was a composite of time-to-first cardiovascular death or nonfatal MI. Subjects received ivabradine at a starting dose of 7.5 mg bid, and the dose could be increased to as high as 10 mg bid to achieve a target heart rate of 55 to 60 bpm.

SIGNIFY enrolled 19,102 subjects between 2009 and 2013 at 1139 centers in 51 countries, not including the United States. Through a median follow-up of 27.8 months, there was no significant difference between the ivabradine and placebo groups on the 1° endpoint: 6.8% vs. 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; $p = 0.20$. The results on numerous 2° endpoints were aligned with the 1° endpoint, as was all-cause death (one of the 2° endpoints). Results as reported in the *N Engl J Med* are shown in Table 2.

Table 2: SIGNIFY - Primary Endpoint and Some Secondary Endpoints

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Withheld portion is taken from Table 2 (N Engl J Med 2014; 371:1091-1099)

SHIFT

The principal evidence of efficacy is provided by SHIFT, which is described in detail here. SHIFT was conducted entirely outside the US by Les Laboratoires Servier, and not conducted under IND. The company did not consult with FDA for advice or guidance during clinical development.

SHIFT was a 6,558-subject, international, randomized, double-blind, placebo-controlled, parallel group trial in clinically stable patients with NYHA functional class II to IV HF with systolic dysfunction, as evidenced by a left ventricular ejection fraction (LVEF) $\leq$ 35%. Patients had to be in sinus rhythm with resting HR $\geq$ 70 beats per minute (bpm), and had to have had a hospital admission for worsening HF within 12 months of study participation.

There was a run-in period of 2 weeks to confirm patient eligibility and clinical stability, during which no study treatment was dispensed.

Patients were randomized to ivabradine or placebo, stratified by baseline beta-blocker use (yes or no) and center. The starting dose of ivabradine was 5 mg BID. After 2 weeks, the dose could be up-titrated to 7.5 mg, maintained at 5 mg BID, or down-titrated to 2.5 mg BID, to achieve a target HR between 50 and 60 bpm.

The 1° endpoint was the composite of the time-to-first event of cardiovascular death (including death from unknown cause) or hospitalization for worsening HF. A Cox proportional hazards model was used to test for statistical significance, adjusted for beta-blocker use at

randomization. The objective was to demonstrate the superiority of ivabradine over placebo, tested using the intention-to-treat principle at a two-sided *p*-value of 0.05.

There were numerous 2° endpoints, to be analyzed as time-to-first event. The applicant's statistical plan noted explicitly that there would be no attempt to control type-I error for any of the 2° endpoints, i.e., no adjustment for multiplicity. Thus, the review team views all 2° endpoints as exploratory in nature:

- Hospitalization for worsening HF
- Cardiovascular death (including death from unknown cause)
- Death from any cause
- Death from heart failure
- Hospitalization for any cause
- Unplanned hospitalization for any cause
- Hospitalization for cardiovascular reason (including hospitalization for undetermined cause)
- Unplanned hospitalization for cardiovascular reason
- Composite of time-to-first cardiovascular death (including death from unknown cause), hospitalization for non-fatal MI, or hospitalization for worsening HF

Three interim analyses were performed by the Data Monitoring Committee. The first one, after 20% of the expected events had accrued, was intended only to detect harm. Additional interim analyses (at 40% and 70% of expected events) were conducted to allow stopping for overwhelming efficacy or harm. Alpha spending was based on the Peto group sequential procedure. The alpha allocated to efficacy for each interim analysis was 0.001, which would have negligible effect on the alpha available for the final analysis. The study would have been stopped for harm if ivabradine had been inferior to placebo with a p-value of ≤ 0.01 on the primary composite endpoint or all-cause death.

There was only a single version of SHIFT's statistical analysis plan (SAP), which, according to the study report, was finalized prior to study unblinding. The completion date for the SAP was May 28, 2010, which followed the April 19, 2010 study completion date. Thus, the sequence of events was: study completion, formalization of the SAP, and unblinding of the data.

The initial SHIFT protocol was written on April 18, 2006. Based on the anticipated effect size, event rates, and length of follow-up, the original sample size was 5,500 patients, with 1,220 events anticipated. When the results of BEAUTIFUL, conducted in a related patient population, became known, there was concern that ivabradine's treatment effect would be less than anticipated. Thus, amendment 5, dated September, 2008, increased the sample size to 7,000 patients and stated that the study would be continued until 1,600 endpoint endpoints had been observed.

Subsequently, because of slower than expected enrollment, amendment 6 (June, 2009) directed that SHIFT would be stopped once 6,500 subjects had been randomized.

Results:

SHIFT was conducted between 2006 and 2010, and enrolled 6,558 subjects at 677 study centers (mean ~10 subjects/center). SHIFT was conducted entirely ex-US, in 37 countries in Eastern and Western Europe, Australia, Canada, Asia, Africa, and South America. The Russian

Federation, Ukraine, Romania, Bulgaria, and Poland were the highest enrolling countries, together accounting for 48% of the subjects.

The applicant excluded 7 patients who neither met entrance criteria nor received the study drug, as well as 46 patients at two centers in Poland because of concerns regarding study conduct. Thus, 6,505 patients were included in the analyses of efficacy. The exclusion of these 53 patients (0.8%) had no effect on the study results.

Follow-up was essentially complete, with only 3 patients lost to follow-up. Overall, 2.0% of patients withdrew consent (2.3 and 1.8% of patients in the ivabradine and placebo groups, respectively).

Although follow-up was excellent, 21.0% and 18.5% of subjects in the ivabradine and placebo groups, respectively, discontinued study drug prematurely, with adverse events accounting for approximately 2/3 of these. The leading adverse event associated with discontinuation was atrial fibrillation/flutter (4.5% and 3.7% in the ivabradine and placebo groups, respectively). As expected, there was an imbalance in discontinuations for bradycardia, 2.2% and 0.4% in the ivabradine and placebo groups, respectively; approximately 1/3 of these patients were symptomatic.

The demographic characteristics, baseline disease characteristics, and notable baseline concomitant drugs are shown in Table 3.

Subjects in the two groups were balanced with respect to baseline factors. Subjects were equally divided between NYHA FC II and III; only 1.7% of subjects were FC IV. Nearly 90% of subjects were taking beta-blockers, but approximately 2/3 of subjects were not taking the target daily doses. Among these subjects, reasons given for not taking the target dose included hypotension (45%), fatigue (32%), dyspnea (14%), and dizziness (12%). Approximately 90% of subjects were taking an ACE or ARB, and 60% were taking an aldosterone antagonist.

It is notable that only 4% of subjects in SHIFT had an implanted pacemaker or defibrillator. Thus, use of these therapies, known to reduce morbidity and mortality, was far less than would be typical for a contemporary US patient population. The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting included 34,810 patients at 167 US outpatient cardiology practices with reduced LVEF ($\leq$ 35%) and chronic HF or previous myocardial infarction. Based on chart review, use of a CRT with a pacemaker or defibrillator ranged from 37 to 66%; use of ICDs was in the range from 50 to 77% (*Circulation* 2010;122:585).

A total of 793 patients experienced a 1° endpoint event in the ivabradine group versus 937 patients in the placebo group. Using a Cox proportional hazards model adjusted for beta-blocker use at randomization, the estimate of the hazard ratio was 0.82 (95% confidence interval [CI] 0.75; 0.90), $p < 0.0001$. Results are shown in Table 4 and Figure 1.

Table 3: SHIFT - Demographic and Baseline Disease Characteristics

		Ivabradine N = 3241	Placebo N = 3264
Age	Mean (SD)	60.7 (11.2)	60.1 (11.5)
Gender	Male (%)	2462 (76%)	2508 (76.8%)
	Female (%)	779 (24%)	756 (23.2%)
Ethnicity	Caucasian (%)	2879 (88.8%)	2892 (88.6%)
	Asian (%)	268 (8.3%)	264 (8.1%)
	Black (%)	32 (1%)	43 (1.3%)
	Other (%)	62 (1.9%)	54 (1.7%)
Weight	Mean (SD)	80.9 (17.2)	80.7 (17.1)
Resting HR	Mean (SD)	79.7 (9.5)	80.1 (9.8)
Sitting SBP	Mean (SD)	122 (16)	121 (16)
Sitting DBP	Mean (SD)	76 (10)	76 (9)
Smoking Habits	Yes (%)	541 (16.7%)	577 (17.7%)
	Stopped (%)	1355 (41.8%)	1364 (41.8%)
	Never (%)	1345 (41.5%)	1323 (40.5%)
Years since CHF diagnosis	Mean (SD)	3.5 (4.2)	3.5 (4.2)
Primary cause of CHF	Ischemic (%)	2215 (68.3%)	2203 (67.5%)
	Idiopathic (%)	664 (20.5%)	685 (21%)
	Hypertensive (%)	226 (7%)	253 (7.8%)
	Valvular (%)	14 (0.4%)	18 (0.6%)
	Other (%)	122 (3.8%)	105 (3.2%)
NYHA FC	Class I (%)	1 (0%)	1 (0%)
	Class II (%)	1585 (48.9%)	1584 (48.5%)
	Class III (%)	1605 (49.5%)	1618 (49.6%)
	Class IV (%)	50 (1.5%)	61 (1.9%)
LVEF	Mean (SD)	29.0 (5.1)	29.0 (5.2)
History of AF/A-flutter	n (%)	263 (8.1%)	259 (7.9%)
BB at baseline	Any (%)	2897 (89.4%)	2923 (89.6%)
	Carvedilol (%)	1323 (40.8%)	1281 (39.2%)
	Bisoprolol (%)	721 (22.2%)	765 (23.4%)
	Metoprolol succinate (%)	399 (12.3%)	416 (12.7%)
	Metoprolol tartrate (%)	303 (9.3%)	315 (9.7%)
	Nebivolol (%)	100 (3.1%)	98 (3%)
Other drug treatments	ACE/ARB n (%)	2963 (91.4%)	2960 (90.7%)
	Digoxin n (%)	706 (21.8%)	710 (21.8%)
	Aldosterone antagonist n (%)	1981 (61.1%)	1941 (59.5%)
Pacemaker or CRT or ICD	n (%)	110 (3.4%)	134 (4.1%)

The analyses of the FDA and applicant differed in 2 important respects:

1. The applicant chose to display all cardiovascular deaths and hospitalizations for worsening heart failure as endpoint events, even for subjects who succumbed to cardiovascular death following a hospitalization for worsening heart failure (Table 4, top). These patients were therefore 'double-counted' in the applicant's table, i.e., the sum of the events for the 2 components of the composite endpoint exceeded the number of events in the planned composite endpoint of time-to-first event. Analyses of all cardiovascular deaths (including those that followed hospitalization) is not unreasonable, but was not planned to be analyzed in a way that controlled type-I error.

