Ivabradine for the treatment of chronic heart failure
STA REPORT

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BMJ Technology Assessment Group

Title: Ivabradine for the treatment of chronic heart failure

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

Authors: Steve Edwards, Head of BMJ-TAG, London

Samantha Barton, Health Technology Assessment Analyst, BMJ-TAG, London

Leo Nherera, Health Economist, BMJ-TAG, London

Nicola Trevor, Health Economics Lead, BMJ-TAG, London

Victoria Hamilton, Health Technology Assessment Analyst, BMJ-TAG, London

Correspondence to: Steve Edwards, Head of Health Technology Assessment, BMJ-TAG, BMJ Evidence Centre, BMJ Group, BMA House, Tavistock Square, London, WC1H 9JP.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Steve Edwards	Project lead: supervised the production of the final report; critical appraisal of the manufacturer's submission; critical appraisal of the clinical evidence; and critical appraisal of the economic evidence
Samantha Barton	Critical appraisal of the manufacturer's submission; critical appraisal of the clinical evidence; cross checking of manufacturer's search strategies; and drafted the summary and clinical results sections
Leo Nherera	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic analysis sections
Nicola Trevor	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic analysis sections
Victoria Hamilton	Critical appraisal of the manufacturer's submission; and critical appraisal of the clinical evidence

All authors read and commented on draft versions of the ERG report

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Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AIC	Akaike's information criterion
ARB	Angiotensin receptor blocker
bd	Twice daily
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
bpm	Beats per minute
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEC	Clinical Events Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
cm	Centimetre
CRT	Cardiac resynchronisation therapy
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EF	Ejection fraction
EQ-5D	EuroQol 5 dimensions questionnaire
ERG	Evidence Review Group
ESC	European Society of Cardiology
EVC	Endpoint Validation Committee
GP	General Practitioner
GPwSI	General Practitioner with Special Interest
HF	Heart failure
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit

ITT	Intention-to-treat
IVRS	Interactive voice response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	Kilogramme
LVSD	Left-ventricular systolic dysfunction
LVEF	Left-ventricular ejection fraction
LYG	Life-years gained
m	Metre
MI	Myocardial infarction
min	Minute
ml	Millilitre
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NYHA	New York Heart Association
OR	Odds ratio
PCT	Primary Care Trust
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QOF	Quality and Outcomes Framework
RCT	Randomised controlled trial
RR	Relative risk
RS_{BBDOSE}	Patients achieving ≥50% of the target beta-blocker dose
SBP	Systolic blood pressure
SD	Standard deviation
SHIfT	Systolic Heart failure treatment with I_f inhibitor ivabradine Trial
SE	Standard error
STA	Single Technology Appraisal
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
vs	versus

Glossary of statistical terms and concepts

Relationships between covariates and dependent variables	Generally, the relationship between covariates and the dependant outcome in a regression equation is linear (i.e. an increase in the covariate results in directly proportional increase in the outcome). However, continuous variables can sometimes have a non-linear relationship with the outcome of interest e.g. cubic. In cases such as this interaction terms that capture the nature of the cubic relationship need to be included in the regression equation.
Forward selection process	This is a process of choosing variables to be included in a regression equation. The process involves adding variables to the model one at a time. At each step, variables that are not already in the model are tested for statistical significance and the most significant of these variables is added to the model. The forward selection process continues until no more variables are deemed statistically significant (the manufacturer used a p-value of 0.1 as the initial threshold for significance).
Backward selection process	This is a process of choosing variables to be included in a regression equation. In the backwards selection process, a regression model saturated with all variables of interest is built. Then, the regression equation is reduced, one variable at a time, starting with the least significant predictor of the outcome of interest (CV mortality). The backwards selection process continues until only statistically significant (initially $p<0.1$ in the MS) variables remain in the model.
Correlation	The strength of any relationship existing between a pair of variables. Two variables are correlated positively if, on average, they move in the same direction; two variables are correlated negatively if, on average, they move in opposite directions
Collinearity	Variables that are highly correlated are described as collinear. The strength of the correlation between them means that it is difficult to determine their individual impact on the outcome of interest.
Interaction effect/ interaction variable	An interaction variable is the product of two other variables that are included in the multiple regression model
Goodness-of-Fit Measure/ model fit	This is a statistic that summaries how well a set of explanatory variables explains a dependent or response variable.
Log likelihood test	A likelihood ratio test is a statistical test used to compare the fit of two models, one of which (the null model) is a special case of the other (the alternative model). The test is based on the likelihood ratio, which expresses how many times more likely the data are under one model than the other. When the logarithm of the likelihood ratio is used, the statistic is known as a log-likelihood ratio statistic
Proportional hazards (PH).	The treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape.
Cox-Snell residuals model fit	Residuals are used to assess the adequacy of linear model especially the fit of autoregressive model
Harrell's concordance measure	This is a measure of the general predictive power of a general regression model.

Parameters	Numerical characteristics of the model.
Regression coefficient	This is an estimate of the effect an explanatory variable has on the outcome of interest.
Bayesian information criterion (BIC)	Measure of the relative goodness of fit of a statistical model. When fitting models, it is possible to improve the fit by adding parameters, but doing so may result in over-fitting. The BIC/AIC resolves this problem by introducing a penalty term for the number of parameters in the model The analyst always looks for a compromise between a model that fits well but does not have too many parameters.
Akaike information criterion (AIC)	
Cholesky decomposition method	Enables correlated values to be sampled from a multivariate normal distribution whilst accounting for the correlation between them.

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The manufacturer of ivabradine (Procoralan®; Servier) submitted to the National Institute for Health and Clinical Excellence (NICE) clinical and economic evidence in support of the effectiveness of ivabradine in the treatment of chronic heart failure (hereafter referred to as heart failure). Ivabradine has marketing authorisation in Europe for the treatment of chronic stable angina and the treatment of heart failure. In heart failure, the licence indicates that ivabradine is appropriate for use in patients who are symptomatic (New York Heart Association [NYHA] class II to IV), have systolic dysfunction and are in sinus rhythm with a resting heart rate ≥75 bpm. The licence states that ivabradine is for use in combination with standard therapy, including beta-blocker therapy, or when beta-blocker therapy is contraindicated or not tolerated.

The clinical evidence presented in the manufacturer's submission deviates from the final scope issued by NICE in restriction of the population to patients with resting heart rate of ≥75 bpm, which was not specified in the final scope. This is because the licence extension for ivabradine to include its use in heart failure (granted subsequent to finalisation of the scope) limited the eligible population to patients with a resting heart rate of ≥ 75 bpm. The source of clinical evidence described in the manufacturer's submission (MS) is derived from the SHIfT randomised controlled trial (RCT). SHIfT enrolled patients with a baseline resting heart rate of ≥70 bpm at randomisation. The manufacturer has submitted evidence based on the subgroup of patients with a baseline resting heart rate of ≥75 bpm (hereafter referred to as the licensed population), which is relevant to the licensed indication and the decision problem that is the focus of this Single Technology Appraisal (STA). All requested outcomes were reported and the comparison with standard care adhered to.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The SHIfT trial assessed the effects of adding ivabradine versus adding placebo to optimised standard therapies for the management of heart failure in patients in sinus rhythm with symptomatic heart failure (NYHA class II to IV) due to left-ventricular systolic dysfunction (left-ventricular ejection fraction ≤35%) and a resting heart rate of ≥70 bpm.

In the SHIfT trial, 6,558 patients were randomised. Data for 6,505 patients were available for analysis, of which 4,150 (63.8%) make up the licensed population. Ivabradine was initiated at a dose of 5 mg twice daily (bd). After two weeks, the dose of ivabradine was increased to 7.5 mg bd, unless resting heart rate was ≤60 bpm, or decreased to 2.5mg bd if resting heart rate was <50 bpm or the patient had signs or symptoms of bradycardia.

In the licensed population of the SHIfT trial, addition of ivabradine to standard care was associated with a statistically significant reduction in the primary composite outcome of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure (26.6% with ivabradine vs 32.8% with placebo; HR 0.76; 95% CI: 0.68 to 0.85). Analyses of the individual components of the primary composite outcome indicate that reduction in hospitalisation for worsening heart failure is the key driver in the clinical effect of ivabradine observed for the primary composite outcome, with a statistically significant risk reduction of 30% for this endpoint relative to placebo (17.7% with ivabradine vs 24.0% with placebo; HR 0.70; 95% CI: 0.61 to 0.80). However, ivabradine also reduced cardiovascular mortality (14.8% with ivabradine vs 17.4% with placebo; HR 0.83; 95% CI 0.71 to 0.97). The greatest relative benefit of ivabradine was associated with the cause-specific outcome of death from heart failure (3.8% with ivabradine vs 6.0% with placebo; HR 0.61; 95% CI: 0.46 to 0.81), which was assessed as a pre-specified secondary outcome.

Health-related quality of life (HRQoL) was evaluated using the generic EuroQoL questionnaire and the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ). Results for the main analysis of the EQ-5D index score (scores death as 0) suggest that ivabradine [redacted] on a patient's HRQoL compared with placebo, whereas the KCCQ suggests that treatment with ivabradine improves a patient's HRQoL. In the case of the KCCQ, the difference in clinical summary score between the ivabradine and placebo groups [redacted]. A 5-point change in score on the KCCQ has been proposed as a clinically meaningful difference. The Evidence Review Group (ERG) notes that the differences in clinical summary score between the ivabradine and placebo groups for all analyses [redacted].

Ivabradine was generally well-tolerated. In the licensed population of the SHIfT trial, adverse effects associated with ivabradine treatment were bradycardia (symptomatic and asymptomatic) and phosphenes, both of which are recognised adverse effects of ivabradine. Compared with the placebo group, patients in the ivabradine group were: 6 times more likely to experience symptomatic bradycardia (4.1% with ivabradine vs 0.7% with placebo; Relative Risk [RR] 6.14; 95% CI: 3.50 to 10.78); 4 times more likely to experience asymptomatic bradycardia (4.8% with ivabradine vs 1.2% with placebo; RR 4.01; 95% CI: 2.60 to 6.20); and 5 times more likely to experience phosphenes (2.8% with ivabradine vs 0.5% with placebo; RR 5.31; 95% CI: 2.79 to 10.09).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers the SHIfT RCT to be a well-conducted trial, and considers the results of the evidence submitted for the licensed population to be applicable to the decision problem that is the focus of this STA.

The ERG notes that the baseline characteristics are reasonably well balanced for the ivabradine and placebo arms in both the full and licensed population of SHIfT. The licensed population had a mean age of about 60 years, a resting heart rate of about 84 bpm, and an LVEF close to 29%. Patients were predominantly male (76.8%) and of NYHA class II or III (97.9%). The larger proportion of patients had heart failure associated with ischaemic causes. At randomisation, most patients were receiving a beta-blocker, an ACE inhibitor, and/or a diuretic.

Based on exploratory analyses, the ERG considers that the beneficial effect of ivabradine could be attenuated in patients with a resting heart rate ≥75 bpm who achieve higher doses of beta-blocker therapy. The ERG carried out exploratory analyses based on various thresholds of beta-blockade; these analyses were not adjusted for baseline resting heart rate. However, the ERG notes that in the licensed indication baseline resting heart rates are similar across the groups assessed based on various thresholds of beta-blockade. In the licensed population as a whole, ivabradine is associated with greatest relative benefit in the cause-specific endpoints of hospitalisation for heart failure and heart failure mortality. Results of the exploratory analysis based on beta-blocker dose are in agreement with this finding.

In the ERG's exploratory analysis, ivabradine is associated with a [redacted] in hospitalisation for worsening heart failure and a [redacted] in death from heart failure irrespective of category of beta-blocker dose assessed, although some of the differences between groups did [redacted]. However, for all other outcomes, including the primary composite outcome, there was a trend [redacted] benefit of ivabradine with increasing beta-blocker dose, and, in some analyses, the relative risk (RR) [redacted] of addition of ivabradine. In the case of the primary composite outcome, the exploratory analyses suggest [redacted] of ivabradine on the primary outcome for patients achieving ≥100% target dose of beta-blocker [redacted].

To illustrate this point further, the key outcome of all-cause mortality is reported here in more detail. The ERG determined that patients receiving no beta-blocker at baseline received [redacted] from addition of ivabradine to their standard care, with a [redacted] in risk of mortality compared with placebo [redacted]

[redacted]. However, with increasing percentage of beta-blockade, the ERG noted a trend [redacted] with ivabradine versus placebo [redacted]. Based on its exploratory analysis, the ERG speculates that, for the licensed population of the SHIfT trial, there is a marked difference in benefit at a threshold of at least [redacted] target beta-blockade, with patients achieving [redacted] target beta-blocker dose receiving the greatest benefit from addition of ivabradine to their standard care. The ERG notes that despite a consistent [redacted] in resting heart rate of [redacted] across beta-blocker categories there [redacted].

NICE guidelines recommend that beta-blockers are initiated in a "start low, go slow" manner, and that heart rate, blood pressure, and clinical status are assessed after each titration. In the submission, the manufacturer emphasises that they support the aggressive up-titration of beta-blockers to target or maximum tolerated doses.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer presents a *de novo* economic evaluation that considers the relative cost-effectiveness of the addition of ivabradine treatment to standard care. No economic evaluations considering ivabradine treatment in chronic heart failure were identified in the published literature. The economic evaluation submitted by the manufacturer was a two-state Markov cohort model constructed in Microsoft© EXCEL from the perspective of the UK NHS. The model included the health states of "alive" or "dead" and proportioned patients in the "alive" health state into different categorisations of severity (based on NYHA classification) and hospitalisation. The model uses a series of regression equations to capture the outcomes of mortality, NYHA distribution, hospitalisation and health related quality of life. The manufacturer developed the regression equations for each outcome of interest from the entire patient population (heart rate ≥70 bpm) of SHIfT. Where appropriate, a heart rate covariate was included in the regression equations to allow the model to predict outcomes for the licensed population. HRQoL data were derived from a sub-study of SHIfT that collected EQ-5D data. Costs and benefits were discounted at 3.5% and a lifetime time horizon was adopted.