2. Twenty-one (21) subjects were hospitalized for worsening heart failure as their first event, but died on the calendar day of hospital admission. The applicant's analytic plan stated that cardiovascular death should be the first event for these patients. Using the planned analysis, the numbers of events in the composite are the same; however, the numbers of subjects hospitalized for worsening heart failure decreased slightly, by 9 and 12 subjects in the ivabradine and placebo groups, respectively (results not shown). More importantly, with proper decomposition of the 1° composite endpoint, such that the sum of the events in each component equals the number of events in the composite (i.e., showing first events only), the results are slightly unfavorable for cardiovascular death (Table 4, bottom, FDA analysis). Thus, cardiovascular death does not contribute to the finding of effectiveness.

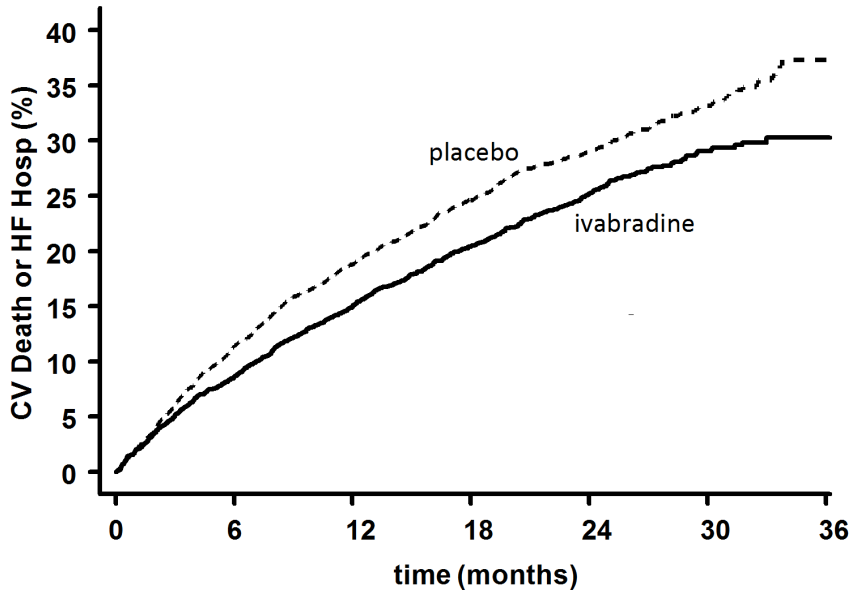
As noted by Dr. Stockbridge and others, omission of the 53 subjects described above (those never treated, and subjects from the 2 sites in Poland) has no effect on SHIFT's findings, and given the persuasive *p*-value on the 1° endpoint, no reasonable sensitivity analysis could have any material effect on the finding of efficacy.

Table 4: SHIFT – 1° Composite Endpoint; Analysis by Applicant (top) and FDA (bottom)

	ivabradine	placebo			
N	3241	3264	Hazard ratio	95% CI	*p* -value
Primary composite endpoint, n (%)	793 (24.5%)	937 (28.7%)	0.82	0.75, 0.90	< 0.0001
hospitalization for HF, n (%)	514 (15.9%)	672 (20.6%)	0.74	0.66, 0.83	-
cardiovascular death, n (%)	449 (13.9%)	491 (15.0%)	0.91	0.80, 1.03	-

N	ivabradine N = 3241	placebo N = 3264	Hazard ratio	95% CI	*p* -value
Composite of hospitalization for worsening HF or CV death, n (%)	793 (24.5%)	937 (28.7%)	0.82	0.75, 0.90	< 0.0001
Hospitalization for worsening HF	514 (15.9%)	672 (20.6%)	0.74	-	-
CV death, without prior hospitalization for worsening HF	279 (8.6%)	265 (8.1%)	1.06	-	-

Figure 1: SHIFT – Kaplan-Meier Plot, 1° Efficacy Endpoint, Time to First Heart Failure Hospitalization or Cardiovascular Death



Number at risk								
	placebo	3264	2868	2489	2061	1089	439	17
	ivabradine	3241	2928	2600	2173	1191	447	16

Subgroup Analyses:

Table 5 shows the results of various subgroup analyses conducted to assess the generalizability of the efficacy findings. Note that the table shows both the absolute event rates and the effect of ivabradine treatment. Results are shown as relative risks ± 95% confidence intervals, rather than as hazard ratios from the Cox model. Findings in subgroups were generally consistent, but some issues merit discussion.

The treatment effect was consistent across subgroups of age, sex, and race, although only 1.2% of patients in SHIFT were Black, such that the confidence intervals around the point estimate are quite broad. Evidence of efficacy in Black patients is discussed below.

Many on the review team were concerned about the applicability of the SHIFT results to US patients, because the practice of medicine in SHIFT differed greatly from medical practice in the US, and I share this concern. Though not a perfect solution, Table 5 shows my analysis of study results for sites considered more 'US-like.' These are centers in Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Turkey, and the United Kingdom. For centers in these countries, the point estimate on the 1° endpoint was consistent with the overall study results, which provides some reassurance. Another major issue is the infrequent use of cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICDs). This is discussed further below.

Table 5: SHIFT – 1° Endpoint by Subgroups

		% of population	% with Primary Endpoint Event		Δ Absolute %	RR (95% CI)
			Ivabradine	Placebo		
All		100%	24.5%	28.7%	4.2%	0.85 (0.78, 0.92)
Age quartile	<54	26.6%	17.4%	25.4%	8.0%	0.69 (0.57, 0.83)
	55 to 60	23 9%	23.0%	24.7%	1.7%	0.93 (0.78, 1.11)
	61 to 69	26 5%	27.7%	30.6%	2.9%	0.91 (0.79, 1.05)
	>69	23.1%	29.9%	35.1%	5.2%	0.85 (0.73, 0.98)
Age	≥ 65	38 0%	30.5%	33 9%	3.4%	0.9 (0.8, 1.01)
	≥ 75	11.1%	33.9%	37.7%	3.8%	0.9 (0.74, 1.09)
Sex	Male	76.4%	25.3%	28 9%	3.6%	0.88 (0.8, 0.96)
	Female	23.6%	21.7%	28 0%	6.3%	0.77 (0.65, 0.92)
Race	Caucasian	88.7%	25.1%	28 9%	3.8%	0.87 (0.8, 0.95)
	Black	1.2%	28.1%	34 9%	6.8%	0.81 (0.41, 1.61)
	Asian	8.2%	17.5%	25 8%	8.2%	0.68 (0.49, 0.95)
	Other/unknown	2.0%	24.2%	29 2%	5.0%	0.83 (0.46, 1.48)
'US-like' geographic location	Canada & Western EU	15 5%	23.4%	29 5%	6.0%	0.8 (0.65, 0.98)
	Rest of world	84 5%	24.7%	28.6%	3.9%	0.86 (0.79, 0.94)
Modal dose (placebo pa ients are combined)	2 5 mg	4.8%	18.8%	28.7%	9.9%	0.65 (0.51, 0.83)
	5 mg	15 5%	25.8%	28.7%	3.0%	0.9 (0.79, 1.03)
	7 5 mg	79.4%	24.7%	28.7%	4.0%	0.86 (0.79, 0.94)
Weight quar ile (all patients)	<=69.4 kg	25 0%	27.8%	35 2%	7.4%	0.79 (0.68, 0.91)
	69.5 to 79.6	25 0%	24.9%	28 0%	3.1%	0.89 (0.76, 1.05)
	79.7 to 91.0	25.7%	22.6%	24.6%	2.0%	0.92 (0.77, 1.09)
	91.1 to 170	24 3%	22.7%	27 0%	4.3%	0.84 (0.71, 1)
Weight: Males by quartile	<74 8 kg	20%	31.5%	37.4%	5.9%	0.84 (0.72, 0.98)
	74 8 to <83.7	20%	24.0%	24 8%	0.8%	0.97 (0.8, 1.18)
	83.7 to <94 3	18%	22.2%	25 2%	3.0%	0.88 (0.72, 1.08)
	>=94.3	19%	23.4%	27.4%	4.0%	0.85 (0.7, 1.03)
Weight: Females by quartile	<62 kg	5.9%	26.8%	33 0%	6.1%	0.81 (0.6, 1.1)
	62 to <70.7	6.2%	18.4%	27 9%	9.5%	0.66 (0.46, 0.95)
	70.7 to <82	5.8%	25.0%	27.7%	2.7%	0.9 (0.64, 1.26)
	>=82	5.7%	16.4%	23.6%	7.2%	0.69 (0.46, 1.04)
Baseline systolic BP by quartile	76 to 110 mmHg	30.7%	30.4%	35 2%	4.8%	0.86 (0.76, 0.98)
	111 to 120 mmHg	23.6%	24.9%	27.4%	2.5%	0.91 (0.77, 1.08)
	121 to 130 mmHg	21 8%	20.0%	24 0%	3.9%	0.84 (0.69, 1.02)
	131 to 180 mmHg	23 9%	20.7%	25 8%	5.0%	0.8 (0.67, 0.96)
NYHA Functional Class	FC II	48.7%	18.9%	22 5%	3.5%	0.84 (0.73, 0.96)
	FC III	49 5%	29.3%	33 5%	4.2%	0.87 (0.79, 0.96)
	FC IV	1.7%	46.0%	62 3%	16.3%	0.74 (0.52, 1.06)
Baseline LV ejec ion fraction by quar ile	<=26%	27.6%	33.9%	37.1%	3.2%	0.91 (0.8, 1.03)
	27 to 30%	25 3%	23.9%	30 2%	6.3%	0.79 (0.67, 0.93)
	31 to 33%	26 0%	20.3%	25 9%	5.6%	0.78 (0.65, 0.93)
	>=34%	21.1%	18.1%	19 0%	1.0%	0.95 (0.76, 1.19)
Baseline beta blocker use	none	12 2%	27.8%	36.6%	8.8%	0.76 (0.62, 0.93)
	>0 to 25%	14 0%	30.8%	40 0%	9.3%	0.77 (0.64, 0.92)
	25 to 50%	25 0%	26.2%	30 8%	4.7%	0.85 (0.73, 0.99)
	50 to 75%	24 0%	21.6%	23 9%	2.3%	0.9 (0.75, 1.08)
	75 to 100%	24 9%	20.2%	21.4%	1.2%	0.94 (0.78, 1.14)
Baseline aldosterone antagonist use	yes	60 3%	28.1%	32.6%	4.5%	0.86 (0.78, 0.95)
	no	39.7%	18.8%	23.1%	4.2%	0.82 (0.7, 0.95)
Baseline digoxin use	yes	21 8%	35.4%	37 9%	2.5%	0.93 (0.81, 1.07)
	no	78 2%	21.4%	26 2%	4.7%	0.82 (0.74, 0.91)
Baseline daily loop diure ic dose (furosemide equivalent)	none or unknown	31 9%	17.5%	18 8%	1.3%	0.93 (0.77, 1.12)
	< 20 mg	13 9%	21.3%	30 8%	9.5%	0.69 (0.55, 0.86)
	20 to 23 mg	14.4%	23.8%	28.4%	4.6%	0.84 (0.68, 1.04)
	25 to 40 mg	25 0%	27.2%	31 2%	4.1%	0.87 (0.75, 1.01)
	> 40 mg	10 0%	37.0%	39.4%	2.4%	0.94 (0.77, 1.14)

Patients with heart failure represent a 'fragile' population with high morbidity and mortality, but there are specific subpopulations where risk is particularly high, and some attention to these subpopulations is in order. Small females with cardiovascular disease tend to do poorly; nevertheless, the point estimate of the treatment effect of ivabradine was favorable in females in the lowest weight quartile. Patients in the lowest baseline blood pressure quartile generally fared poorly in SHIFT, but again, ivabradine's treatment effect was favorable here. As expected, outcomes were less favorable for patients with lower ejection fractions and more advanced NYHA functional class. For both of these subgroups, there were favorable point estimates for ivabradine's treatment effect.

The clinical and statistical reviewers paid much attention to the baseline utilization of beta-blockers on the outcomes of interest. Expressing baseline beta-blocker doses in quartiles based on the percentage of guideline-directed dose, there were fewer events in both treatment groups with increasing beta-blocker use. It is noteworthy that the treatment effect of ivabradine waned (the hazard ratio increased) with increasing utilization of beta-blockers, and the hazard ratio approached unity with full use of beta-blockers. The review team calculated a hazard ratio of 0.99 at $\geq$ 100% of guideline-directed beta-blocker doses. (Results not shown.)

Interpretation of these results is difficult, however, because both ivabradine and beta-blockers decrease heart rate, and because it is generally more difficult to achieve guideline-directed doses of beta-blockers in sicker patients. Suffice it to say that ivabradine will be indicated for patients *on maximally tolerated doses of beta-blockers*, or patients with a contraindication for beta blockers.

Dr. Marciniak performed numerous analyses with respect to concomitant use of loop diuretics, and concluded that ivabradine has benefical effects when used concomitantly with loop diuretics, but deleterious effects in the absence of loop diuretics. Dr. Stockbridge expended considerable energy in trying to interpret Dr. Marciniak's analyses, and enumerated a number of critical concerns on pages 7 and 8 of his memo. I agree with Dr. Stockbridge's analysis and conclusions. Dr. Marciniak provided no adjustment for multiplicity for the 7 classes of drugs he analyzed. His focus was on cardiovascular death, despite the fact that this endpoint did not reach nominal statistical significance for the overall study. His confirmation was based on a complex model, with 13 interaction terms selected out of a possible 200 terms, and no rationale for the selection of these terms was provided.

I will add that Dr. Marciniak's analyses are fundamentally dependent on calculation of the baseline loop diuretic dose for each subject, and Dr. Marciniak did not explain how daily furosemide-equivalent doses were determined. When I attempted to replicate his analyses, I encountered a number of difficulties. Baseline diuretic doses for 67 subjects were reported in terms of a number of tablets, with no strength specified. For 221 subjects, the schedule was "on request," and not further specified. A number of subjects had their baseline doses recorded in grams, rather than mg, and the dosing interval was weekly or monthly in almost 1000 subjects. For my analysis shown in Table 5, above, subjects whose baseline dose could not be calculated were included with subjects who were not reported to be taking a loop diuretic ("none or unknown"). Based on my analysis of the 1° endpoint by quartile of baseline loop diuretic dose, there appears to be little interaction.

The mechanism of action underlying ivabradine's treatment effect is negative chronotropism. Over the course of the trial, ivabradine decreased heart rate by approximately 10 bpm relative to

placebo. With respect to the 1° endpoint, the interaction term for baseline heart rate (dichotomized at the median heart rate of 77, uncorrected for multiple comparisons) was nominally statistically significant. The drug effect tended to be greater in patients with higher baseline heart rates, and the review team focused much attention here. Although the study enrolled subjects with baseline heart rate ≥ 70, some on the review team considered a more restrictive indication statement, i.e., an indication for patients with baseline heart rate ≥ 75. Dr. Stockbridge noted that interactions by heart rate and beta blocker dose were mechanistically plausible, but thought that changes in heart rate were likely entangled with effects by beta-blocker use and cautioned that such findings could be spurious.

Figure 2 and Table 6 display the results of my analyses of the 1° endpoint by baseline heart rate. Baseline heart rate quartiles were calculated for all subjects, and for males and females separately (Table 6).

I also calculated event rates within baseline heart rate deciles (Figure 2). In both treatment groups, event rates increased with higher baseline heart rate (this trend is easily seen in Figure 2; these data are also tabulated in Table 6).

The blue graph in Figure 2 shows the relative risk for the 1° endpoint for each baseline heart rate decile. The treatment effect of ivabradine is more apparent at higher baseline heart rates, and seems less apparent at lower baseline heart rates. In examining Figure 2, however, it is not clear where one would draw a line to differentiate treatment-responsive from non-treatment-responsive patients. One might conclude that the treatment effect is present in only the 3 highest contiguous baseline heart rate deciles (heart rate ≥ 82), and write such an indication.