The manufacturer's base case incremental cost-effectiveness ratio (ICER) for adding ivabradine to standard care was £8,498 per quality adjusted life year (QALY) gained. Extensive sensitivity analysis

indicated that the model was robust to variation in key parameters and structural assumptions. In addition, the manufacturer performed subgroup analyses around patients on different levels of beta-blockade. The ICERs associated with patients on no beta-blockade, beta blockade < 50% of target dose, beta blockade ≥ 50% but less than 100% of target dose, and 100% of target dose were £5,361, £7,726, £9,689, and £10,374, respectively.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG notes that the modelling approach taken by the manufacturer is reasonable and consistent with other published economic studies evaluating interventions used in the treatment of heart failure. Furthermore, the ERG notes that the model was well constructed and largely transparent and that patient-level rather than cohort data were used to improve the accuracy of the model's base case results. The ERG accepts the manufacturer's base case ICER is likely to represent the expected cost-effectiveness of adding ivabradine to standard care. However, the ERG notes that the ICER is potentially biased against ivabradine.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The ERG considers the submitted evidence on the effect of adding ivabradine to optimised standard care to be derived from a well-conducted trial. The SHIfT trial is a large, multi-centred, international RCT with a commonly used primary composite outcome of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure.

The manufacturer's submitted economic model was well constructed and conservative (i.e. bias is against ivabradine) and all outcomes of interest have been captured either explicitly (e.g. cardiovascular mortality) or implicitly (e.g. adverse events). Recommended methods for the estimation and extrapolation of survival have been followed. In addition, methodological recommendations for the assessment and extrapolation of relative treatment effect have been adhered to. Furthermore, regression equations developed to support the assessment of relative cost-effectiveness have been derived using systematic and rigorous methodology, in conjunction with expert clinical advice.

Extensive sensitivity analysis has been carried out to assess the sensitivity of the model to key parameters and structural assumptions. In addition, several subgroup analyses were carried out to assess the impact of patient characteristics.

Health related quality of life data based on EQ-5D were collected alongside the SHIfT clinical trial and all costs and resource use calculations were transparent and appropriate for a UK population.

1.6.2 Weaknesses and areas of uncertainty

The manufacturer submitted evidence from only one trial, albeit a large, well-conducted trial, assessing the effects of adding ivabradine to optimised standard care for heart failure. Furthermore, the licensed indication for ivabradine is patients with resting heart rate ≥75 bpm, and thus submitted evidence is based on a *post hoc* subgroup analysis and as such should be interpreted with a level of caution.

The ERG considers that there is uncertainty around the benefit of adding ivabradine to optimised standard care [redacted]. Although a [redacted] of ivabradine is observed, [redacted] increasing beta-blocker dose and [redacted] assessed in the ERG's exploratory analyses. Moreover, there does not seem to be a [redacted].

The manufacturer's regression analysis suggests a level of uncertainty associated with the treatment effect of ivabradine on cardiovascular mortality; the treatment effect of ivabradine on cardiovascular mortality was statistically non-significant and the treatment effect of ivabradine on heart failure mortality was of borderline statistical significance. By contrast, beta-blockade of 50% of target dose or more was associated with a statistically significant reduction in the risk of cardiovascular mortality and beta-blockade of any level was associated with a statistically significant reduction in the risk of heart failure mortality. The ERG notes that the manufacturer's regression analyses are adjusted for baseline resting heart rate. Therefore, the risk reduction of ivabradine and beta-blockade is over and above the attenuating effect of heart rate.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

No additional exploratory or sensitivity analyses were undertaken by the ERG as the extensive sensitivity and subgroup analyses provided by the manufacturer covered all areas of uncertainty considered likely to be important by the ERG.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

In the Context section of the manufacturer's submission (MS; Section 2), the manufacturer provides an overview of the key aspects of chronic heart failure (hereafter referred to as heart failure) relevant to the decision problem, including aetiology, prevalence, and prognosis of heart failure. In addition, the manufacturer outlines the association between elevated heart rate and cardiovascular outcomes, with a focus on implications for patients with heart failure.

Summaries of aetiology (Box 1), prevalence (Box 2), and prognosis of heart failure (Box 3) are presented in Boxes 1 to 3. Box 4 discusses the impact of heart failure on a patient's quality of life.

All information presented in boxes is taken directly from the MS, unless otherwise stated (references have been renumbered).

Box 1. Aetiology of heart failure

Chronic heart failure (CHF), referred to hereafter as 'heart failure' (HF), is a complex syndrome characterised by symptoms such as breathlessness, fatigue and fluid retention.[1] It may be caused by either structural or functional cardiac disorders that impair the ability of the heart to work as a pump and thus support the circulation.[1] The most common causes of heart failure today in the UK are ischaemic heart disease and hypertension with many patients having both.[1] Approximately two-fifths of patients have heart failure associated with LVSD[2;3] which manifests in a reduced LVEF, while others have heart failure with a preserved ejection fraction. Most of the evidence in the field of heart failure treatment relates to heart failure associated with LVSD.[1]

Heart failure patients are often shown to have markedly elevated heart rates; this is thought to be due to compensatory neurohormonal activation resulting in an increased and persistent sympathetic overdrive, as the heart works harder to meet the body's oxygen demands.[4] In the short term, such compensatory mechanisms can provide some benefit to the patient. However, as the condition persists, these mechanisms may provoke further detrimental effects on the myocardium with subsequent LVSD. In addition to the increased mortality risk that this is associated with, there is also a significantly greater risk of hospitalisation.[5]

Evidence now increasingly suggests that elevated heart rate is associated with increased risk of all-cause mortality, cardiovascular mortality, and development of cardiovascular disease in a number of populations including the general population, hypertensives, diabetics, patients with pre-existing coronary artery disease, and also in heart failure patients.[6-13]

Heart rate reduction is associated with improved outcomes in heart failure.[4] A meta-regression of 23 beta-blocker RCTs in heart failure patients indicated that, for every 5 bpm reduction in heart rate

achieved (baseline to first visit post titration period), an 18% (95% CI: 6–29%) reduction in all-cause mortality was observed.[14]
Abbreviations used in box: LVSD, left-ventricular systolic dysfunction; LVEF, left-ventricular ejection fraction.

Box 2. Prevalence of heart failure

The prevalence of heart failure is approximately 1–2% of the UK population; however this rises significantly with age. For example, in men aged over 75 the prevalence rises to 16%.[1] In addition, the number of patients with heart failure is set to increase due to a combination of an aging population and improved survival rates in patients with other cardiovascular diseases, especially those surviving a heart attack.[1] The prevalence of definite heart failure in the UK in patients ≥45 years is 2.3%.[3] Cowie 1999[15] estimates that there are 63,000 new cases of heart failure per annum.

Box 3. Prognosis for patients with heart failure

Despite the range of existing treatments, many of which have substantially improved outcomes in the past two decades, prognosis remains poor. Mortality in heart failure patients ranges between 10–50% per year depending on severity, and newly diagnosed patients have a 40% risk of dying within the first year following diagnosis. These survival rates are at least comparable, and possibly worse than those for breast and prostate cancer.[1]

The manufacturer highlights that, as well as limiting a patient's physical activity, heart failure has a detrimental effect on a patient's lifestyle and health-related quality of life (Box 4).[16]

Box 4. Impact of heart failure on quality of life

Along with the poor prognosis, heart failure is a physically and emotionally debilitating condition that impacts significantly on HRQL.[16] This may result in financial implications for patients associated with inability to work or reduced ability to work. The impact on HRQL in heart failure patients has been shown to be greater than in other chronic conditions such as chronic lung disease, arthritis, or other cardiac conditions.[2] In addition, heart failure is often associated with other co-morbidities;[2] over one third of patients are thought to suffer from prolonged and severe depression.[1]
Abbreviation used in box: HRQL, health-related quality of life.

The Evidence Review Group (ERG) considers the manufacturer's overview of the underlying health problem to be accurate, but considers that expansion of some points may be informative.

With reference to the association between heart failure and left-ventricular systolic dysfunction (LVSD), the ERG considers it relevant to the decision problem to note that LVSD is typically defined in clinical practice as a left-ventricular ejection fraction (LVEF) of <40% of normal ejection fraction.[2]

To expand the manufacturer's overview of prevalence, the National Heart Failure Audit (2010–2011)[1] reports that the age of onset of heart failure differs between men and women: on average, men are admitted to hospital for heart failure at an age 5 years younger than that of women (74.9 years for

men vs 80.2 years for women). In addition, patients with heart failure who are aged <75 years are more likely to be male. Above the age of 75 years, the proportions of men and women with heart failure are comparable.

The ERG notes that, after a diagnosis of heart failure, the New York Heart Association (NYHA) classification system[17] may be used to determine the severity of a patient's heart failure. The NYHA system categorises patients based on the level of limitation during physical activity (Table 1).

Table 1. New York Heart Association classification of heart failure[17]

Class	Description
I	No limitation of physical activity: ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea
II	Slight limitation of physical activity: comfortable at rest but ordinary physical activity results in fatigue, palpitations, or dyspnoea
III	Marked limitation of physical activity: comfortable at rest, but less than ordinary activity causes fatigue, palpitations, or dyspnoea
IV	Unable to carry out any physical activity without discomfort: symptoms of cardiac insufficiency are present at rest and discomfort increases with any physical activity is undertaken

To underpin the manufacturer's discussion of the importance of elevated heart rate on outcomes, the ERG considers it useful to note that resting heart rate varies with age, gender and lifestyle, but for a healthy adult would be expected to lie between 50 and 75 beats per minute (bpm), depending on the listed variables.[18] There is consensus that women have a higher resting heart rate compared with men of the same age.[18] By contrast, although there is some evidence that resting heart rate decreases with increasing age, there is a lack of consensus on this association, possibly as a result of variations in populations and methodologies used in studies.[18]

2.2 Critique of manufacturer's overview of current service provision

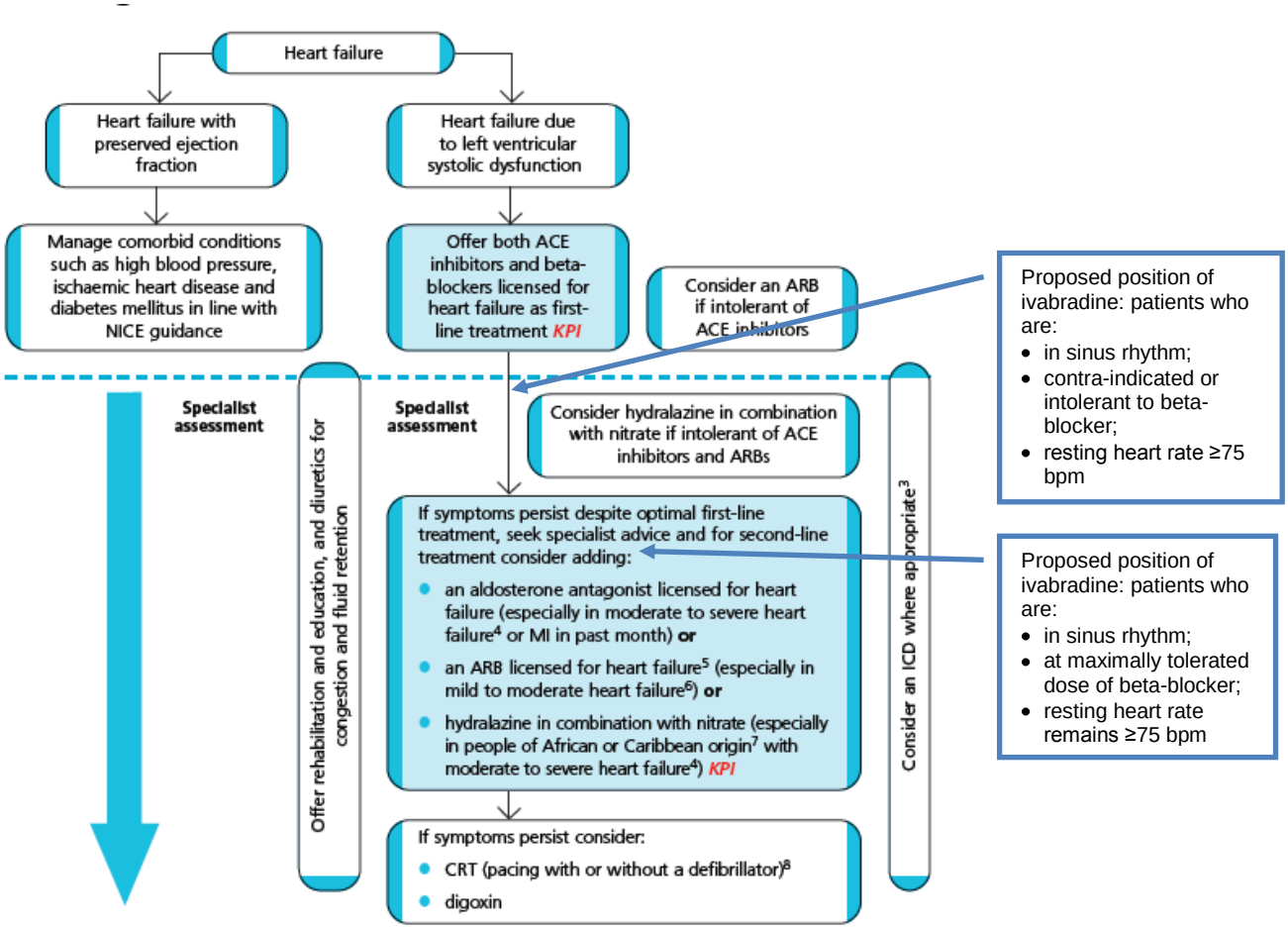
The manufacturer presents the treatment algorithm for symptomatic heart failure as recommended by the National Institute for Health and Clinical Excellence (NICE; Figure 1). In addition, the manufacturer outlines the proposed position of ivabradine in the treatment pathway (Box 5), and estimates the number of patients in the UK who would be eligible for treatment with ivabradine (Box 6). The manufacturer lists NICE guidelines and technology appraisals relevant to the decision problem (summarised in Table 2).

As the manufacturer notes, for patients with heart failure due to LVSD, NICE guideline CG108[19] recommends offering both an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker (also referred to as beta-adrenoreceptor antagonists) licensed for heart failure as first-line treatment (Figure 1), unless treatments are contraindicated or not tolerated. The manufacturer emphasises that they support the aggressive up-titration of beta-blockers and ACE inhibitors to target or maximum tolerated

doses, as recommended in CG108[19] (see Table 2) and underscored in NICE Quality Standards for heart failure in adults.[20]

Despite these recommendations, as reported by the manufacturer, the recent National Heart Failure Audit (2010–2011)[1] highlights that prescription rates for beta-blockers are suboptimal, with only 65% of patients with a diagnosis of heart failure due to LVSD being prescribed this class of drug on discharge from hospital. By contrast, in the same group of patients, treatment rates for diuretics and ACE inhibitors/ARBs (one or both of an ACE inhibitor and ARB) are high, with 86% and 81% of patients discharged from hospital being prescribed these agents, respectively. The National Heart Failure Audit[1] also reports that treatment rates for ACE inhibitors/ARBs and beta-blockers are substantially higher when patients are admitted to cardiology wards rather than general medical wards. In the case of beta-blockers, 78% of patients discharged from a cardiology ward were prescribed a beta-blocker compared with 63% of patients discharged from a general medicine ward. An important finding of the report was that mortality rates for patients receiving key medical treatments (defined as ACE inhibitors/ARBs, beta-blockers, and aldosterone antagonists) were lower than rates for patients not receiving these treatments. Furthermore, mortality rates after discharge are lower for patients who receive cardiology follow up (18% vs 31%) and those referred to heart failure specialist nursing services (22% vs 27%) compared with patients who do not.

Figure 1. Algorithm for the treatment of symptomatic heart failure presented in NICE guideline CG108[19]



3 Consider an ICD in line with 'Implantable cardiovascular defibrillators for arrhythmias' (NICE TA95).
4 NYHA class III–IV.
5 Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors.
6 NYHA class II–III.
7 This does not include mixed race. For more information see CG108
8 Consider CRT in line with 'Cardiac resynchronisation therapy for the treatment of heart failure' (NICE TA120).
Abbreviations used in figure: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; ICD, Implantable cardiovascular defibrillator; KPI, key performance indicator; MI, myocardial infarction; NYHA, New York Heart Association.

Table 2. NICE guidance and technology appraisals evaluating treatments for heart failure

Related NICE guideline/technology appraisal	Recommendations
CG108[19] National clinical guideline for diagnosis and management in primary and secondary care	**Recommendations relating to first-line treatment with ACE inhibitors and beta-blockers**: *ACE inhibitors (first-line treatment)* • Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the optimal tolerated or target dose is achieved • Measure serum urea, creatinine, electrolytes and eGFR at initiation of an ACE inhibitor and after each dose increment *Beta-blockers (first-line treatment)* • Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including:

	• older adults and
	• patients with:
	  • peripheral vascular disease;
	  • erectile dysfunction;
	  • diabetes mellitus;
	  • interstitial pulmonary disease;
	  • chronic obstructive pulmonary disease without reversibility
	• Introduce beta-blockers in a 'start low, go slow' manner, and assess heart rate, blood pressure, and clinical status after each titration
	• Switch stable patients who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure due to left ventricular systolic dysfunction, to a beta-blocker licensed for heart failure

TA120[21]
Cardiac resynchronisation therapy
	Recommends CRT with a pacing device for people with heart failure who:
	• are experiencing or have recently experienced NYHA class III–IV symptoms;
	• in sinus rhythm with:
	  • either a QRS duration of 150 ms or longer estimated by standard electrocardiogram (ECG);
	  • or a QRS duration of 120–149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography.
	• left ventricular ejection fraction of 35% or less;
	• receiving optimal pharmacological therapy.
	Recommends that CRT with a defibrillator device can be considered for people who fulfil the criteria for implantation of a CRT with a pacing device and who also separately fulfil the criteria for the use of an ICD device (as recommended in TA95[22])

TA in preparation: Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120): expected date of publication September 2013.[23] Abbreviations used in table: CG, clinical guideline; CRT, cardiac resynchronisation therapy; NYHA, New York Heart Association; TA, technology appraisal.	

Box 5. Proposed position of ivabradine in treatment pathway for heart failure

Whilst the benefits of beta-blockers are well established, a number of patients are either contraindicated to therapy or are unable to tolerate target dosages. Furthermore, despite the best attempts to up-titrate the dose of beta-blockers according to CG108 there remains a significant proportion of patients with an elevated heart rate.[24] These issues together highlight an unmet need. Consistent with the indication, ivabradine should be considered in heart failure due to left-ventricular systolic dysfunction, under the advice of a specialist, in the following circumstances: 1. Patients (in sinus rhythm) who are contraindicated to beta-blockers or are intolerant to these agents and have a resting HR ≥75 bpm; 2. Patients (in sinus rhythm) on beta-blockers at maximally tolerated doses whose resting HR remains ≥75 bpm.
Abbreviations used in box: bpm, beats per minute; HR, heart rate.

With reference to service provision, the manufacturer anticipates that minimal additional resource will be required to implement treatment with ivabradine. The manufacturer anticipates that ivabradine treatment would be initiated by a clinician experienced in the management of heart failure (as recommended in the Summary of Product Characteristics[25] [SPC]), and suggests that this would be a consultant cardiologist, a primary care GP with special interest (GPwSI), or another appropriately qualified member of a multidisciplinary heart failure team. The SPC does not expand on the recommended level of experience. The ERG considers it important to note that NICE guideline CG108[19] on the management of heart failure states that "the term 'specialist' denotes a physician with subspecialty interest in heart failure (often a consultant cardiologist) who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care. The team will involve, where necessary, other services (such as rehabilitation, tertiary care and palliative care) in the care of individual patients. ...specialist assessment or management refers to assessment or management by this specialist multidisciplinary heart failure team. The team will decide who is the most appropriate team member to address a particular clinical problem". The ERG notes that the definition does not include a GPwSI.

Considering treatment initiation, the manufacturer proposes that, other than acquisition cost, no additional resources will be required as eligible patients will previously have had a diagnosis for heart failure associated with LVSD and should be receiving optimised standard therapy, as outlined in CG108.[19] Moreover, the only assessment for eligibility that the clinician need make is resting pulse rate, to verify that the patient's resting heart rate is ≥75 bpm, as indicated in the licence issued by the European Medicines Agency (EMA) for ivabradine.[26] As the manufacturer reports, recording resting pulse rate is described in CG108[19] as a component of routine monitoring of patients with heart failure. Additional resource could be required should a patient require adjustment of the dose of ivabradine. The manufacturer suggests that titration of ivabradine dose will most likely be carried out by a GP or a specialist heart failure nurse. For patients who have been hospitalised and are started on ivabradine before discharge, the manufacturer anticipates that up-titration of dose will most likely be carried out by a member of the multidisciplinary heart failure team as part of the routine 2-week clinical assessment.

As part of the clarification process, the ERG asked the manufacturer whether post-titration of ivabradine dose patients can be safely discharged to continuous maintenance treatment by a non-specialist GP. The manufacturer confirmed that, in the long-term, patients can be monitored and maintained on treatment by a non-specialist GP, stating that:

- GPs in the UK are accustomed to the continuous maintenance of ivabradine for its indication in angina (including dose adjustment of ivabradine), for which it has been available in the UK for six years. The maintenance approach in heart failure is similar;
- GPs routinely manage the continuous maintenance of other treatments in heart failure, including beta-blockers, which have similar clinical considerations.

Considering the proposed position of ivabradine in the treatment pathway, based on the treatment algorithm depicted in Figure 1, the manufacturer suggests that ivabradine be added to a patient's standard care prior to consideration of implantation of a cardiac resynchronisation therapy (CRT). Based on feedback from clinical experts, the ERG considers it important to note that evidence for the use of CRT has emerged from trials in which patients were receiving optimised ACE inhibitor and beta-blocker prior to CRT.[27;28] The SHIfT trial was not designed to consider patients undergoing CRT and thus there is limited evidence on the effectiveness of adding ivabradine to optimised standard care for those patients for whom CRT may be a treatment option.

Overall, the ERG considers the manufacturer's overview to be an accurate representation of current service provision and recommended treatment algorithms.

Box 6. Manufacturer's estimate of the number of patients with heart failure who would be eligible for treatment with ivabradine

The prevalence of definite heart failure in the UK in patients ≥45 years is 2.3%.[3] Cowie 1999[15] estimates that there are 63,000 new cases of heart failure per annum. The annual mortality rate from HF is estimated to be 9% in the ECHOES study. Therefore, the net number of patients in England and Wales with definite heart failure is approximately 551,000.

Of these, it is estimated 41.3% have systolic dysfunction.[3] A recent audit analysis by Cleland & Goode *et al*. allows us to determine that 16% of patients with heart failure due to LVSD may be considered suitable for ivabradine therapy based on the licensed indication (i.e. NYHA class II–IV, in sinus rhythm, and with resting heart rate ≥75 bpm).[29] Therefore approximately 36,000 patients in England and Wales would be eligible for ivabradine therapy (~66 per 100,000 population).

The ERG was unable to replicate the manufacturer's estimate of number of patients in England and Wales potentially eligible for treatment with ivabradine. In addition, the ERG notes that the data cited by the manufacturer for prevalence and number of new cases of heart failure per annum are from studies published over a decade ago, and that these data may not reflect the current UK population.[3;15] The ERG considers it important to highlight that there are conflicting data in the

literature on the number of patients with heart failure in the UK. NICE guideline CG108[19] (published in 2010) estimates that there are about 900,000 patients in the UK living with heart failure compared with the manufacturer's estimate of 551,000 for England and Wales. By contrast, data collected as part of the Quality and Outcomes Framework (QOF) for 2010/2011 indicate that, of those patients on the disease register, there are 392,853 patients with heart failure in England[30] and 29,029 patients in Wales,[31] to give a total of 421,882 patients. Moreover, separate data are reported for the subset of patients with heart failure due to left-ventricular dysfunction: total of heart failure due to either systolic or diastolic left-ventricular dysfunction. Based on QOF data for 2010/2011, the number of patients in England and Wales registered with heart failure due to left-ventricular dysfunction is 229,861 (213,759 in England plus 16,102 in Wales).[30;31]

In addition, the ERG identified more recently published statistics on the epidemiology of heart failure than the study cited by the manufacturer[3] that suggest the prevalence of heart failure is 0.9% in men and 0.7% in women in the UK.[32] In terms of new cases of heart failure per annum, the reference cited by the manufacturer reports that there are 1.3 new cases per 1,000 population,[15] rather than estimating that there are 63,000 new cases per year. The ERG notes that a more recent reference estimates the rate of new cases of heart failure per year to be considerably lower at a little over 27,000.[32]

The manufacturer reports that 16% of patients with heart failure due to LVSD would be eligible for treatment with ivabradine. The ERG notes that the reference cited in support of this estimate is as yet unpublished.[29] The authors of this study report data that support the manufacturer's estimate of proportion of patients with heart failure due to LVSD and eligible for treatment with ivabradine as 16%, but this is based on an LVEF of ≤45%. In addition, the authors propose four potential scenarios for eligibility of treatment with ivabradine by applying two thresholds for resting heart rate (≥70 bpm vs ≥75 bpm) and for LVEF (≤35% vs ≤45%) to patients with follow-up data at 4 months who had heart failure in sinus rhythm, and were NYHA class II–IV. The study initially assessed [redacted] referred with suspected heart failure but, based on Figure 3 in the report, [redacted] were followed-up at 4 months. In the population most similar to that of the licensed population in the SHIfT trial[33] (resting heart rate ≥75 bpm and LVEF ≤35%), the percentage of patients eligible for treatment with ivabradine at 4 months is [redacted] (data summarised in Table 3). It is worth noting that the authors of the unpublished report commented that assessment of LVEF is considered to be a subjective evaluation.[29] However, due to the unpublished nature of this work, at this time, the ERG considers that these data should be interpreted with caution.

Table 3. Proportion of patients with heart failure potentially eligible for treatment with ivabradine

LVEF	Heart rate[a]		Heart rate[b]	
	≥70 bpm	≥75 bpm	≥70 bpm	≥75 bpm
≤35%	[redacted]	[redacted]	[redacted]	[redacted]
≤45%	[redacted]	[redacted]	[redacted]	[redacted]

[a] Data based on full population of patients with suspected heart failure followed-up at 4 months.

[b] Data based on patients with heart failure due to LVSD.

Abbreviations used in table: bpm, beats per minute; LVSD, left-ventricular systolic dysfunction; LVEF, left-ventricular ejection fraction.

In the submission, the manufacturer cites data from another UK audit,[34] the goal of which was to identify the number of patients eligible for treatment with ivabradine who were attending a community heart failure clinic. Patients referred to the heart clinic were predominantly referred by GPs and secondary care physicians. Patients attending the clinic may not have been previously diagnosed with heart failure and thus would require initiation of standard heart care therapies, or patients may have had an existing diagnosis of LVSD or heart failure requiring optimisation of heart failure therapies during the 12 months of follow-up. The authors analysed four datasets focusing on patients with heart failure caused by LVSD (LVEF ≤50%). The four datasets were made up of patients who were seen at the heart failure clinic at baseline, 4- or 12-month clinic review and a subset of patients who had attended all clinic visits. Patients were classed as eligible for treatment with ivabradine if they had LVEF of ≤35%, sinus rhythm, and a resting heart rate of ≥70 bpm: at this point, the analysis does not consider NYHA class. The authors report that the proportion of patients with heart failure due to LVSD who were eligible for ivabradine at baseline visit was 19.4% (429/2,211). However, at 4 months, proportion of patients eligible for ivabradine had fallen to 14.1% (185/1,309) and, at 12 months, only 9% (82/910) of patients were eligible. Exclusion of patients with NYHA class I and/or receiving no beta-blocker therapy reduces the proportion of eligible patients further to 5.3% (48/910) at 12 months. The ERG notes that the analyses was carried out prior to issue of the European licence for ivabradine in heart failure,[26] and includes those with a resting heart rate of 70–74 bpm. Therefore, exclusion of these patients would further reduce the proportion of patients eligible for ivabradine treatment at each follow-up visit.