Figure 2: SHIFT - 1° Endpoint by Baseline HR Decile

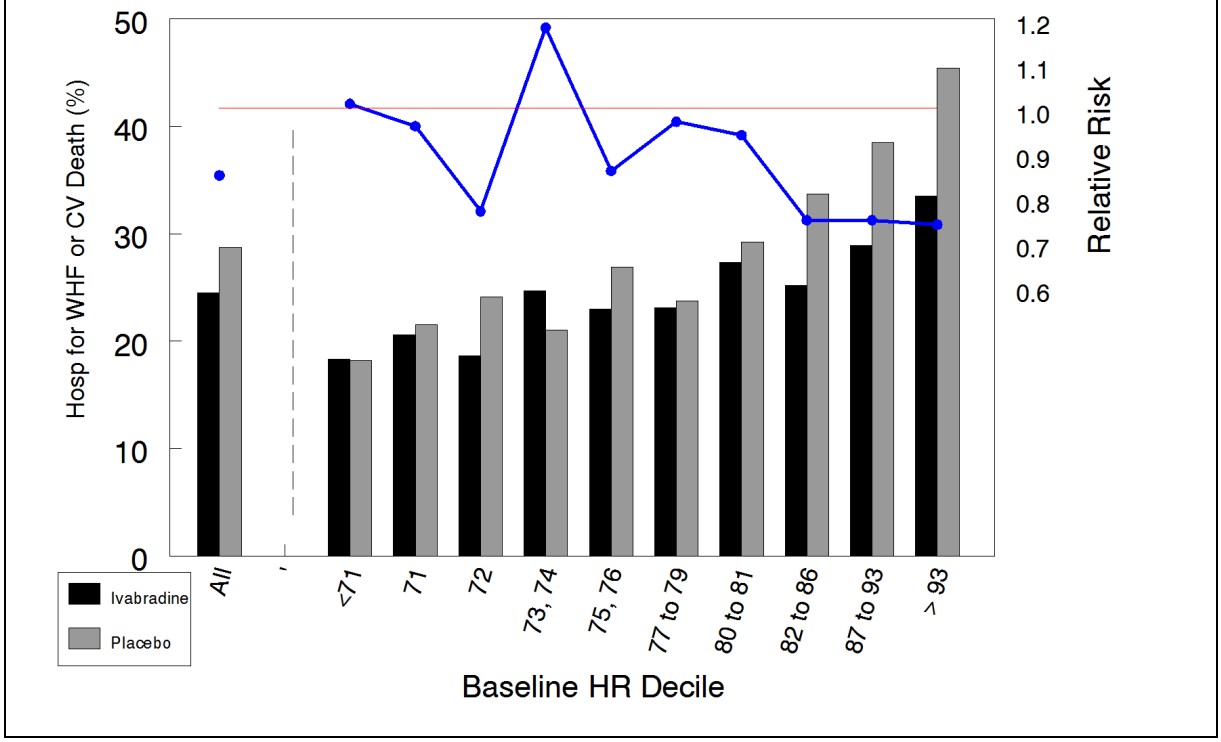


Table 6: SHIFT – 1° Endpoint by Pre- and Post-Treatment Heart Rate; Use of CRT and ICD

		% of population	% with Primary Endpoint Event		Δ Absolute %	RR (95% CI)
			Ivabradine	Placebo		
All		100%	24.5%	28.7%	4.2%	0.85 (0.78, 0 92)
Baseline HR quartile	48 to 73	30.1%	20.1%	21.8%	1.7%	0.92 (0.77, 1 09)
	74 to 77	22.2%	23.4%	25 0%	1.6%	0.94 (0.78, 1.13)
	78 to 84	23.1%	25.9%	27 2%	1.3%	0.95 (0.8, 1.12)
	85 to 142	24.4%	29.8%	41.6%	11.8%	0.72 (0.63, 0.82)
Baseline HR: Males by quartile	58 to 73	22.8%	20.8%	21 9%	1.0%	0.95 (0.78, 1.16)
	74 to 77	17.3%	23.4%	24.3%	0.9%	0.96 (0.78, 1.18)
	78 to 84	17.4%	26.4%	27.5%	1.1%	0.96 (0.79, 1.16)
	85 to 134	18.9%	31.8%	42.6%	10.8%	0.75 (0.65, 0.87)
Baseline HR: Females by quartile	48 to 72	6 0%	16.4%	21 0%	4.5%	0.78 (0.52, 1.18)
	73 to 77	6.3%	23.7%	26.6%	2.9%	0.89 (0.64, 1 24)
	78 to 84	5.7%	24.1%	26.1%	2.0%	0.92 (0.65, 1.31)
	85 to 142	5.5%	22.9%	38.4%	15.5%	0.6 (0.43, 0.83)
Baseline HR decile	<71	7.6%	18.3%	18 2%	-0.1%	1.01 (0.69, 1.47)
	71	7.6%	20.6%	21.5%	0.9%	0.96 (0.68, 1.35)
	72	9 2%	18.6%	24.1%	5.5%	0.77 (0.56, 1 05)
	73, 74	11.7%	24.7%	21 0%	-3.7%	1.18 (0.91, 1.53)
	75, 76	12.2%	23.0%	26 9%	3.8%	0.86 (0.67, 1.1)
	77 to 79	11.6%	23.1%	23.7%	0.7%	0.97 (0.75, 1 26)
	80 to 81	7.7%	27.3%	29 2%	1.8%	0.94 (0.71, 1 24)
	82 to 86	12.1%	25.2%	33.7%	8.5%	0.75 (0.6, 0.93)
	87 to 93	10.0%	28.9%	38.5%	9.6%	0.75 (0.6, 0.93)
	> 93	10.3%	33.5%	45.4%	11.9%	0.74 (0.61, 0.9)
On-treatment HR quintile (post-randomization; separate quintiles for ivabradine and placebo)	<58 | <67	19.7%	15.4%	14.1%	-1.3%	1.09 (0.84, 1.42)
	58 to 62 | 67 to 71	19.8%	16.3%	19 9%	3.6%	0.82 (0.65, 1 04)
	62 to 67 | 72 to 76	19.9%	20.7%	27 0%	6.3%	0.77 (0.63, 0 94)
	67 to 74 | 77 to 84	19.8%	30.1%	34.4%	4.3%	0.88 (0.75, 1 03)
	> 74 | >84	19.9%	39.0%	46.5%	7.5%	0.84 (0.74, 0 95)
Cardiac resynchonization therapy (CRT)	yes	3.1%	60.3%	55.4%	-4.9%	1.09 (0.86, 1.39)
	no	96.9%	23.6%	27.7%	4.1%	0.85 (0.78, 0 92)
Implantable cardioverter-defibrillator (ICD)	yes	6.1%	41.8%	41 9%	0.1%	1 (0.79, 1.26)
	no	93.9%	23.5%	27.7%	4.3%	0.85 (0.78, 0 93)
CRT or ICD	yes	7.1%	44.6%	44 2%	-0.4%	1.01 (0.82, 1 24)
	no	92.9%	23.1%	27.4%	4.2%	0.84 (0.77, 0 92)

Alternatively, one might reasonably conclude that the variation in the relative risk represents random noise within relatively small subgroups. In particular, note the diametrically opposed relative risks in adjacent deciles: particularly favorable for subjects with a baseline heart rate of 72; yet unfavorable for a baseline heart rate of 73 to 74. In my view, these differences are most likely a result of random variation within these small subsets. The possibility that ivabradine would provide a treatment benefit for patients with a heart rate of 73, but not 72; or for patients with a heart rate of ≥ 82, but not < 82, does not pass any test of reasonableness! For these reasons, and because the indication statement should not deviate from the population studied in the trial unless there is an important reason to do so, we will align the indication statement with the SHIFT inclusion criterion, i.e., patients with baseline heart rate ≥ 70.

Table 6 also displays the 1° endpoint results in subgroups by on-treatment heart rate and CRT and/or ICD use.

For each subject, the mean heart rate on treatment was calculated from the datafile ECG.xpt as the average of all heart rate observations (ECGHR), where the variable NUMVISC indicated that the observation was neither pre-treatment (i.e., NUMVISC = asse) nor post-treatment (NUMVISC = last post randomization). I made no attempt to eliminate observations of heart rate when subjects were not on their assigned drug.

Determination of CRT and ICD use was based on notations in the CRT.xpt and ICD.xpt datafiles, respectively. I made no attempt to determine whether CRT and/or ICDs were activated and functional.

Note that on-treatment heart rate is a post-randomization variable; therefore, caution must be exercised in interpretation (data shown in yellow in Table 6.) Furthermore, on-treatment heart rate quintiles were calculated for each treatment group separately. Given that heart rate in the ivabradine group was ~10 bpm lower than in the placebo group, quintiles constructed across the entire study population would grossly over-represent ivabradine subjects at the lower heart rate quintiles and over-represent placebo subjects at higher heart rates. Thus, the heart rate parameters for quintiles for the ivabradine and placebo groups are shown separately in the table. As expected, the heart rate cut-offs are approximately 10 bpm lower for the ivabradine group than the placebo group.

In both treatment groups, there is a striking increase in event rates as heart rates increase. The point estimates for relative risk are fairly consistent across the quintiles of on-treatment heart rate, except in the lowest baseline heart rate quintile, where the relative risk is >1. Again, these data are difficult to interpret, but it can be concluded with confidence that increasing heart rate is associated with increased morbidity.

Dr. Dunnmon expressed concern that few patients in SHIFT received CRT or an ICD – in striking contrast to contemporary standard practice recommendations in the US. SHIFT actually excluded subjects in whom CRT had been started within 6 months. He noted emphatically: "…It is unclear that ivabradine would confer any additional mortality and/or hospitalization benefit in the CRT or CRT-D treated population…there is no reason to think that patients with an ICD (without CRT) would not derive the same benefit from ivabradine as did patients in SHIFT."
I agree with Dr. Dunnmon. It is possible to assess the outcomes for such subjects in SHIFT, although the numbers are meager. Based on my analyses, the relative risk for the 1° endpoint was essentially unity for subjects with use of CRT and/or ICDs at any time during SHIFT (Table 6, bottom). In light of the small sizes of these subgroups and the wide confidence intervals around the relative risks, however, it is not possible to predict ivabradine's treatment effect with much certainty. Because CRT and ICDs have been shown to reduce mortality and the need for hospitalization in selected patients with heart failure, it is likely that in a contemporary US population appropriately managed with CRT and ICDs, ivabradine's treatment effect would be less than that observed in SHIFT.

Although one might like to believe that Blacks and Caucasians with heart failure would respond similarly to ivabradine, hydralazine/isosorbide dinitrate provides an example of a drug, approved for self-identified Blacks with heart failure, where the treatment effect differs in Blacks and Caucasians.