Based on QOF data for patients with heart failure due to left-ventricular dysfunction in England and Wales (229,861 patients), and results from Cullington *et al*.[34] (using data at baseline and at 12 months), the ERG estimates that the number of patients eligible for treatment with ivabradine could potentially be between 12,000 and 44,500; as the ERG's estimate is based on results presented by Cullington *et al*.[34] it is not adjusted for resting heart rate of ≥75 bpm. Considering the data as a whole, the ERG suggests that there is considerable uncertainty around the number of patients in the UK eligible for treatment with ivabradine.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The manufacturer provided a summary of the final decision problem issued by the National Institute for Health and Clinical Excellence (NICE; MS, pg 34),[35] together with the rationale for any deviation from the decision problem (Table 4).

Table 4. Summary of decision problem as outlined in the manufacturer's submission

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults in sinus rhythm with symptomatic chronic HF (NYHA class II to IV) due to left-ventricular systolic dysfunction who have been prescribed standard optimal HF therapy	Adults in sinus rhythm with symptomatic chronic HF (NYHA class II to IV) due to left-ventricular systolic dysfunction who have been prescribed standard optimal HF therapy and have a resting heart rate ≥75 bpm	The licensed indication has limited the population to patients with resting heart rate ≥75 bpm
Intervention	Ivabradine	Ivabradine	
Comparator(s)	Standard treatment without ivabradine	Standard treatment without ivabradine	Servier intend to explore potential heterogeneity in cost effectiveness according to beta-blocker usage (i.e., in patients at target dose or not, and in patients contraindicated to a beta-blocker)
Outcomes	• Cardiovascular mortality • All-cause mortality • Hospitalisation due to HF • All-cause hospitalisation • Adverse effects of treatment • Health-related quality of life	• Cardiovascular mortality • All-cause mortality • Hospitalisation due to HF • All-cause hospitalisation • Adverse effects of treatment • Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from	As per final scope A lifetime horizon has been considered in the base case and shorter time horizons have been explored in sensitivity analysis	

	an NHS and Personal Social Services perspective		
Subgroups to be considered	None specified	Servier intend to assess subgroups based on both pre-specified analyses and also those which appear particularly relevant to the decision problem and the cost-effectiveness estimates. The subgroups used in the model to modify either baseline risk or the treatment effect of ivabradine will be guided by the SHIfT trial protocol	To investigate potential heterogeneity in cost-effectiveness estimates
Special considerations, including issues related to equity or equality	None specified	None specified	
Abbreviations used in table: HF, heart failure; NHS, National Health Service; NYHA, New York Heart Association.			

3.1 Population

The SHIfT trial[33] enrolled patients with symptomatic moderate-to-severe heart failure due to left-ventricular systolic dysfunction (LVSD). To be eligible for randomisation in SHIfT, patients were required to:

- have a resting heart of ≥70 bpm;
- be in sinus rhythm;
- have a left-ventricular ejection fraction (LVEF) ≤35% (documented within previous 3 months);
- have heart failure classified as New York Heart Association (NYHA) class II–IV (for ≥4 weeks and in stable condition for ≥4 weeks before selection);
- have been hospitalised for worsening heart failure within the 12 months before selection;
- optimised and unchanged heart failure medications and dosages for ≥4 weeks.

The clinical evidence presented in the manufacturer's submission deviates from the final scope issued by NICE[35] in restriction of the population to patients with resting heart rate of ≥75 bpm, which was not specified in the final scope. Subsequent to finalisation of the scope, the European Medicines Agency (EMA) approved a licence extension for ivabradine to include use in "chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated".[26] Thus, the ERG considers the restriction of data submitted by the manufacturer to that of the licensed population to be appropriate.

In 2005, ivabradine was granted a licence by the EMA for the treatment of chronic stable angina in patients with normal sinus rhythm.[26] Post-publication of the results from the SHIfT trial,[33] the manufacturer applied for an extension of indication to include chronic heart failure in adults in sinus rhythm with symptomatic heart failure and resting heart rate ≥70 bpm.[36] As part of its evaluation, the Committee for Medicinal Products for Human Use (CHMP) noted that benefit associated with ivabradine seemed to be inversely related to target dose of beta-blocker achieved. The largest protective effect of ivabradine on the primary outcome of interest (composite of time to first event to cardiovascular death or hospitalisation for heart failure) was in patients not receiving beta-blocker as part of their standard care (HR 0.68; 95% CI: 0.52 to 0.88).[33;36] By contrast, the clinical effectiveness of ivabradine was reported to be lowest in patients achieving ≥50% target beta-blocker dose (HR 0·90; 95% CI: 0·77 to 1·04). The CHMP commented that there was uncertainty around the level of benefit that would be achieved on adding ivabradine to beta-blocker administered at target dose. The CHMP requested that the manufacturer discuss the potential relationship between clinical benefit of ivabradine and percentage beta-blocker dose achieved "with respect to the overall impact on the benefit/risk balance in patients treated with (near) optimal beta-blocker doses and the implications of these findings for the indication".[36]

The CHMP went on to comment that patients achieving higher doses of beta-blocker could be expected to have a lower heart rate at baseline, and are the patients likely to receive the least benefit from addition of ivabradine to their heart failure therapies.[36] In a separate publication assessing the association between baseline heart rate and outcomes in the SHIfT trial,[6] it was noted that higher resting heart rates were associated with lower use of beta-blocker; the CHMP cited these data in support of the proposal of decreased benefit from adding ivabradine to regimens in which patients are achieving higher dose of beta-blocker.[36] The CHMP requested that the manufacturer discuss the potential implications of these findings. In addition, based on data reported by Böhm *et al.*,[6] the CHMP questioned whether the correct threshold for initiating ivabradine treatment "may be higher than 70, probably above 75":[36] for the primary outcome assessed in the SHIfT trial, subgroup analysis based on baseline resting heart rate showed that, for baseline heart rates of <75 bpm, the effect size for adding ivabradine versus adding placebo approached 1 (indicates addition of ivabradine has limited effect on outcomes).[6]

The manufacturer's re-analysis of the results identified the threshold for mortality benefit of ivabradine at a resting heart rate of ≥75 bpm.[6] The manufacturer suggested this threshold to the CHMP, which subsequently granted a European licence for ivabradine for use as outlined earlier.[26]

Based on expert opinion, the ERG considers that the licensed population in the SHIfT trial comprises patients with more severe heart failure than would typically be seen in clinical practice in England and Wales. Compared with the typical characteristics reported for patients with heart failure due to LVSD

in a recent UK-based audit of a community heart failure clinic,[34] the licensed population of the SHIfT trial:

- is younger (median age of 60 years vs median age of 72 years[34]);
- has a higher proportion of men (76.8% vs 73%[34]);
- have more severe symptoms based on NYHA class III/IV (52% vs 33%[34])
- have been hospitalised for worsening heart failure within the 12 months before selection.

The ERG's clinical advisor has highlighted that patients who have prior hospitalisation are at increased risk of re-hospitalisation for worsening heart failure and of other cardiovascular events compared with other patients with heart failure who have not been hospitalised.

Ivabradine is licensed for treatment of patients with symptomatic heart failure classed as NYHA class II–IV. However, the proportion of patients with severity of heart failure NYHA class IV recruited to the SHIfT trial represents a small component of the trial population (2.1% in the licensed population), and thus there is little evidence on the effects of ivabradine in patients with heart failure of this severity. The ERG considers that the proportion of patients with NYHA class IV in SHIfT is analogous to that seen in clinical practice in the UK; a recent audit carried out in the UK reported that 2% of patients with heart failure due to LVSD were NYHA class IV.[34]

Although the characteristics of the licensed population in the SHIfT trial indicate more severe heart failure compared with patients with heart failure due to LVSD in England and Wales, the ERG agrees with the manufacturer's statement that the population analysed is similar to the populations included in other key heart failure trials;[27;37-46] baseline characteristics of patients in other heart failure trials are presented in Appendix 1. It has been reported that clinical trials assessing treatments in heart failure due to LVSD tend to recruit younger, predominantly male patients:[1] LVSD is more likely to be the cause of heart failure in younger patients, and, furthermore, younger patients with heart failure are more likely to be male.

3.2 Intervention

The ERG notes that the MS provides a comprehensive overview of the regulatory status and mode of action of ivabradine. As noted in Section 3.1, ivabradine has had a European licence for the treatment of chronic stable angina since 2005,[26] which was extended in 2012 to include heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥75 bpm. In addition, ivabradine has been approved in all European Union countries, and also in The Philippines, Thailand, Russia, Colombia and Turkey. A recent update of ESC guidelines lists a new indication for ivabradine as a treatment for patients with symptomatic (NYHA class II–IV) heart failure who are in sinus rhythm.[47] The guideline indicates that the benefit associated with ivabradine is less certain

compared with other treatments for heart failure, classifying the level of evidence in patients with persisting symptoms despite optimised treatment as "weight of evidence/opinion is in favour of usefulness/efficacy". The ERG notes that the guideline also highlights that data are based on a single RCT.

Ivabradine is a first-in-class medication, and has a novel mode of action compared with other treatments for heart failure. Ivabradine is highly specific and selectively targets the cardiac pacemaker I_f current, which is important for regulating pacemaker activity in the sinoatrial node. Inhibition of the I_f current decreases cardiac pacemaker activity through reduction of the slope of spontaneous diastolic depolarisation, which leads to an increase in the time required to reach the voltage threshold for action potential initiation and thus a reduction in spontaneous firing and consequently heart rate. A reduction in heart rate allows more time for blood to flow to the myocardium,[36] which could be associated with improved cardiovascular outcomes. In addition, in contrast to other therapies used to treat heart failure, because ivabradine selectively inhibits the I_f current it confers benefit through the lowering of heart rate alone.[25]

Ivabradine selectively inhibits the pacemaker I_f current in a dose-dependent manner. At usual recommended doses, heart rate reduction has been reported to be approximately 10 bpm at rest and during exercise.[25]

3.3 Comparator

The SHIfT trial[33] assesses adding ivabradine versus adding placebo to baseline treatment with standard heart failure therapies. An inclusion criterion for the SHIfT trial was that patients be receiving optimum and stable background treatment for ≥4 weeks before selection. Standard heart failure therapies used in SHIfT comprised: angiotensin-converting enzyme (ACE) inhibitors; beta-blockers; angiotensin receptor blockers (ARBs); diuretics; and aldosterone antagonists.

The ERG considers the comparator to be appropriate to the decision problem.

3.4 Outcomes

For the licensed population in the SHIfT trial, the manufacturer has addressed all the outcomes listed in the final scope issued by NICE:[35]

- cardiovascular mortality;
- all-cause mortality;
- hospitalisation due to heart failure;
- all-cause hospitalisation;
- adverse effects of treatment;
- health-related quality of life.

The pre-specified primary outcome reported in SHIfT[33] is a composite of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure: the separate components of the composite outcome were pre-specified secondary outcomes in SHIfT.

In the clinical section of the MS, the manufacturer has submitted evidence on all listed outcomes for the licensed population of SHIfT.

3.5 Timeframe

The median duration of follow-up was 22.9 months. The protocol for SHIfT states that first included patients would be treated for a maximal expected follow-up of 36 months, and it was planned that the last included patients would have a minimal follow-up of 12 months. It was estimated that duration of enrolment for all patients would be 24 months. The follow-up of the active double-blind treatment period (ivabradine versus placebo) was extended up to a maximal duration of 52 months.

The ERG considers the duration of follow-up to be sufficient to assess the long-term effects of ivabradine in the treatment of heart failure.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

4.1.1 Description and discussion of appropriateness of manufacturer's search strategy

The manufacturer's submission (MS) gave detailed descriptions of the search terms and strategies used to identify relevant studies assessing the clinical effectiveness and cost effectiveness of ivabradine in the treatment of patients with chronic heart failure. Initially, the manufacturer searched the literature up to May 2011 and subsequently carried out a second literature review to update the results from that date to January 2012 to ensure that all studies relevant to the decision problem were identified. The ERG noted minor differences between the search terms and strategies used for the initial and update reviews. The manufacturer helpfully reported that the literature search carried out in May 2011 was performed in EMBASE.com (EMBASE and Medline databases) and the Cochrane Library, whereas the update search was carried out via OVID (EMBASE, MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R)) and in the Cochrane Library. The manufacturer clarified that the original systematic review did not search MEDLINE(R) In-Process, and thus it was necessary to develop the search strategy for the update systematic review. The ERG considers the manufacturer's approach to be appropriate.

The manufacturer listed the specific databases searched, the time period covered by the search, and the date the searches were run. The manufacturer supplemented the search by searching the US National Institutes of Health clinical trials registry (ClinicalTrials.gov) and the Australian New Zealand Clinical Trials Registry (ANZCTR). In addition, to identify Clinical Study Reports (CSRs), the manufacturer searched the Servier Therapeutic Goods Administration dossier for ivabradine as part of the initial systematic review (May 2011). The ERG considers the search strategy used by the manufacturer to be comprehensive, with appropriate search terms. As the manufacturer highlights, the search strategy did not limit the search to randomised controlled trials (RCTs); the search strategies also identified controlled non-RCTs. However, the MS states that only RCTs were included in the assessment on the clinical effectiveness of ivabradine. The manufacturer used multiple search terms for heart failure and ivabradine. It is not clear whether reference lists of identified RCTs were evaluated for additional suitable studies. The manufacturer reports that identified studies were independently assessed by a reviewer to determine whether the study met the pre-defined inclusion criteria, and any uncertainties were resolved by discussion with a second reviewer.

The ERG validated the manufacturer's search strategy via OVID (EMBASE, MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)), and the Cochrane Library (02/05/2012; flow diagram presented in Appendix 2). The ERG generated fewer studies for screening compared with the manufacturer's search (195 studies screened by the manufacturer vs 159 studies screened by the ERG). The ERG does not have access to EMBASE.com or the manufacturer's in-house database and was therefore unable to replicate the manufacturer's search. The ERG considers the discrepancy in number of studies identified is to be expected. After deduplication of the search results, abstracts and titles were appraised by one reviewer (SB) against the inclusion/exclusion criteria used by the manufacturer. Based on the criteria listed, the ERG identified the full publication of the SHIfT trial,[33] and associated publications;[6;48-51] no additional studies in the population of interest relevant to the decision problem and reporting on outcomes specified in the final scope[35] were identified.

4.1.2 Inclusion/exclusion criteria used in study selection

Inclusion/exclusion criteria applied by the manufacturer for their systematic review are summarised in Table 5.

Table 5. Eligibility criteria for clinical effectiveness and adverse events used in the manufacturer's original and updated systematic review strategy

Characteristic	Inclusion criteria	Exclusion criteria
Population	Patients with systolic heart failure	Patients without systolic heart failure, or population not consistent with ivabradine SPC
Intervention(s)	Ivabradine	Studies not including ivabradine
Outcomes	*Mortality endpoints*: • All-cause mortality; • Cardiovascular mortality; • Death from heart failure. *Morbidity endpoints*: • All-cause hospital admission; • Hospital admission for worsening heart failure; • Any cardiovascular admission	Surrogate outcomes (e.g., change in exercise capacity) rather than the final endpoints of mortality and morbidity
Study design	Randomised, double-blind controlled trials	• Studies that were not randomised; • Letters; • Commentaries; • Notes; • Editorials; • Reviews; • Methodological papers.
Language restriction	None	None
Abbreviation used in table: SPC, Summary of Product Characteristics.		

With reference to the criteria for outcomes, the ERG notes that the manufacturer has not listed health-related quality of life (HRQoL) or adverse effects as criteria for either inclusion or exclusion, both of which are listed as outcomes of interest to the decision problem. During abstract appraisal, the ERG did not exclude studies based on outcome assessed.

The ERG considers that the clinical-effectiveness literature review process, as described in the MS, follows systematic review practices outlined by the Centre for Reviews and Dissemination.[52]

4.1.3 Included and excluded studies in review of clinical effectiveness

The manufacturer provided appropriate flow diagrams, outlining the processes for the initial and update systematic reviews (MS; pgs 248 and 249). Taken together, the flow diagrams indicate that eight publications were identified in the manufacturer's systematic review. Of these, one is the key RCT assessing the effects of ivabradine in the treatment of heart failure (SHIfT[33]), which forms the basis of the evidence submitted by the manufacturer: an erratum accompanying the full publication of SHIfT was also identified.[50] The remaining six publications all relate to the SHIfT trial. Identified studies included a publication describing the rationale and design of SHIfT[49] and a CSR.[53] Other studies reported on various analyses of results from the SHIfT trial, including the association between heart rate and outcomes in SHIfT,[6] HRQoL,[48] and effect of ivabradine on left-ventricular remodelling and function.[51] In addition, the manufacturer identified a sub-study of the SHIfT trial reporting on patient-reported outcomes, which is reported in the CSR CL3-16257-063.[53]

The manufacturer excluded one RCT[54] in patients with heart failure due to LVSD, citing the reason for exclusion as "surrogate outcomes measured rather than the 'hard endpoints' of morbidity and mortality". The ERG independently identified and assessed the RCT.[54] Although the ERG agrees with the manufacturer that the RCT does not report on outcomes of interest relevant to the manufacturer's review criteria, the ERG notes that the RCT reports on HRQoL. On appraising the full text, the ERG observed that the study uses a disease-specific questionnaire (Minnesota Living with Heart Failure Questionnaire) rather than the EQ-5D, which is the preferred measure of utilities by NICE. In addition, the RCT is small (60 patients) and reports data at only 3 months' follow-up. For these reasons, the ERG excluded the RCT from its review and this RCT is not discussed further.

No relevant non-RCTs were identified by the manufacturer.

4.1.4 Quality assessment

The manufacturer assessed the SHIfT trial[33] against criteria adapted from guidance for undertaking reviews in health care issued by the Centre for Reviews and Dissemination,[52] as provided in NICE's template for manufacturer/sponsor submission of evidence to the Single Technology Appraisal (STA)

process.[55] The ERG independently validated SHIfT and agrees with the manufacturer's assessment (Appendix 3). The ERG considers SHIfT to be a well-designed RCT.

4.2 Summary and critique of submitted clinical effectiveness evidence

Evidence submitted on the clinical effectiveness of ivabradine in the treatment of heart failure comes from a subgroup of patients enrolled in one large double blind, placebo-controlled trial – the SHIfT trial.[33] As discussed in Section 3.1, although SHIfT enrolled patients with a resting heart rate of ≥70 bpm at randomisation, the population of interest relevant to the decision problem is patients with resting heart rate of ≥75 bpm.

In brief, a pre-specified subgroup analysis of data from SHIfT indicated that ivabradine was associated with a greater clinical benefit in patients with a higher baseline resting heart rate (<77 bpm vs ≥77 bpm). As part of the evaluation for the manufacturer's application for an extension to the licensed indication of ivabradine, the manufacturer presented results from a *post hoc* analysis of data from SHIfT that identified the threshold resting heart rate at which the mortality benefit associated with addition of ivabradine as ≥75 bpm.[6] Based on this analysis, the manufacturer proposed the threshold for treatment initiation with ivabradine as resting heart rate of ≥75 bpm,[6] which was accepted by the CHMP and the licence extended accordingly.[26;36]

In their submission to NICE, the manufacturer presents data for both the full trial population of SHIfT (i.e., resting heart rate of ≥70 bpm) and the licensed population (i.e., resting heart rate of ≥75 bpm). In its evaluation of data on clinical effectiveness, the ERG presents and discusses the results for only the licensed population: data on the primary and secondary outcomes for the full population of the SHIfT trial are presented in Appendix 4. Data for the licensed population are taken from the MS and from manufacturer's responses to the Evidence Review Group's (ERG's) clarification questions.

4.2.1 Description of the SHIfT trial

The SHIfT trial[33] was designed to assess the superiority of adding ivabradine versus adding placebo to optimised standard heart failure therapy (including angiotensin-converting enzyme [ACE] inhibitors and beta-blockers) in patients with moderate to severe heart failure, with left-ventricular systolic dysfunction (LVSD), in sinus rhythm and a resting heart rate of ≥70 bpm: key characteristics of the SHIfT trial are outlined in Table 6. The pre-specified primary outcome evaluated was a composite of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure: outcome definitions used in the SHIfT trial are presented in Table 7. Pre-specified secondary outcomes assessed included the individual components of the primary outcome and the primary outcome in the subgroup of patients who achieved ≥50% of the target beta-blocker dose (RS_{BBDOSE}).

Table 6. Key trial characteristics of SHIfT[33]

Study: Design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
6,505 patients with heart failure Double blind, placebo controlled RCT Two armed RCT assessing the superiority of adding ivabradine to standard therapy Event-driven International multicentre RCT: 37 countries with 625 centres Patients randomised 1:1 to ivabradine bd or placebo Randomisation stratified by: • beta-blocker intake (yes/no); • centre at time of randomisation	Oral ivabradine bd All patients were prescribed ivabradine 5 mg bd (ivabradine or matching placebo) at Day 0. Depending on resting heart rate and tolerability, the dose was then either maintained, up-titrated to the target dose of ivabradine 7.5 mg bd or down-titrated to ivabradine 2.5 mg bd Comparator: placebo The active double-blind treatment period (ivabradine versus placebo) lasted from 12 months to 36 months, extended to a maximal duration of 52 months Treatments not allowed at inclusion and during the study included non-dihydropyridine calcium-channel blockers, class I antiarrhythmics, and strong inhibitors of cytochrome P450 3A4	Eligible patients were men or women: • aged 18 years and older; • in sinus rhythm; • with resting heart rate of ≥70 bpm, as measured on 12-lead ECG after at least 5-min rest on two consecutive visits before randomisation; • with stable symptomatic chronic heart failure of ≥4 weeks' duration; • with a previous admission to hospital for worsening heart failure within the previous 12 months; • left-ventricular ejection fraction of ≤35%. Patients needed to be on optimum and stable background treatment for at least 4 weeks. Any cause of heart failure was allowed apart from congenital heart disease or primary severe valvular disease	Main exclusion criteria were: • recent (<2 months) myocardial infarction or coronary revascularisation; • scheduled coronary revascularisation; • severe primary valvular disease; • scheduled surgery of valvular heart disease; • stroke or transient cerebral ischaemia within previous 4 weeks; • active myocarditis; • congenital heart diseases; • on list for cardiac transplantation; • ventricular or atrioventricular pacing operative for ≥40% or more of the day or with stimulation threshold at the atrial or ventricular level ≥60 bpm; • permanent atrial fibrillation or flutter; • sick sinus syndrome, sinoatrial block, second and third degree atrioventricular block; • CRT started within the previous 6 months; • history of symptomatic or sustained (≥30 s) ventricular arrhythmia unless a cardioverter/defibrillator implanted; • cardioverter/defibrillator shock within previous 6 months; • family history or congenital long QT syndrome or treated with selected QT-prolonging products; • severe or uncontrolled hypertension (SBP >180 mmHg or DBP >110 mmHg);	Primary composite endpoint: • First event of cardiovascular death (including death from unknown cause) or hospitalisation for worsening HF Secondary endpoints: • The primary composite endpoint in patients receiving at least half of the target daily dose of beta-blockers at randomisation (RS_{BBdose}); • Hospitalisation for worsening HF; • Cardiovascular death (including death from unknown cause); • Death from any cause; • Death from HF; • Hospitalisation for any cause; • Unplanned hospitalisation for any cause; • Hospitalisation for cardiovascular reason (including hospitalisation for undetermined cause); • Unplanned hospitalisation for cardiovascular reason. Secondary composite endpoint:

			• sitting SBP <85 mmHg or current symptomatic hypotension; • known moderate or severe liver disease, known severe renal disease or known anaemia.	• First event among cardiovascular death (including death from unknown cause), hospitalisation for non-fatal MI or hospitalisation for worsening HF
Abbreviations used in table: bpm, beats per minute; bd, twice daily; CRT, cardiac resynchronisation therapy; DBP, diastolic blood pressure; ECG, electrocardiogram; HF, heart failure; LVSD, left-ventricular systolic dysfunction; MI, myocardial infarction; SBP, systolic blood pressure.				

Table 7. Summary of outcome definitions used in SHIfT[33]

Outcome	Definition
Components of primary outcome	
Hospitalisation for worsening HF	Any attendance at hospital requiring completion of the hospital admission procedures and/or at least an overnight stay or until death of the patient. An event leading to the prolongation of an on-going hospitalisation, with or without the transfer of the patient in a specialised hospital department, was considered as a hospitalisation. The adjudication process specified if the hospitalisation was considered planned or unplanned. A hospitalisation was considered unplanned when triggered by a clinical event. An unplanned hospitalisation could be delayed from the causal event. Satisfying the outcome "hospitalisation for worsening HF" was dependent on the patient simultaneously satisfying the following four pre-specified criteria: 1. patient should be hospitalised (see definition above) AND; 2. new or increasing symptoms of HF (e.g., dyspnoea, fatigue) AND; 3. new or increasing signs of HF including signs of fluid retention (e.g., pulmonary rales, peripheral oedema, raised jugular venous pressure, weight gain), or objective evidence of heart failure (such as for instance pulmonary oedema/congestion in chest X-ray) AND; 4. a significant change in the treatment to improve HF defined by initiation of intravenous diuretics or other intravenous medications (excluding cardiac glycosides) or mechanical ventilation or mechanical support (intra-aortic balloon pump, ventricular assist device). In the presence of the criteria listed above, HF was adjudicated even in the presence of other causes for hospital admission, related or not to the episode of worsening HF (e.g., pneumonia, anaemia, atrial fibrillation). In the case of concomitant occurrence of MI and worsening HF, the cause considered by EVC members as being the main reason for hospital admission was adjudicated. Planned or unplanned hospitalisation for heart transplant was adjudicated as unplanned hospitalisation for worsening HF. Patients with cardiogenic shock fulfilled the definition of HF
Cardiovascular death	• Death due to HF; death due to MI, arrhythmic death or presumed arrhythmic death OR; • Other cardiovascular death; for example, a stroke, ruptured aneurysm, or pulmonary embolism OR; • Death of unknown cause: corresponded to non-violent or traumatic deaths for which it was not possible to specify whether they were cardiovascular or not. At the time of the final statistical analysis, death of unknown cause was considered as cardiovascular death.
Secondary outcomes	
Death from any cause	• Cardiovascular deaths; • Non-cardiovascular deaths; • Deaths of unknown cause.
Death from HF	Death occurring from worsening or uncontrolled HF: • with or without hospitalisation; • HF was considered a major factor leading to death; • even if the terminal event is an arrhythmia and unless there is an obvious other cause for the death.
Hospitalisation for cardiovascular reason (including hospitalisation for undetermined	• Hospitalisation for worsening HF (as in primary outcome); • Hospitalisation for MI (as in primary outcome); • Other cardiovascular hospitalisation: must be caused by a fully documented cardiovascular cause (e.g., unstable angina, stroke, arrhythmia, hospitalisation related to a vascular procedure/operation, ruptured aneurysm, pulmonary embolism,

cause)	hypotension, syncope, hypertensive emergency); • Hospitalisation for undetermined cause: corresponded to hospitalisations for which it was not possible to specify whether they were cardiovascular or not. At the time of the final statistical analysis, hospitalisation of undetermined cause was considered as cardiovascular hospitalisation.
Hospitalisation for any cause	As in primary outcome
Unplanned hospitalisation for any cause	As in primary outcome
Unplanned hospitalisation for cardiovascular reason	As defined in "hospitalisation for cardiovascular reason"
Abbreviations used in table: EVC, Endpoint Validation Committee; HF, heart failure; MI, myocardial infarction.	

Trial conduct

SHIfT[33] was a large, international, multicentre trial carried out in 625 centres across 37 countries. The ERG considers the SHIfT trial to be a well-designed randomised controlled trial. As discussed in Section 3.1, the licence for ivabradine in the treatment of heart failure restricts treatment to those with a resting heart rate of ≥75 bpm. Therefore, all analyses are based on a subgroup of the full trial population.