Given the limited number of Blacks in SHIFT, however, the results on the 1° endpoint in this subgroup are difficult to interpret. The point estimate is consistent with that of the overall study population, but provides only weak reassurance of efficacy because the 95% CI is quite wide.

Ivabradine's mechanism of action is negative chronotropism, and an assessment of its pharmacodynamic effects in Blacks and non-Blacks can provide some degree of support for its utility in Blacks. As shown in Table 7 (my analysis), changes in heart rate are similar in Caucasians, Blacks, and Asians. This finding is consistent with a pharmacodynamic effect in Blacks, and provides some reassurance about the treatment effect in Blacks.

Table 7: SHIFT – Change in Heart Rate by Race, Mean (SD)

	% of population	Ivabradine	Placebo
Asian	8.2	-14 (11)	-4 (11)
Black	1.1	-11 (8)	-3 (9)
Caucasian	88.7	-13 (10)	-4 (9)

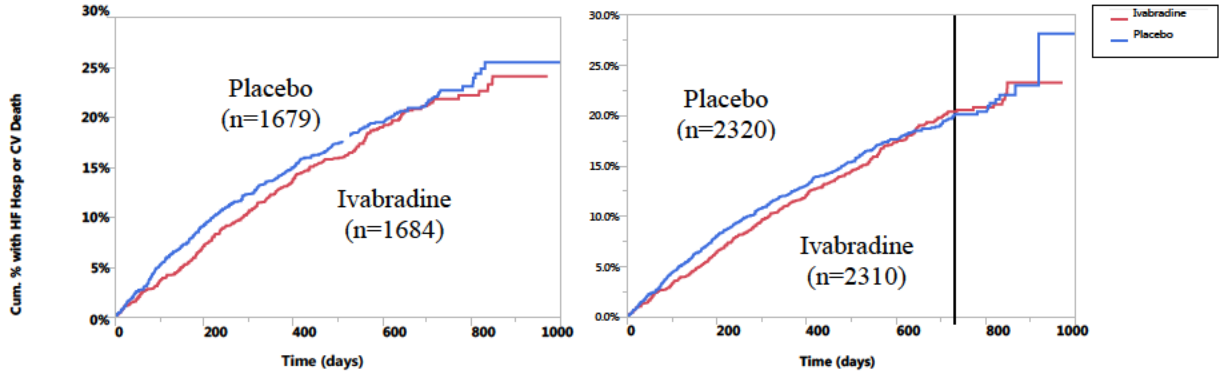
The SHIFT-like Sub-population from BEAUTIFUL

Although BEAUTIFUL was neutral on its composite 1° endpoint, the applicant reported 2 *post hoc* analyses that attempted to extract a "SHIFT-like" population from BEAUTIFUL and evaluated the treatment effect on the SHIFT 1° composite endpoint. They reported an analysis limited to subjects who were NYHA class II/III at baseline, with heart rate ≥ 70 bpm. These criteria were said to select 3,363 of BEAUTIFUL's 10,917 subjects (~31%). The treatment effect on the composite endpoint was not statistically significant (hazard ratio = 0.93; $p = 0.34$), but the applicant considered the results to represent "…*a numeric trend toward a beneficial effect of ivabradine compared to placebo*….". In attempting to conduct some analyses of the "SHIFT-like" population of BEAUTIFUL myself, I was initially unable to confirm the applicant's results. After receiving an explanation of the methods used by the applicant, I was able to reproduce their results.

Prior to receiving information from the applicant, I had used the variable HR70 to select subjects with baseline heart rate ≥ 70 bpm. I had included subjects where HR70 = 1 (i.e., heart rate at baseline ≥ 70 bpm). The applicant used a different selection method, selecting subjects based on reported heart rate ≥ 70 at two times: both screening and baseline visits.

Although this subtle difference in methods would not be expected to affect the results importantly, use of HR70 selected considerably more subjects (4,630 instead of 3,363), and the hazard ratio was actually unfavorable at 2 years. Figure 3 compares the applicant's results (left) and my results (right). The vertical line in the right graph denotes 2 years. The point here is simply to demonstrate the fragility of the applicant's finding. In other words, the results are sensitive to a minor modification of the *procedure* used to select subjects with a baseline heart rate ≥ 70 bpm. The nominal *p*-values (log-rank) are 0.34 for the analysis on the left, and 0.65 for the analysis on the right – again based only on a small change in the method used to select patients with baseline heart rate ≥ 70.

Figure 3: BEAUTIFUL – SHIFT-Like Subjects; SHIFT 1° Endpoint; Analyses by Applicant (left) and FDA (right)



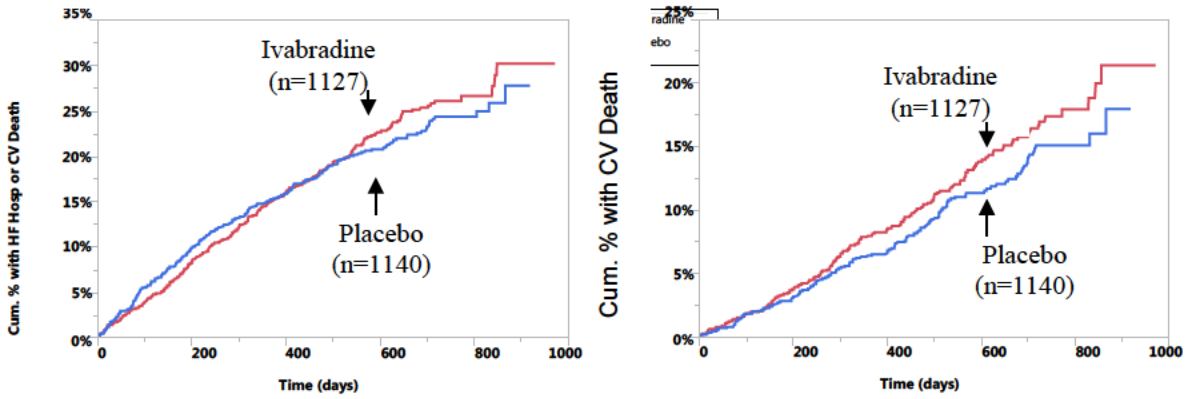
The applicant also submitted the results of an ultra-selective *post hoc* analysis, defining a 1203-subject subgroup (11% of total subjects) using a "calibration approach." This approach selected a sub-population of BEAUTIFUL subjects with baseline characteristics more similar to the SHIFT population. Factors taken into account included NYHA class, ejection fraction, baseline heart rate, previous myocardial infarction, anti-aldosterone use, diuretic use, and age. In this "calibrated" subpopulation, ivabradine reduced the risk of hospitalization for worsening heart failure or cardiovascular death with a hazard ratio of 0.77, and the result was nominally statistically significant. (b) (4)

More germane, however, would be an analysis of the sub-population of BEAUTIFUL subjects who would have met enrollment criteria for SHIFT, and for whom ivabradine would be indicated if the drug were approved. Such a sub-population would include subjects who were symptomatic (NYHA FC II/ III), with ejection fraction < 35%, and heart rate ≥ 70 bpm. Of note, symptom-limiting symptoms were queried for all subjects, and captured in the data file 0017/M5/datasets/np27426/tabulations/legacy/SPECNDT.xpt. The variable 'ITEM002C' could be reported as either: 1) "fatigue/palpitation/dyspnea;" or 2) "anginal pain." To select a heart failure population, I included only subjects who reported "fatigue/palpitation/dyspnea" as the limiting symptom in this analysis. Use of these selection factors selected a sub-population of 2,267 subjects, ~21% of the total BEAUTIFUL population.

For the analysis of the SHIFT 1° endpoint in this sub-population, the results trend unfavorably: the K-M event rates at 2 years are 26.1% for ivabradine and 24.4% for placebo (p = NS). For cardiovascular mortality, the K-M event rates at 2 years are 17.0% with ivabradine and 15.1% with placebo (p = 0.17).

Recognizing that this was a *post hoc* exploratory analysis, the main point is to highlight the fragility of the applicant's findings from the "SHIFT-like" sub-population of BEAUTIFUL, (b) (4)

Figure 4: BEAUTIFUL – Baseline NYHA FC II/III, HR ≥ 70, EF < 35%, Limiting Symptom Dyspnea/Fatigue/Palpitations – Time to 1st Hospitalization for HF or Cardiovascular Death (left); Time to 1st Cardiovascular Death (right)



Safety: The safety database from SHIFT includes 3,260 subjects who received ivabradine, with > 5,400 patient-years of exposure. BEAUTIFUL and SIGNIFY add an additional 15,000 subjects and 30,000 patient-years. Thus, the development program afforded the opportunity to compare reported rates of adverse events across the 3 trials, and consistency across trials helped establish or refute drug-relatedness of adverse events.

Dr. Beasley performed a thoughtful and comprehensive analysis of safety, and ensured that related preferred terms were tabulated together. Adverse events with differences in reported rates between ivabradine and placebo in more than one study include bradycardia, atrial fibrillation/flutter, hypertension, and phosphenes, and these will be included in labeling – the former two as warnings. Bradycardia, sinus arrest, and heart block are the major safety concerns for ivabradine. Although bradycardia was reported in 10% of subjects with a relative risk of 4.2, it was reported as a serious adverse event in less than 1% of subjects. *Importantly, excesses of the important sequelae of bradycardia, e.g., syncope, falls, fractures, were not reported.*

Based on the time-to-event analyses performed by Dr. Beasley, it is clear that reports of drug-related bradycardia attributable to ivabradine occur largely in the first 6 weeks of treatment (Figure 5). Note that slopes in the ivabradine and placebo groups are similar after 6 weeks. The labeling will remind prescribers to monitor heart rate.