In the SHIfT trial, 6,558 patients were randomised. Data for 6,505 patients were available for analysis, of which 4,150 (63.8%) make up the licensed population. The trial design included a 2-week pre-randomisation run-in period without study treatment to confirm patient's eligibility. Randomisation was computer-generated through a telephone interactive voice response system. In addition, randomisation was stratified by two factors: (i) centre; and (ii) beta-blocker intake at randomisation. The ERG considers the method of randomisation to be robust. Patients were randomised 1:1 to ivabradine or placebo added to their on-going heart failure therapy. The manufacturer states that optimised baseline background therapies were maintained after treatment initiation with ivabradine and were maintained throughout the study. Treatments not allowed at selection and during the study included non-dihydropyridine calcium-channel blockers, class I antiarrhythmics, and strong inhibitors of cytochrome P450 3A4.

Ivabradine was initiated at a dose of 5 mg twice daily (bd). After two weeks, the dose of ivabradine was increased to 7.5 mg bd, unless resting heart rate was ≤60 bpm, or decreased to 2.5mg bd if resting heart rate was <50 bpm or the patient had signs or symptoms of bradycardia. Subsequent follow-up visits were scheduled at day 28, and month 4, after which visits were scheduled to take place every 4 months until study closure.[49] Ivabradine dose could be titrated at each visit, based on patient's resting heart rate (as at week 2). Patients and clinicians were blinded to treatment.

Large multicentre, international trials, such as SHIfT, are typically subject to rigorous quality control and routine monitoring to standardise procedures outlined in the protocol across the centres involved. However, despite concerted efforts to ensure adherence across centres, variation in general practice in the different countries involved may lead to deviation from the protocol. The CSR for SHIfT[53] states that study monitors undertook source data verification on site for critical data, in addition to ensuring that all data were completed in the electronic case report form. Monitors made regular visits to each study centre. The ERG considers that the manufacturer endeavoured to ensure that the trial procedures were implemented across study centres. The manufacturer highlights that the protocol of SHIfT encouraged clinicians to optimise standard therapy and outlined criteria for hospitalisation for worsening heart failure.

The ERG considers it important to note that only 12 (0.2%) patients out of the 6,558 originally enrolled in the SHIfT trial were recruited from the UK. The manufacturer comments that the UK is a poor recruiter, which the manufacturer proposed may be related to the challenges of gaining study approval within the UK. In addition, it has been proposed that identification of appropriate heart failure patients may have been difficult if patients were attending heart failure centres and had good titration of beta-blocker therapy.[34]

An advisory board convened by the manufacturer to review the economic model raised the issue of the presence of potential variation across countries involved in treatment practice for heart failure: 66% (4,621/6,505) of SHIfT patients were of Eastern European origin and, consequently, may have been treated differently to UK patients. In addition, it was also highlighted that patients in SHIfT could be at increased risk of event and thus the clinical event rate in SHIfT may be elevated compared with the UK population of a similar age; an inclusion criterion of SHIfT was that patients were required to have been hospitalised for worsening heart failure within the 12 months prior to selection, and are therefore at increased risk of cardiovascular events. The manufacturer asserts that an increase in hospitalisation events due to increased risk of event is likely to be offset by the reduction in hospitalisation events expected in an Eastern European population relative to a Western European (UK) population, and by the low mean age of the SHIfT cohort. The ERG's clinical advisor fed back that this is a reasonable assumption.

The ERG notes that the baseline characteristics are reasonably well balanced for the ivabradine and placebo arms in both the full and licensed population of SHIfT (baseline characteristics presented in Table 8). The ERG notes that in both populations the proportion of patients of New York Heart Association (NYHA) class IV is slightly larger in the placebo arm. However, as the proportion of patients with NYHA class IV represents only 2.1% of the licensed population, the ERG proposes that the impact of this variation on the difference between groups in clinical effectiveness will be minimal. In summary, the licensed population had a mean age of about 60 years, a resting heart rate of about 84

bpm, and an LVEF close to 29%. Patients were predominantly male (76.8%) and of NYHA class II or III (97.9%). The larger proportion of patients had heart failure associated with ischaemic causes. At randomisation, most patients were receiving a beta-blocker, an ACE inhibitor, and/or a diuretic. Data supporting clinical effectiveness of ivabradine are based on a *post hoc* subgroup analysis and as such should be interpreted with a level of caution. Patients were not stratified based on resting heart rate and thus it not ensured that the randomised groups are balanced in terms of heart rate. In addition, there is an increased risk of imbalance between the groups in potential unknown confounders. Baseline characteristics for the licensed population are similar across the ivabradine and placebo groups and the ERG considers that the results are of sufficient robustness to inform the decision problem that is the focus of this STA.

As discussed in Section 3.1, although baseline characteristics are well-balanced, based on expert advice, the ERG considers that the licensed population in SHIfT is younger, has a higher proportion of men, and more severe heart failure than would be expected for a patient with heart failure in UK clinical practice. However, as the manufacturer states, the baseline characteristics of patients in the licensed population of the SHIfT trial[33] are comparable to those in other key heart failure trials (Appendix 1).[27;37-45] In addition, although inclusion criteria allow for recruitment of patients with NYHA IV class heart failure, patients of this class represent only a small proportion of the overall trial population (2.1% of the licensed population). The ERG's clinical advisor fed back that this is to be expected as patients categorised as NYHA class IV are unlikely to be enrolled in clinical trials as clinicians would be reticent to trial new treatments in this group of patients.

Table 8. Baseline characteristics of participants in SHIfT (full trial population [heart rate ≥70 bpm at baseline] and licensed population [heart rate ≥75 bpm at baseline])

Characteristic	**Heart rate ≥70 bpm at baseline (N = 6,505)**		**Heart rate ≥75 bpm at baseline (N = 4,150)**	
	Ivabradine N = 3,241	**Placebo N = 3,264**	**Ivabradine N = 2,052**	**Placebo N = 2,098**
Age (years)				
Mean ± SD	60.7 ± 11.2	60.1 ± 11.5	59.7 ± 11.23	59.5 ± 11.71
Median (range)	61 (19; 89)	60 (19; 92)	60 (52; 68)	60 (52; 68)
Gender, n (%)				
Male	2,462 (76.0)	2,508 (76.8)	1,570 (76.5)	1,617 (77.1)
Ethnic origins, n (%)				
Caucasian	2,879 (88.8)	2,892 (88.6)	[redacted]	[redacted]
Asian	268 (8.3)	264 (8.1)		
Black	32 (1.0)	43 (1.3)		
Other	62 (1.9)	65 (2.0)		
Height (cm)				
n	3,240	3,264	[redacted]	[redacted]
Mean ± SD	169.6 ± 8.8	169.6 ± 8.8		
Median (range)	170 (135; 197)	170 (109[a]; 198)		

Weight (kg)				
Mean ± SD	80.9 ± 17.2	80.7 ± 17.1	[redacted]	[redacted]
Median (range)	80 (27; 159)	79 (29; 170)	[redacted]	[redacted]
Body mass index (kg/m^2)				
n	3,240	3,264	2,052	2,098
Mean ± SD	28.0 ± 5.1	28.0 ± 5.0	28.1 ± 5.3	27.9 ± 5.1
Median (range)	27.4 (13.7; 51.6)	27.3 (15.1; 59.5)	27.4 (24.4; 31.2)	27.2 (24.4; 30.7)
Heart rate (bpm)				
n	3,240	3,261	2,052	2,098
Mean ± SD	79.7 ± 9.5	80.1 ± 9.8	84.3 ± 9.1	84.6 ± 9.4
Median (range)	77 (48; 130)	77 (58; 142)	[redacted][c,d]	[redacted][c,d]
Sitting SBP (mmHg)				
Mean ± SD	122.0 ± 16.1	121.4 ± 15.9	121.6 [redacted][c]	121.2 [redacted][c]
Median (range)	120 (76; 179)	120 (78; 180)	[redacted][c,d]	[redacted][c,d]
Sitting DBP (mmHg)				
Mean ± SD	75.7 ± 9.6	75.6 ± 9.4	75.8 [redacted][c]	75.7 [redacted][c]
Median (range)	77 (42; 110)	76 (40; 120)	[redacted][c,d]	[redacted][c,d]
eGFR (creatinine clearance) (ml/min/1.73m^2)				
n	3,233	3,252	[redacted]	[redacted]
Mean ± SD	74.6 ± 22.9	74.8 ± 23.1	75.7 ± 23.5	75.5 ± 23.1
Median (range)	73 (23; 263)	73 (17; 331)	[redacted]	[redacted]
Smoking habits, n (%)				
Yes	541 (16.7)	577 (17.7)	381 (18.6)	402 (19.2)
Previous	1,355 (41.8)	1,364 (41.8)	847 (40.9)[c]	857 (40.9)
Never	1,345 (41.5)	1,323 (40.5)	824 (40.2)[c]	839 (40.0)
Alcohol consumption n (%)				
Yes	988 (30.5)	940 (28.8)	[redacted]	[redacted]
Previous	628 (19.4)	648 (19.9)	[redacted]	[redacted]
Never	1,625 (50.1)	1,676 (51.4)	[redacted]	[redacted]
Chronic heart failure				
Duration since diagnosis of HF (years)				
Mean ± SD	3.5 ± 4.2	3.5 ± 4.2	3.5 ± 4.1	3.4 ± 4.0
Primary cause of HF, n (%)				
Ischaemic	2,215 (68.3)	2,203 (67.5)	1,359 (66.2)	1,363 (65.0)
Non-ischaemic	1,026 (31.7)	1,061 (32.5)	693 (33.8)	735 (35.0)
Documented hospitalisation for worsening HF in previous 12 months, n (%)				
No	42[b] (1.3)	37 (1.1)	[redacted]	[redacted]
Yes	3,199 (98.7)	3,227 (98.9)	[redacted]	[redacted]

NYHA class				
Class II, n (%)	1,585 (48.9)	1,584 (48.5)	977 (47.6)	975 (46.5)
Class III, n (%)	1,605 (49.5)	1,618 (49.6)	1,035 (50.4)	1,076 (51.3)
Class IV, n (%)	50 (1.5)	61 (1.9)	40 (1.6)	47 (2.2)
LVEF (%)				
Mean ± SD	29.0 ± 5.1	29.0 ± 5.2	28.7 ± 5.18	28.54 ± 5.27
Median (range)	30.0 (9; 39)	30.0 (7; 37)	30.0 (9; 39)	30.0 (7; 36)
Other medical histories, n (%)				
Coronary artery disease	2,361 (72.9)	2,371 (72.6)	[redacted]	[redacted]
Hypertension	2,162 (66.7)	2,152 (65.9)	1,333 (65.0)	1,349 (64.3)
Myocardial infarction	1,829 (56.4)	1,837 (56.3)	1,124 (54.8)	1,138 (54.2)
Diabetes	973 (30.0)	1,006 (30.8)	638 (31.1)	665 (31.7)
Atrial fibrillation and/or flutter	263 (8.1)	259 (7.9)	154 (7.5)	162 (7.7)
Stroke	228 (7.0)	295 (9.0)	141 (6.9)	189 (9.0)
Renal failure	218 (6.7)	202 (6.2)	122 (6.0)	121 (5.8)

[a] Patient with bilateral amputation of lower extremities.

[b] Excludes 1 patient with a deviation for undocumented hospitalisation for worsening HF within previous 12 months who was confirmed as having a hospitalisation by the investigator.

[c] Data submitted by manufacturer in response to clarification questions from Evidence Review Group.

[d] For licensed population the range for median heart rate is given as heart rate, (Q1;Q3) (min;max).

Abbreviations used in table: bpm, beats per minute; cm, centimetre; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; kg kilogramme; LVEF, left-ventricular ejection fraction; m, metre; min, minute; ml, millilitre; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

Baseline standard cardiovascular care

The manufacturer emphasises that the SHIfT trial protocol[(49)] was designed to ensure patients received optimal doses of established heart failure therapies as their standard care, with a focus on baseline beta-blocker dose. Patients in the licensed population of SHIfT were receiving recommended standard heart failure treatments at randomisation: 90% were taking an ACE inhibitor and/or an angiotensin receptor blocker (ARB); 87% were taking a beta-blocker; 84.0% were taking a diuretic; and 61.6% were taking an aldosterone antagonist (baseline treatments presented in Appendix 5). The manufacturer presents data from UK clinical practice audits that, in the ERG's opinion, support their assertion that patients in SHIfT received optimal background therapy in line with NICE guideline CG108[(19)] (summarised in Table 9). Data presented indicate that a larger proportion of patients in the licensed population of the SHIfT trial received standard therapies at baseline compared with patients undergoing treatment for heart failure in the audits.

The ERG considers it important to note that the use of devices in the SHIfT trial was low, with only [redacted] of the licensed population having an implantable cardioverter defibrillator (ICD) and [redacted] having cardiac resynchronisation therapy (CRT). In the full publication of the SHIfT trial,[(33)] the authors comment that the low representation of people with devices was as a result of the exclusion of some patients with pacemakers: a pre-specified exclusion criterion of the SHIfT

trial was ventricular or atrioventricular pacing operative for ≥40% the day or pacing threshold at the atrial or ventricular level of ≥60 bpm. The authors go on to comment that the proportion of patients with a device included in the SHIfT trial corresponds to the frequency of device use in countries outside North America and some Western European countries. The ERG notes that a recent publication by Heart Rhythm UK indicates that, despite a substantial increase in rate of implantation of devices (ICD and CRT) in the past decade, in 2009, the rate of implantation in the UK remained low compared with other European countries.[56]

Despite recommendations in the SHIfT trial protocol,[57] in the licensed population, of those receiving a beta-blocker recommended by the European Society of Cardiology (ESC; [redacted] of those taking a beta-blocker),[58] only 26.2% achieved recommended target dose and 55.4% achieved ≥50% recommended target dose: the SHIfT trial protocol specified prescription of beta-blockers recommended by the ESC[58] at the dose listed (presented in Table 10). The small proportion of patients achieving target beta-blocker dose in the full (26%) and licensed population of the SHIfT trial raises the question as to whether patients not achieving target dose of beta-blocker had been optimally treated, as noted by the CHMP during its evaluation of the manufacturer's application for an extension to the licensed indication of ivabradine.[36]

The manufacturer acknowledges that the number of patients achieving target beta-blocker dose is low but emphasises that the proportion of patients achieving target dose beta-blocker is larger than typically seen in UK clinical practice. The manufacturer presents data from a UK practice (community heart failure clinic) audit[34] in support of their assertion (summarised in Table 11). The ERG notes that there were minor differences among studies in the thresholds used for low and moderate dose, and in the dose of beta-blocker listed as target dose. In SHIfT,[33] low dose of beta-blocker was defined as <50% target dose and moderate dose as ≥50% target dose, based on doses recommended in the ESC guidelines for the treatment of heart failure.[58] By contrast, the audit of the community heart failure clinic defined thresholds for the individual beta-blockers assessed, and analysed patients prescribed an additional five beta-blockers (atenolol, timolol, propranolol, sotalol and celiprolol). The ERG considers it important to note that NICE guideline CG108[19] recommends prescribing a beta-blocker licensed for heart failure, of which there are three: bisoprolol; carvedilol; and nebivolol. In addition, over 12 months' follow-up in the community heart failure clinic, the proportion of patients achieving target dose of beta-blocker approaches that of patients at randomisation in the SHIfT trial.