Figure 5: Time to First Adverse Event of Bradycardia or Heart Rate Decreased

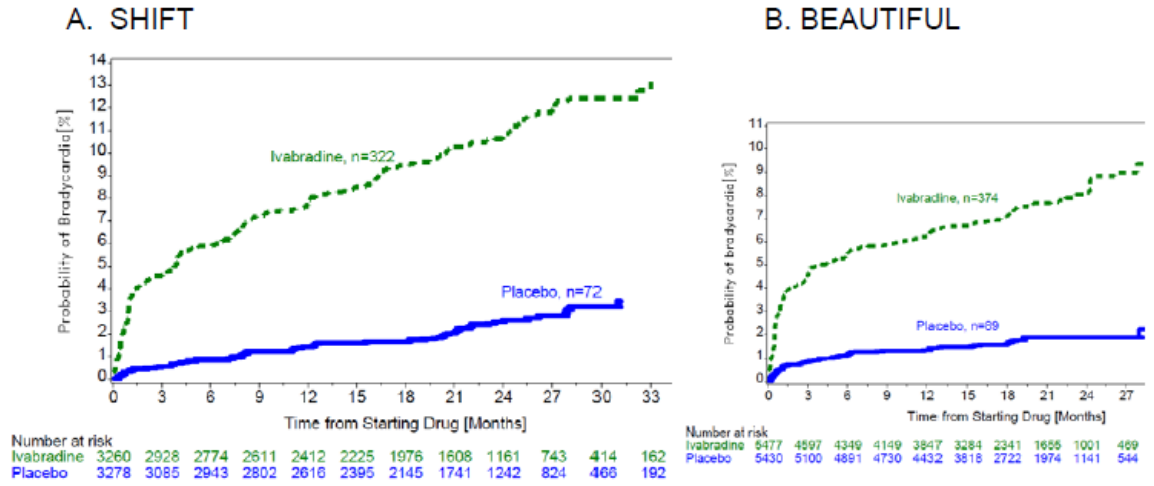


Table 8 shows these 4 adverse events by subgroup, an analysis performed largely to facilitate development of ivabradine's drug snapshot. Of note, in some cases the relatively low numbers of subjects with adverse events coupled with the small patient subsets render the data difficult to interpret, but there are some interesting findings.

The results regarding bradycardia (blue area) are notable in two respects. Not surprisingly, the risk of bradycardia increases with increasing age in both treatment groups. The absolute and relative risks attributable to ivabradine vary by age quartile, but patients at all ages seem to be at similar risk.

The relative risk of bradycardia is much higher for the modal dose of 2.5 mg than for the other doses, but this difference exists because patients who had bradycardia had their dose reduced.

The intensity of beta blocker use at baseline does not appear to predict the risk of bradycardia.

The frequency of hypertension (yellow area) increases sharply with increasing baseline systolic blood pressure, but the relative risk with ivabradine is similar across baseline blood pressure quartiles.

For atrial fibrillation/flutter (green area), advanced age and worse NYHA functional class appear to increase the risk, but the relative risks with ivabradine are similar across these groups. There also appears to be an association between atrial fibrillation and higher weight.

The frequency of reported phosphenes (beige area) appears consistent across all subgroups.

Table 8: SHIFT – Adverse Events by Subgroup

		% of subjects	↓ HR Ivab	↓ HR Placebo	RR	↑ BP Ivab	↑ BP Placebo	RR	A Fib/Flutter Ivab	A Fib/Flutter Placebo	RR	Phosphenes Ivab	Phosphenes Placebo	RR
All			10.1%	2.4%	4.2	9.0%	8.0%	1.1	10.3%	8.8%	1.1	2.8%	0.5%	5.3
Age quartile	<54	27%	8.5%	1.0%	8.4	7.1%	7.5%	0.9	5.8%	5.8%	0.9	3.4%	0.8%	4.2
	55 to 60	24%	9.9%	2.8%	3.5	8.9%	8.1%	1.1	9.5%	5.9%	1.5	2.8%	0.5%	5.4
	61 to 69	27%	9.1%	2.8%	3.2	9.0%	8.3%	1	11.6%	10.4%	1.1	3.4%	0.4%	9.8
	>69	23%	13.1%	3.2%	4.1	11.1%	8.0%	1.3	14.6%	13.8%	1	1.4%	0.4%	3.4
Age	> 65	38%	12.2%	3.1%	3.8	10.4%	8.8%	1.1	13.3%	12.7%	1	2.0%	0.4%	4.7
	> 75	11%	13.0%	3.1%	4.1	11.1%	7.6%	1.4	16.0%	13.9%	1.1	1.9%	0.6%	3.3
Sex	Male	76%	9.6%	2.6%	3.6	8.3%	7.7%	1	10.5%	9.3%	1.1	2.6%	0.4%	7.3
	Female	24%	11.6%	1.6%	7.2	11.2%	9.0%	1.2	9.8%	7.4%	1.3	3.2%	1.1%	3
Race	Caucasian	89%	10.3%	2.6%	3.9	9.7%	8.6%	1.1	11.0%	9.3%	1.1	2.9%	0.6%	5.2
	Black	1%	9.4%	0.0%	-	9.4%	4.7%	-	12.5%	7.0%	1.7	0.0%	0.0%	-
	Asian	8%	8.6%	0.8%	11.3	2.6%	2.3%	1.1	4.1%	4.5%	0.9	2.2%	0.4%	5.9
	Other	2%	8.1%	0.0%	-	1.6%	6.2%	-	3.2%	6.2%	0.5	0.0%	0.0%	-
Modal dose	2.5 mg	5%	32.6%	2.4%	13.6	10.3%	8.0%	1.3	8.9%	8.8%	1	4.6%	0.5%	8.9
	5 mg	16%	16.6%	2.4%	6.9	7.7%	8.0%	1.0	10.7%	8.8%	1.2	4.2%	0.5%	8.1
	7.5 mg	79%	4.8%	2.4%	2	9.3%	8.0%	1.2	10.4%	8.8%	1.1	2.0%	0.5%	3.9
Weight quartile	<=69.4 kg	25%	11.3%	2.3%	4.9	5.5%	6.3%	0.8	10.7%	6.1%	1.7	1.7%	0.4%	4.7
	69.5 to 79.6	25%	9.0%	2.2%	4.1	8.8%	7.2%	1.2	9.0%	8.8%	1	3.8%	0.4%	10
	79.7 to 91.0	26%	11.0%	2.1%	5.3	12.2%	7.1%	1.7	9.6%	10.0%	0.9	3.1%	0.6%	5
	91.1 to 170	24%	9.0%	3.1%	2.9	9.4%	11.4%	0.8	12.0%	10.4%	1.1	2.5%	0.8%	3.2
Baseline HR quartile	48 to 73	30%	12.3%	3.1%	3.9	9.4%	7.6%	1.2	10.7%	7.2%	1.4	2.7%	0.4%	6.5
	74 to 77	22%	10.2%	3.2%	3.2	9.4%	8.4%	1.1	9.7%	9.5%	1	2.2%	0.8%	2.6
	78 to 84	23%	10.4%	2.0%	5.1	9.2%	7.7%	1.2	10.1%	9.3%	1	2.6%	0.4%	6.5
	85 to 142	24%	6.8%	1.2%	5.6	7.9%	8.3%	0.9	10.6%	9.6%	1.1	3.5%	0.5%	7.2
Baseline systolic BP by quartile	76 to 110	31%	7.8%	1.8%	4.4	2.8%	4.0%	0.7	9.9%	8.6%	1.1	3.1%	0.0%	-
	111 to 120	24%	12.6%	2.5%	4.9	7.6%	6.3%	1.2	9.5%	9.5%	1	3.2%	0.6%	5.1
	121 to 130	22%	10.7%	2.6%	4.1	9.7%	7.2%	1.3	9.2%	7.3%	1.2	2.2%	0.9%	2.5
	131 to 180	24%	10.1%	2.9%	3.4	17.2%	15.6%	1.1	12.6%	9.9%	1.2	2.4%	0.8%	3
NYHA Functional Class	FC 2	49%	10.0%	2.3%	4.2	9.3%	9.1%	1	9.5%	7.3%	1.3	3.3%	0.8%	4.4
	FC 3	50%	10.3%	2.5%	4.1	8.8%	6.9%	1.2	11.0%	10.1%	1	2.2%	0.3%	7.2
	FC 4	2%	6.0%	1.6%	3.6	2.0%	6.6%	0.3	14.0%	14.8%	0.9	2.0%	0.0%	-
Baseline beta blocker use	none	12%	8.5%	1.8%	4.7	7.8%	4.8%	1.6	13.5%	8.9%	1.5	1.3%	0.5%	2.4
	>0 to 25%	14%	8.3%	2.6%	3.2	5.8%	5.6%	1	8.7%	12.2%	0.7	2.1%	0.9%	2.2
	25 to 50%	25%	11.0%	2.5%	4.4	8.7%	6.6%	1.3	11.0%	9.1%	1.2	3.6%	0.8%	4.3
	50 to 75%	24%	10.9%	2.9%	3.7	11.5%	10.2%	1.1	10.3%	8.8%	1.1	3.5%	0.1%	27
	75 to 100%	25%	10.2%	2.0%	5.1	9.3%	9.9%	0.9	9.0%	6.7%	1.3	2.5%	0.4%	6.6

***Concerns of the Review Team*:**

The major concerns of the review team are discussed below:

1. Mortality claim

Members of the review team held a range of views on the indication statement. The primary reviewer who evaluated efficacy, Dr. Dunnmon, recommended a split indication for reduction of cardiovascular death in patients who cannot take a beta-blocker at any dose (± in patients with heart rate >75 bpm), but did not recommend a mortality claim for patients who are taking a maximally tolerated dose of beta-blockers. Dr. Beasley, the primary reviewer who performed the safety evaluation, did not support an efficacy claim (personal communication from Dr.

Beasley). The primary statistical and clinical pharmacology reviewers, Drs. Bai and Sahre, respectively, did not comment on the cardiovascular mortality claim. The Cross-Discipline Team Leader, Dr. Marciniak, proposed giving ivabradine a mortality claim, but only when used with a loop diuretic. Dr. Grant argued that reduction of mortality should not be included in the indication statement. Dr. Stockbridge opined that the findings from SHIFT support a reduction in the combined risk of cardiovascular death and hospitalization for worsening heart failure, and that the claim should reflect that wording and not be restricted to hospitalization.

Cardiovascular mortality was evaluated in SHIFT as one of two components of the 1° composite endpoint; hospitalization for worsening heart failure was the second component. The treatment effect on the composite was driven entirely by hospitalizations for worsening HF. When the 1° endpoint is deconstructed, ivabradine's effect on cardiovascular mortality is neutral – with 279 and 265 cardiovascular deaths in the ivabradine and placebo groups, respectively – a hazard ratio that is slightly on the wrong side of 1. When cardiovascular death is analyzed separately as a 2° endpoint, including deaths that followed a hospitalization, the hazard ratio is 0.91 with a nominal *p*-value of 0.13, but there was no prospective plan to control Type-I error for this or any other 2° endpoint, and there is no obvious reason why the favorable effect on cardiovascular death would show up only later.

As noted above, for the sub-population within BEAUTIFUL for whom ivabradine would be indicated, cardiovascular mortality is neutral or even trends negatively, depending on the method of selecting the sub-population (Figure 4).

For the majority of cardiovascular drugs that have been approved on the basis of a composite endpoint, the indication statement has described the components of the endpoint. When the composite endpoint has been driven by the treatment effect on the component that is less medically important, however, the indication statement has typically communicated the strength of the finding on the more clinically significant component. For example, given a composite endpoint that includes myocardial infarction, stroke, and death, the indication statement may note that the results were driven by myocardial infarction if neither strokes nor deaths contributed to the strength of the overall finding. Conversely, when a composite endpoint has been driven by the treatment effect on the more medically significant event (e.g., reduction of stroke for a composite endpoint of time-to-first stroke or systemic embolism), the indication statement has typically been relatively silent about the components, even if the composite is mentioned. In the present case, the mortality component of the 1° endpoint clearly did not contribute.

Many on the review team have pointed out that the results of SHIFT seem only somewhat generalizable to the US patient population. The underuse of CRT and ICDs in SHIFT relative to use in the US is a major limitation. We have few data here, and some members of the review team suggested that these concerns undercut the already marginal evidence of a mortality benefit.

These issues raise considerable uncertainty regarding the mortality finding in SHIFT, particularly the failure to see an effect in the 1° endpoint. It seems clearly appropriate to omit cardiovascular death from the indication statement and simply describe the findings in Section 14 of labeling.

2. Robustness of the results

The review team had concerns regarding the delay of finalization of the statistical analytical plan until after all of the data had been collected (i.e., all patient visits were complete). There was also some concern regarding sample size changes directed by protocol amendments in September, 2008 and June, 2009.

In order to address these concerns, Dr. Bai provided an analysis of the *p*-values from the Cox proportional hazards model for the 1° endpoint as a function of study date. He showed that SHIFT attained a nominal *p*-value of < 0.05 on June 17, 2008, and that it remained below 0.05 throughout the study. Thus, prior to the sample size adjustments and the finalization of the statistical plan, the study was successful on its 1° endpoint. Presumably, if individuals responsible for making these decisions had inappropriate access to the data, they would not have decided to increase the sample size. In short, Dr. Bai's analyses provide reassurance that no one associated with the study made decisions about sample size or the analytical plan with knowledge at hand.

3. Lack of financial disclosure information

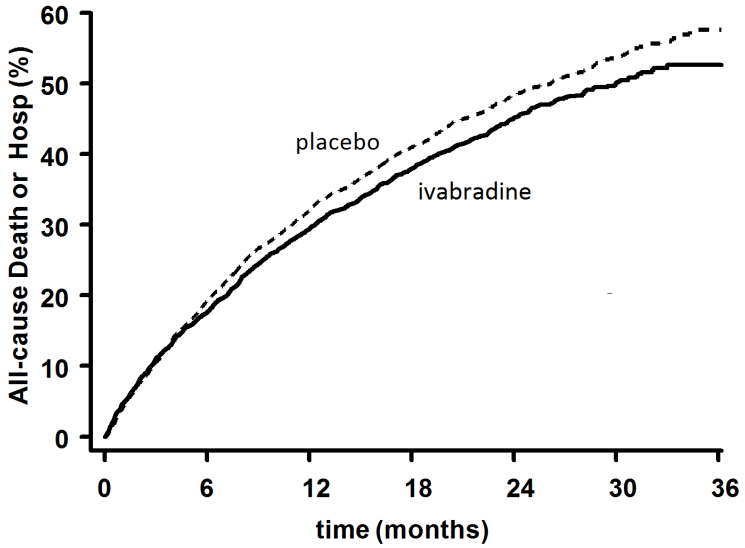
After completion of SHIFT, Servier attempted to collect financial disclosure information from the study sites. Approximately 46% responded to the request and reported no disclosable relationships, 2% responded and reported disclosable relationships, and 52% did not respond to the request. With respect to the hazard ratio for the 1° endpoint, Dr. Bai found that the results from sites that either disclosed no interest or did not respond to the request were consistent with the overall study results. Of note, the results at sites that disclosed relationships were unfavorable for ivabradine, with a hazard ratio of 1.2. These findings are reassuring. As Dr. Stockbridge noted, given the time elapsed between conduct of the study and collection of the data, it appears that a good faith effort was made to obtain this information, and there are no concerns.

4. Potential unblinding from heart rate lowering effects

In line with ivabradine's negative chronotropism, the drug was found to decrease mean heart rate by approximately 10 bpm in SHIFT. It is possible, therefore, that some degree of unblinding could have occurred in SHIFT. If so, perceived knowledge of treatment assignment could have influenced investigators' decisions to hospitalize patients, affected judgments in deciding whether hospitalizations were related to worsening heart failure, and influenced opinions of whether or not deaths were cardiovascular in nature.

One way to consider the potential effects of bias on the primary endpoint is to examine a composite endpoint of all-cause hospitalization and all-cause mortality. In this exploratory analysis, where all deaths and hospitalizations are included (as if the events had not been adjudicated), ivabradine still has a nominally statistically significant treatment effect ($p < 0.05$, Figure 6). In light of these findings, there is little need to be concerned about potential unblinding from heart rate effects, or bias in the adjudication of hospitalizations and/or deaths.

Figure 6: SHIFT: Kaplan-Meier Plot, Exploratory Analysis, Time to First All-Cause Hospitalization or All-cause Death



5. The results of SHIFT in the context of 2 additional large outcome studies that failed on their primary endpoints

The submission included 3 randomized placebo-controlled outcome trials, together enrolling > 36,500 subjects. Of note, the evidence of efficacy is supported only by SHIFT, with 6,500 subjects. The remaining 30,000 subjects were enrolled in BEAUTIFUL and SIGNIFY, and neither study was positive.

SIGNIFY had a slightly unfavorable hazard ratio (1.08) on its 1° endpoint of cardiovascular death or non-fatal MI, but, as noted above, the population enrolled in SIGNIFY did not have heart failure, so that the population in SIGNIFY and the proposed indicated patient population are mutually exclusive. No one on the review team was particularly concerned about the results of SIGNIFY, and as Dr. Dunnmon pointed out, the ivabradine dose in SIGNIFY was higher than the to-be-marketed dose. I agree with the review team on these points; I am not concerned about the lack of a positive finding in SIGNIFY.

BEAUTIFUL has been discussed in detail. The study enrolled subjects with coronary artery disease and left ventricular dysfunction, although generally less left ventricular dystrophin than in SHIFT. Some of the patients had clinical heart failure, as indicated by a 'flag' for "fatigue/palpitation/dyspnea" rather than "anginal pain" in one of the datasets. For subjects who were NYHA functional class II/III with heart rate ≥ 70 bpm at baseline, the applicant's findings, said to trend positively, are too fragile to be reassuring. More importantly, in my analyses of the to-be-indicated sub-population from BEAUTIFUL, the results are neutral.

Thus, I do not agree with the prevailing interpretation of BEAUTIFUL from the applicant and some on the review team – that the results are generally consistent with SHIFT, and that as one moves away from the SHIFT demographic characteristics, ivabradine works progressively less well; I am not reassured by the results from BEAUTIFUL. Nevertheless, the results from SHIFT

are broadly consistent and statistically persuasive with a *p*-value < 0.0001, and so they are strong enough to overcome a neutral result on a second study – one that was not designed to evaluate a 1° endpoint specific for heart failure in a heart failure population.