As the manufacturer highlights, the proportion of patients achieving target dose of beta-blocker in the full and licensed populations of the SHIfT trial is considerably smaller than those reported in the key heart failure trials evaluating beta-blockers.[39;40;42;43;45] Reported proportions of patients achieving target level of beta-blockade range from 42.6% in CIBIS II[39] to 78% in COMET[40] (data presented in

Appendix 1). In the trials, treatment was initiated at a low dose followed by up-titration of dose over a set time period until either the patient could not tolerate further up-titration or the target dose was achieved. Up-titration of dose could be slowed or stopped at the discretion of the investigator based on patient response. The manufacturer highlights that many studies excluded contraindicated or co-morbid patients (e.g., those with respiratory disease) and highlights that there may have been selection bias in the trials in that patients were recruited who were predisposed to tolerate beta-blockade. The ERG considers that as the trials were designed to assess the effects of beta-blockers, it would be necessary to exclude patients with signs or symptoms of contraindication to beta-blockers. The manufacturer goes on to comment that "patients could often not be maintained on the doses achieved after the titration phase and had to reduce or interrupt treatment due to intolerance during the maintenance phase[45]". However, the ERG considers it important to note that two trials reported that doses achieved were generally maintained through the trial, with about 70% of the patients in the SENIORS trial[45] continuing on the maintenance dose achieved until the end of the study.[40;45]

Furthermore, the manufacturer observes that the management of heart failure has changed in the 15–20 years since these trials were carried out, with an increase in prescribing of concomitant blood pressure lowering agents (e.g., aldosterone antagonists). As a consequence, patients are more likely to have hypotension and thus have contraindication to increase in beta-blockade. In the licensed population in SHIfT, the principal reason reported for not achieving beta-blocker target dose was [redacted]. Other common reasons were [redacted] (summarised in Appendix 5). Hypotension, bradycardia, and deteriorating symptoms of heart failure (e.g., fatigue) are recognised adverse effects associated with beta-blockers, and it is recommended that patients receiving beta-blockers are assessed for signs of these effects as part of the routine monitoring of their condition.[59] However, the ERG considers it important to note that it has been reported that only 3–5% of patients eligible for treatment with beta-blockers are unable to tolerate beta-blockers due to hypotension or bradycardia.[60]

Table 9. Comparison of proportion of patients receiving standard heart care therapies in SHIfT versus UK clinical practice

Therapy	**SHIfT**[33] Baseline	**National Heart Failure audit (2010–2011)**[1] On discharge from hospital	**HOOPS**[61] [b] Pharmacist-led intervention in primary care Baseline (year 1 for intervention group)	**Community heart failure clinic audit**[34] [b,c] Baseline (4 months)
Beta-blocker	89%	65% (78%[a])	62% (64%)	58% (81%)
ACE inhibitor/ARB	91%	81%	86% (85%)	79% (90%)
Diuretic	84%	86%	61% (NR)	74% (77%)
Aldosterone antagonists	60%	36%	5% (NR)	25% (29%)
Cardiac glycosides	22%	NR	14% (NR)	18% (19%)

Table adapted from MS: Table 29, pg 103. The manufacturer also presented data from an unpublished study,[29] which, due to the unpublished nature of the data, the ERG has chosen not to present here.

[a] If discharged from a cardiology ward.

[b] Both clinical practice audits assessed patients with heart failure due to LVSD.

[c] It should be noted that the community heart failure clinic audit specified a target dose of 400 mg for metoprolol compared with 200 mg recommended by the ESC,[36] which could result in an underestimation of the number patients achieving target dose.

Abbreviations used in table: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NR, not recorded.

Table 10. Target doses of blockers as used in large heart failure trials (recommended by the ESC[58])

Beta-blocker	**Target dose (mg/day)**
Bisoprolol	10
Metoprolol succinate CR	200
Carvedilol	50
Nebivolol	10
Abbreviation used in table: CR, controlled release.	

Table 11. Comparison of beta-blocker dosage in SHIfT versus in UK clinical practice

Beta-blocker dose	**SHIfT**[33] Baseline	**Community heart failure clinic audit**[34] [a]			**National Heart Failure Audit (2010–2011)**[1] [b] <75 years, on discharge from hospital		
		Baseline (N = 2,211)	4 months (N = 1,309)	12 months (N = 910)	All patients (N = 4,615)	Tertiary centres (N = 1,127)	Cardiology care (N = 3,141)
None	11%	42%	19%	14%	28%	16%	18%
Low dose	40%	29%	40%	36%	44%	45%	48%
Moderate dose	26%	23%	27%	34%	27%	37%	32%
Target dose	23%	7%	13%	19%	1%	2%	2%

Table reproduced from MS: Table 30, page 104.

[a] It should be noted that the community heart failure clinic audit specified a target dose of 400 mg for metoprolol compared with 200 mg recommended by the ESC,[36] which could result in an underestimation of the number patients achieving target dose.

[b] Percentages as a proportion of patients who have beta-blocker dose recorded (*ca.* one third). Patients have had limited opportunity for dose optimisation, hence only 1–2 % are on target dose.

Note: The ERG was unable to validate the data reported from the National Heart Failure Audit[1] as the ERG believes that the reference cited does not report on beta-blocker prescription on discharge from hospital.

The ERG considers that the manufacturer made every effort to ensure that, in SHIfT, established heart failure therapies were given at optimal doses and in accordance with guidelines.[19;58] The ERG also considers that the potential effect of variation in beta-blocker dose achieved on the clinical effect of ivabradine warrants further investigation, and discusses this area in more detail in Section 4.3.4.

Blinding

Patients and investigators were blinded to treatment group allocation. In addition, the placebo tablets matched the ivabradine tablets in taste and appearance. The CHMP noted a potential issue with maintenance of blinding in that patients and investigators may have been able to attribute the observed reduction in heart rate to treatment with ivabradine (mean heart rate reduction of about 15 bpm in ivabradine group vs about 5 bpm in the placebo group).[36] The CHMP went on to highlight that "reduced heart rates (up to 15 bpm) were observed in 16% to 20% of the placebo patients whereas up to 14% to 18% of the ivabradine patients had a reduction less than 5 bpm". The ERG considers that the key outcomes assessed in SHIfT are objective outcomes and thus are unlikely to be influenced by the patient or the investigator.

Outcomes assessed

As noted in Section 3.4, the pre-specified primary outcome in SHIfT[33] was a composite of first event of hospitalisation for worsening heart failure or cardiovascular mortality. The individual components of the primary outcome were assessed as pre-specified secondary outcomes.

There has been considerable debate around the use of composite outcomes when assessing treatments in heart failure. In its report, the CHMP[36] noted that the composite of cardiovascular morbidity and all-cause mortality is a recommended outcome in the *EMA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure*.[62] However, as the CHMP stated,[36] the guideline indicates that a key outcome of interest is overall mortality. The assessment of a composite outcome including cardiovascular death is becoming more widely recognised as appropriate, with the caveat that there is no negative effect on the outcome of all-cause mortality.

Pre-specified secondary outcomes in SHIfT[33] are listed as:

- time to occurrence of all cause death;
- time to occurrence of cardiovascular death;
- time to first occurrence of hospitalisation for worsening heart failure;
- time to first occurrence of all cause hospitalisation;
- time to first occurrence of any cardiovascular hospitalisation;
- time to occurrence of death from heart failure;
- time to occurrence of the first event among the following events (composite outcome):
    - cardiovascular death;
    - hospitalisation for worsening heart failure;
    - hospitalisation for non-fatal myocardial infarction.

In addition, the manufacturer also presents data on change in patient's functional capacity, based on NYHA classification, and changes in patient-reported and physician-reported global assessment. The CHMP[36] highlighted that the manufacturer did not implement objective measures of functional status, such as NT-proBNP (N-terminal pro-B-type natriuretic peptide) measurements, 6 min tests, spiroergometries, or regular exercise tolerance tests. In the submission, the manufacturer highlights that NT-proBNP was assessed in a specific sub-study carried out in selected centres but the manufacturer deemed this study not to be relevant to the decision problem that is the focus of this STA. The ERG agrees with the manufacturer on this point.

Generalisability to UK clinical practice

Only 12 patients of 6,558 patients recruited to the full SHIfT trial were from the UK. Rationales proposed for the low level of recruitment from the UK are that the UK is a particularly poor recruiter for clinical trials and difficulties may have been encountered in identifying eligible patients. As patients from the UK contribute a negligible component to the overall trial population, and therefore the licensed population, for the results of the SHIfT trial to be generalisable to UK clinical practice it is important that patients were receiving standard heart failure therapies comparable to UK clinical practice. The ERG considers that the manufacturer has provided evidence to demonstrate that patients

received standard treatments at optimal doses and thus the results of the SHIfT trial are generalisable to a UK population. The ERG notes that patients in the licensed population of the SHIfT trial are younger (median age of 60 years vs median age of 72 years) and have more severe heart failure than patients typically seen in UK clinical practice. As highlighted by the manufacturer, the characteristics of the patients recruited to the SHIfT trial are similar to those of patients recruited to other key heart failure clinical trials (characteristics summarised in Appendix 1). In addition, patients with heart failure due to LVSD recruited to clinical trials are typically younger than comparable patients seen in clinical practice.

4.2.2 Description and critique of statistical approach used

The manufacturer presented comprehensive details in the MS on the statistical approaches used in the SHIfT trial. The primary objective of the SHIfT trial[33] was to demonstrate superiority of ivabradine over placebo when added to standard heart failure therapy in the reduction of cardiovascular mortality or hospitalisation for worsening heart failure (the primary composite outcome). To test the effectiveness of ivabradine in reducing the primary outcome, the manufacturer used a survival analysis carried out using all randomised patients, on a time-to-first event basis, and based on the intention-to-treat (ITT) principle. The manufacturer used a Cox's proportional hazards model adjusted for beta-blocker intake at randomisation to estimate the treatment effect, the 95% confidence interval (95% CI), and the associated two-sided p-value (significance level: 5%). The proportionality of hazard was checked by addition of an interaction between log (time) and randomised treatment to the Cox model.

The secondary objectives of the SHIfT trial were to investigate each component of the primary composite endpoint, all-cause mortality, and morbidity (all cause hospitalisation and cardiovascular hospitalisation) using the same statistical methods as planned for the primary composite endpoint. In addition, another pre-specified objective was to evaluate the effect of ivabradine on clinical symptoms (NYHA, Patient and Physician Global Assessment).

The manufacturer reports that time-to-event curves were estimated with the Kaplan-Meier method. All survival analyses were done on adjudicated endpoints for the entire population and for the subgroup with ≥50% of the target daily dose of beta-blocker. Treatment effects and 95% CIs were calculated in pre-specified subgroups from Cox models containing treatment effect, baseline beta-blocker status, and subgroup status. P-values for interaction between randomised treatment and subgroup status were also provided by adding treatment by subgroup interaction to the model.

The ERG considered the statistical approaches used in the SHIfT trial[33] to be appropriate for the planned analyses carried out on the full population of the SHIfT trial (i.e., recruited patients with resting heart rate ≥70 bpm). However, the ERG notes that the evidence submitted in support of the

application is based on a subgroup that was not pre-specified in the SHIfT trial protocol.[57] The ERG appreciates that the manufacturer has submitted evidence in line with the licence issued for ivabradine in the treatment of heart failure (i.e., patients with resting heart rate ≥75 bpm),[36] but thinks it important to note that analyses of effectiveness are therefore *post hoc* analyses, and as such should be interpreted with a degree of caution.

The submitted clinical evidence for ivabradine is based on data from a subgroup analysis from the SHIfT trial,[33] which is the only study evaluating the effects of ivabradine in the treatment of heart failure due to LVSD. Consequently, the manufacturer did not carry out a meta-analysis or indirect comparison.

4.2.3 Summary statement

The ERG considers that the manufacturer's systematic review followed recommended methodological practices. Moreover, the manufacturer's transparent reporting enabled the ERG to replicate their search results. The submitted clinical evidence is based on a subgroup analysis of one large, multicentre trial (SHIfT[33]). The manufacturer presented a clear overview of the methods of the SHIfT trial. In addition, the manufacturer presented evidence to support the generalisability of the results to UK clinical practice. The SHIfT trial was a well-designed trial with a primary objective of assessing the superiority of ivabradine over placebo in reducing time to first event of cardiovascular death or hospitalisation for worsening heart failure (the primary composite outcome of the trial). The manufacturer presented data for the individual components of the composite outcome, in addition to data on all other outcomes relevant to the decision problem as outlined in the final scope issued by NICE.[35] The ERG notes that the population that is relevant to the decision problem is younger and has more severe heart failure compared with patients typically seen in UK clinical practice, but recognises that the population is similar to those seen in other key trials in heart failure. The ERG considers that the presented analyses can be used to inform the decision problem, but notes that, because data come from numerous subgroup analyses, the results should be interpreted with a degree of caution.