6. Findings in subgroups, in particular, subgroups at high risk, and those defined on the basis of loop diuretic use

A myriad of subgroup analyses are discussed above, and results are reasonably consistent. Although results in Blacks are consistent with SHIFT as a whole, there are too few Blacks to be entirely reassured with respect to efficacy. Ivabradine's negative chronotropic effects appear to be demonstrable in Blacks, which is at least somewhat reassuring. I am in full agreement with Dr. Stockbridge with respect to the concerns of Dr. Marciniak regarding loop diuretics. I do not find the interaction with loop diuretics to be credible; indeed, as Dr. Stockbridge noted, "…it is based upon deep dives into subgroups of an end point that had no overall finding. I would make no mention of this in labeling."

7. Whether the indication should limit use at lower baseline heart rates, and if so, the specific heart rate cut-off

This issue was discussed at length in the reviews. Based on a decile analysis shown graphically in Figure 2 and the discussion that followed, I am not enthusiastic about limiting use to any heart rate other than 70 bpm, the criterion for enrollment in SHIFT.

8. Whether the label should include a limitation of use statement for patients with implantable cardiac defibrillators and/or cardiac resynchronization therapy devices

Limitations of use are intended to describe circumstances of use where there is reasonable concern or uncertainty about the benefit-risk profile of a drug – when the evidence falls short of a contraindication but nevertheless suggests that use of the drug is not advisable.

Data regarding patients with CRT and/or ICDs from SHIFT are sparse. Although it seems reasonably likely that the benefit in such patients would be reduced, there is some uncertainty about this. Surely there is no evidence that ivabradine is more harmful in such patients, and so the benefit-risk is not likely to be very unfavorable. In any case, the label will explain that: "Few patients had an implantable cardioverter-defibrillator (3.2%) or a cardiac resynchronization therapy device (1.1%)." Parenthetically, I will note that SHIFT provides far less data for Blacks than for patients with CRT or ICDs.

9. Efficacy with pacemakers

With respect to pacemakers, it will not be possible to achieve a target heart rate of 50 to 60 bpm for patients with demand pacemakers where the pacing rate is ≥ 60 bpm. This may not be obvious to practitioners, and will be explained in labeling. Moreover, it is not clear the drug will have efficacy if heart rate is maintained with a pacemaker.

10. Whether the target HR should be the same for men and women

This was not discussed by the review team, but has been a concern of mine. If one assumes that resting heart rate is greater in women than men, it might not make sense to target both

sexes to the same heart rate. Surprisingly, the baseline heart rates for men and women in SHIFT were the same, 80 bpm. Thus, there doesn't seem to be a good rationale to target different heart rates in men and women.

11. The correct starting dose

In discussions after the primary reviews were filed, we considered the possibility of lowering the starting dose from 5 mg BID to 2.5 mg BID for all patients, and increasing the dose to achieve the target heart rate of 50 to 60 bpm. Essentially, this would involve an additional visit for all patients in order to achieve the desired heart rate, and this could require an additional 2 weeks. Given that achieving the correct dose is not an emergency, this seemed like a rational approach to reduce bradycardia.

In labeling negotiations, the applicant pointed out that few subjects in SHIFT required dose reduction for bradycardia, and even fewer required dose reduction for symptomatic bradycardia. The applicant made the point that the reduced risk of bradycardia that might be achieved by starting all patients at 2.5 mg BID might be more than offset by the loss in efficacy in patients who would experience a delay in achieving an adequate dose, or who might be started at a dose of 2.5 mg BID and never have their dose increased. The review team recognized that the strategy of up-titrating patients from the lowest dose would likely lead to a lower average dose than one based on down-titration.

After considering the advantages and disadvantages of a lower starting dose, we accepted the applicant's position, although the label will suggest a starting dose of 2.5 mg BID in patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise

12. Whether the fetal effects merit a contraindication for use in pregnancy, or only a warning

Although the pharmacology-toxicology reviewers initially recommended a contraindication in pregnant women, particularly during cardiac organogenesis, the review team ultimately reached the conclusion that there are circumstances when a pregnant woman, cognizant of these risks, might reach a positive benefit-risk conclusion on starting or continuing the drug. Thus, we opted to include the risk as a warning rather than a contraindication.

Benefit-Harm

Ivabradine's benefit is summarized in Table 9, to be displayed in Section 14 of the package insert. The absolute benefit, versus placebo, is 17.7 - 14.5 = 3.2 endpoint events per 100 patient-years. This difference is driven by hospitalizations for worsening heart failure. The contribution of cardiovascular death is difficult to estimate, but is at best small. Considering cardiovascular death as a discrete endpoint not confounded by the competing risk of prior hospitalization, the risk difference is 0.8 per 100 patient-years, but the 95% confidence interval of the hazard ratio does not exclude 1.

Table 9: Benefit as Provided in Labeling

Endpoint	Corlanor (N = 3241) n	%	% PY	Placebo (N = 3264) n	%	% PY	Hazard Ratio	[95% CI]	p-value
Primary composite endpoint: Time to first hospitalization for worsening heart failure or cardiovascular death	793	24.5	14.5	937	28.7	17.7	0.82	[0.75 , 0.90]	<0.0001
Hospitalization for worsening heart failure	505	15.6	9.2	660	20.2	12.5			
Cardiovascular death as first event	288	8.9	4.8	277	8.5	4.7			
Subjects with events at any time									
Hospitalization for worsening heart failure[b]	514	15.9	9.4	672	20.6	12.7	0.74	[0.66 , 0.83]	
Cardiovascular death	449	13.9	7.5	491	15.0	8.3	0.91	[0.80 , 1.03]	

A principal issue in estimating benefit is the concern raised by Dr. Dunnmon and others: ivabradine's treatment effect in patients appropriately managed with CRT and/or ICDs is unknown, but is expected to be less than the benefit observed in SHIFT. Thus, the benefit is, *at most*, avoidance of 3.2 hospitalizations per 100 patient-years. These figures translate into benefit in 1 of 31 patients, i.e., to avoid 1 event over the course of a year, the number needed to treat (NNT) is 31. This calculus underscores one of the issues inherent in many therapies for cardiovascular diseases – they are *preventive* in nature, and the absolute number of events prevented is small.

Of note, an individual patient taking ivabradine will never know whether he/she is receiving benefit – or not receiving benefit. It seems unlikely, therefore, that patients will receive an interpretable signal to warn that the drug is not working – information that could be used to inform when it would be reasonable to stop the drug.

To the best of our ability to estimate the absolute risks, the important ones are as follows (expressed per 100 patient-years):

symptomatic bradycardia	2.2
atrial fibrillation	1.1
hypertension	~1
phosphenes	1.3

If one simply sums these numbers, the absolute risk would be approximately 5 to 6 per 100 patient-years. Such a conclusion would be entirely misleading, however, because the importance of these risks is probably far less important to patients than the reduction in the probability of hospitalization for heart failure. Moreover, ivabradine-induced bradycardia, hypertension, and phosphenes are largely not associated with clinically important sequelae. (Had bradycardia been associated with syncope, falls, or fractures, one would view that risk

more seriously.) Thus, the risk of irreversible harm seems quite low, but would probably be estimated at <1%.

Finally, because these risks are largely reversible and cause symptoms, patients with side effects can simply elect to stop the drug. Ironically, individual patients will never know if the drug prevents a hospitalization, but they will know if they experience a side effect.

Summary/Conclusions

Ivabradine, a negative chronotrope, represents a first-in-class drug for heart failure. Its effectiveness is well established from SHIFT, a 6,500-subject randomized, double-blind, placebo-controlled trial. Analyses of various subsets from BEAUTIFUL, an 11,000-subject trial in a related patient population, do not support the findings in SHIFT. Although we would have greater confidence in the results of SHIFT if BEAUTIFUL had been positive as well, the review team is unanimous in its belief that the results of SHIFT are strong enough to overcome the lack of substantiation from BEAUTIFUL.

Ivabradine's benefit is in reducing the need for hospitalization for heart failure by ~3 per 100 patient-years, but this number should be discounted to some extent when extrapolating to a US patient population, because few patients in SHIFT had received CRT or ICDs, and these are effective therapeutic modalities that are standard in contemporary US practice.

On the positive side, ivabradine's treatment effect was evident when added to adequate background medical therapy (ACEs or ARBs, aldosterone antagonists, and diuretics; beta blockers were used only to the extent possible – by design). Moreover, although the reduction in heart failure hospitalizations was modest, it must be considered in the context of the enormity of the public health problem. Heart failure is the *leading cause* of hospitalization and re-hospitalization in the US. Thus, even small treatment effects can have considerable impact on the public health because of the size of the patient population and burden of hospitalization.

The risks are manageable, as noted above. Most of the side effects cause symptoms that would lead patients to seek medical attention, and most are reversible.

The typical patient in SHIFT was a 60 year-old Caucasian male from Eastern Europe who had not received CRT or an ICD. Important information missing in this NDA includes better estimates of ivabradine's efficacy with concomitant use of CRT and ICDs, and a more precise estimate of efficacy in Blacks. Although women were under-represented in the development program, SHIFT provides ample evidence of efficacy in women, with over 750 subjects in each treatment group.

Having negotiated the labeling with the applicant, ivabradine will be approved with agreed upon labeling and the following indication statement:

"Corlanor is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq$ 35%, who are in sinus rhythm with resting heart rate $\geq$ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use."

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/s/

ELLIS F UNGER
04/15/2015