4.3 Summary of clinical effectiveness results

4.3.1 Overall clinical effectiveness in licensed population

In their submission to NICE, the manufacturer presents data on primary and secondary outcomes for both the full trial population of SHIfT (i.e., resting heart rate of ≥70 bpm) and the licensed population (i.e., resting heart rate of ≥75 bpm). In its evaluation of data on clinical effectiveness, the ERG presents and discusses the results for only the licensed population. For completeness, data on the primary and secondary outcomes for the full population of the SHIfT trial[33] are presented in

Appendix 4. In addition, the manufacturer presents analyses from a sub-study of SHIfT assessing the effect of ivabradine on HRQoL (PRO-SHIfT[53]).

As noted in Section 4.2.1, the ERG cautions that the submitted evidence is based on *post hoc* subgroup analyses of the full trial population.

Primary outcome

In the subgroup of patients in the SHIfT trial with a resting heart rate of ≥75 bpm, addition of ivabradine to optimised standard care was associated with a statistically significant reduction in the composite of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure compared with addition of placebo (Hazard Ratio [HR] 0.76; 95% CI: 0.68 to 0.85; p <0.0001): summary of outcome data is presented in Table 12 and the Kaplan-Meier analysis for the primary outcome is provided in Appendix 6.

The manufacturer reports that, in the licensed population, treatment with ivabradine for 1 year would prevent one cardiovascular death or hospital admission for worsening heart failure for every 16 patients treated (MS; Table 12, pg 69).

Secondary outcomes

Data for the individual components of the primary outcome were pre-specified secondary outcomes (Table 12). In addition, all-cause mortality and all-cause hospitalisation, which were specified as outcomes of interest in the final scope issued by NICE,[35] were also pre-specified secondary outcomes.

As the manufacturer notes in the MS, analyses of the individual components of the primary composite outcome indicate that reduction in hospitalisation for worsening heart failure is the key driver in the clinical effect of ivabradine observed for the primary composite outcome, with a statistically significant risk reduction of 30% for this endpoint relative to placebo (HR 0.70; 95% CI: 0.61 to 0.80; p <0.0001). The clinical benefit of ivabradine was consistent across secondary outcomes, with a statistically significant reduction in all secondary outcomes assessed that favoured ivabradine (Table 12).

For the pre-specified secondary outcomes, the ERG notes that the greatest benefit of ivabradine relates to reduction in death from heart failure (HR 0.61; 95% CI: 0.46 to 0.81). The manufacturer states in the MS that, in the full trial population of SHIfT, SHIfT results were generally driven by the cause-specific endpoints of hospitalisation for heart failure and heart failure death. The ERG considers that this statement also applies to the licensed population.

Table 12. Summary of treatment effectiveness data for ivabradine in the treatment of heart failure in patients with a resting heart rate of ≥75 bpm

Outcome	Ivabradine N = 2,052	Placebo N = 2,098	HR[a] (95% CI)	p-value
Primary outcome				
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	545 (26.6)	688 (32.8)	0.76 (0.68 to 0.85)	<0.0001
Secondary outcomes				
Cardiovascular death, n (%)	304 (14.8)	364 (17.4)	0.83 (0.71 to 0.97)	0.0166
Hospitalisation for worsening HF, n (%)	363 (17.7)	503 (24.0)	0.70 (0.61 to 0.80)	<0.0001
Death from any cause, n (%)	340 (16.6)	407 (19.4)	0.83 (0.72 to 0.96)	0.0109
Death from HF, n (%)	78 (3.8)	126 (6.0)	0.61 (0.46 to 0.81)	0.0006
Hospitalisation for any cause, n (%)	796 (38.8)	932 (44.4)	0.82 (0.75 to 0.90)	<0.0001
Hospitalisation for cardiovascular reason, n (%)	640 (31.2)	779 (37.1)	0.79 (0.71 to 0.88)	<0.0001

[a] For the primary outcome, HR is an estimate of the HR between treatment groups based on an unadjusted Cox proportional hazards model. For secondary outcomes, HR is an estimate of the HR between treatment groups based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate.

Abbreviations used in table: CI, confidence interval; HF, heart failure; HR, Hazard ratio.

Reduction in heart rate

At day 28, ivabradine was associated with a mean decrease in heart rate from baseline of 17.4 bpm compared with 5.7 bpm for placebo (summarised in Table 13). Data at last visit suggest that the effect of ivabradine is maintained, with a mean reduction in heart rate of 14.5 bpm in the ivabradine group versus 5.8 bpm with placebo. The approximate 10–11 bpm difference between the groups equates to the expected reduction in heart rate associated with the usual recommended dose of ivabradine (heart rate reduction is approximately 10 bpm at rest and during exercise).[(25)] The manufacturer states that trials of ivabradine have shown that the observed reduction in heart rate is proportional to the resting heart rate, with greater reductions in heart rate in patients with a higher baseline resting heart rate. The ERG notes that, based on the finding that a reduction in heart rate of 5 bpm (with use of beta-blockers) is associated with an 18% decrease in all-cause mortality,[(14)] the placebo group appears to be receiving a benefit from no additional treatment.

Table 13. Change in heart rate in licensed population

	Ivabradine (N = 2,052)	Placebo (N = 2,098)
Mean baseline heart rate, bpm (SD)	84.3 (±9.1)	84.6 (±9.4)
Mean change in heart rate, bpm (SD)		
Day 28	–17.4 (±11.5)	–5.7 (±11.3)
Last visit	–14.5 (±13.8)	–5.8 (±13.5)
Abbreviations used in table: bpm, beats per minute; SD, standard deviation.		

NYHA class

New York Heart Association (NYHA) classification is a measure of the severity of a patient's heart failure based on physical limitations. A larger proportion of patients in the ivabradine group improved by ≥1 NYHA class at their last visit from their baseline classification compared with the placebo group (summarised in Table 14). The manufacturer did not report on the statistical significance of the result, but the ERG's calculation indicates that the difference between the ivabradine and placebo groups is statistically significant and favours ivabradine [redacted]. The ERG found [redacted] between groups in the proportion of patients with worsening NYHA classification [redacted].

Table 14. Change in NYHA class from baseline to last post-randomisation visit for licensed population

NYHA classification	Ivabradine n (%) [redacted]	Placebo n (%) [redacted]	RR[a] (95% CI)	p-value
Improvement	[redacted]	[redacted]	[redacted]	[redacted]
Stability	[redacted]	[redacted]	[redacted]	[redacted]
Worsening	[redacted]	[redacted]	[redacted]	[redacted]
[a] RR calculated by ERG (ivabradine vs placebo: for improvement, RR >1.0 favours ivabradine, for worsening, RR <1 favours ivabradine). Abbreviation used in table: NYHA, New York Heart Association.				

Potential effects of beta-blocker dose achieved on clinical effect of ivabradine

A key pre-specified secondary outcome in the SHIfT trial[33] was evaluation of the primary composite outcome in the subgroup of patients achieving at least 50% of the target dose of beta-blocker (RS_{BBDOSE}). In the full population of the SHIfT trial (i.e., resting heart rate ≥70 bpm), although there was a trend towards benefit with ivabradine in the RS_{BBDOSE} subgroup, the reduction in risk of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure did not reach statistical significance (HR 0.90; 95% CI: 0.77 to 1.04). Moreover, the CHMP[36] noted that the

beneficial effect of ivabradine was attenuated in patients (resting heart rate ≥70 bpm) who achieved target beta-blocker dose, with no difference between ivabradine and placebo for the primary composite endpoint (HR 0.99; 95% CI: 0.79 to 1.24).[36] For the individual elements of the primary outcome, although there was a trend towards benefit for ivabradine for hospitalisation due to worsening heart failure, the difference did not reach statistical significance (HR 0.84; 95% CI: 0.63 to 1.11).[36] Moreover, there was a small increase in risk of cardiovascular mortality with ivabradine treatment, but again the difference between groups did not reach statistical significance (HR 1.08; 95% CI: 0.78 to 1.48). The manufacturer did not present data on the primary outcome for the RS_{BBDOSE} subgroup or the subgroup of patients achieving target dose of beta-blocker within the licensed population in their submitted evidence for this STA. With the goal of clarifying the potential influence of beta-blocker dose on effect of ivabradine in the licensed population, as part of the clarification process, the ERG requested data for various subgroups based on beta-blocker dose achieved. The results of these analyses are discussed in more detail in Section 4.3.4.

4.3.2 HRQoL results from PRO-SHIfT

The manufacturer presented results from a pre-planned sub-study (PRO-SHIfT[53]) that compared the effects of adding ivabradine versus adding placebo on HRQoL in a subgroup of patients (N = 5,038 patients) from the full population of the SHIfT trial.[33] The patients assessed in PRO-SHIfT were reported to be a representative sample set of the overall population of the SHIfT trial. Separate data for the subgroup that forms the licensed population of the SHIfT trial were not presented in the MS. The manufacturer presents results from one generic (EuroQol 5 Dimensions [EQ-5D][63]) and one disease-specific (Kansas City Cardiomyopathy Questionnaire [KCCQ][16]) questionnaire used to assess HRQoL.

Patients in countries in which translations of the study questionnaires were available (35 out of 37 countries) were invited to participate. Patients who consented to participate (N = 5,038) completed the questionnaires at baseline visit, and subsequently at 4 months, 12 months, 24 months and their final visit. Endpoints analysed were:

- EQ-5D Index Score;
- EQ-5D Visual Analogue Scale (EQ VAS) of the EQ-5D questionnaire: assessed from 0 (worst health state) to 100 (highest status);
- descriptive system for each of the five dimensions of the EQ-5D;
- clinical summary score (previously functional status score) of the KCCQ;
- overall summary score of the KCCQ;
- other domain scores of the KCCQ.

The manufacturer's rationale for presenting data from both questionnaires is that the applicability of generic questionnaires across a wide range of health conditions results in the loss of sensitivity to clinically important changes in health when applied to a specific patient population, such as patients with heart failure. For completeness, the ERG presents and discusses the results for both the EQ-5D and the KCCQ (Table 15) but emphasises that NICE has specified the EQ-5D as its preferred method of utility measurement.

Based on results from the EQ-5D questionnaire, the manufacturer found that over time HRQoL deteriorated [redacted] in both the ivabradine and the placebo group, with a decrease in mean EQ-5D score at last visit from baseline visit (Table 15). However, the difference between ivabradine and placebo [redacted]. In the main analysis, for deceased patients, the last post-baseline value was substituted by 0, which does not account for improvements in quality of life that may have occurred prior to death. In a second analysis that combined the last observed value before death for the deceased patients with data for surviving patients, a small improvement in HRQoL was observed in both the ivabradine and the placebo group treatment groups, with the difference between groups [redacted]. However, there was [redacted] between groups in change in EQ-5D index score at 12 months [redacted]. Considering results from the KCCQ questionnaire, all analyses indicated [redacted] difference between the ivabradine and the placebo group in change in mean KCCQ clinical summary score, [redacted] (Table 15). The differences between groups in mean KCCQ clinical summary score were [redacted] for the main analysis (last post-baseline value substituted by 0 for deceased patients), [redacted] for analysis of surviving patients, and 2.6 for change from baseline at 12 months. The ERG notes that it has been proposed that a 5-point change in score on the KCCQ is a clinically meaningful difference.[64] Based on this proposed threshold, the [redacted] in KCCQ score is the deterioration in HRQoL observed in the placebo group in the main analysis. None of the between group differences in KCCQ score [redacted].

The manufacturer notes that there is a limited evidence base on the effects of heart failure treatments in general on HRQoL, and thus it is difficult to contextualise the results generated from the EQ-5D questionnaire on the effects of ivabradine compared with placebo. The manufacturer goes on to highlight that the limited evidence available suggests that beta-blockers, ACE inhibitors, and ARBs have no effect on HRQoL, neither improving nor impairing HRQoL.[65-67]

Table 15. Summary of results of change in EQ-5D index and KCCQ scores

Measure	Ivabradine	Placebo	Difference in change in score[a,b,c] Ivabradine – placebo (± SE) [95% CI] p value
EQ-5D index score			
Change from baseline to last assessment			
EQ-5D index score[d], (mean ± SD), including scoring death as 0			
	[redacted]	[redacted]	
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	
Δ	[redacted]	[redacted]	[redacted]
EQ-5D index score[d], (mean ± SD), analysis of surviving patients			
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	
Δ	[redacted]	[redacted]	[redacted]
Change from baseline to month 12			
EQ-5D index score[d], (mean ± SD), including scoring death as 0			
	[redacted]	[redacted]	
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	
Δ	[redacted]	[redacted]	[redacted]
KCCQ			
Change from baseline to last assessment			
Clinical summary score[e], (mean ± SD), including scoring death as 0			
	N = 968	**N = 976**	
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	
Δ	[redacted]	[redacted]	[redacted]
Clinical summary score[e], (mean ± SD), analysis of surviving patients			
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	
Δ	[redacted]	[redacted]	[redacted]

Change from baseline to month 12			
Clinical summary score[e], (mean ± SD), including scoring death as 0			
	N = 872	**N = 882**	
Baseline	68.9 (20.0)	68.6 (20.5)	
Final	71.4 (24.4)	68.7 (25.5)	
Δ	2.6 (21.72)	0.1 (21.8)	2.6 (0.9) [0.7 to 4.5] p = 0.008

[a] Change in score from baseline to last post-baseline value, with last-post baseline value = 0 for deceased patients.

[b] Results from mixed linear model on change in EQ-5D index score, adjusted for baseline score, beta-blocker intake at randomisation, and country (random effect).

[c] Results from mixed linear model on change in KCCQ clinical summary score, adjusted for baseline KCCQ clinical summary score, beta-blocker intake at randomisation, and country (random effect).

[d] An EQ-5D index score is converted from an EQ-5D health state by applying a formula based on the valuation of EQ-5D health states from general population samples. The EQ-5D Index score ranges from –0.594 to 1.000.

[e] Clinical summary score is the mean of the physical limitation and total symptom domain scores; the higher score indicates better function.

Abbreviations used in table: EQ-5D, EuroQol 5 Dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; SD, standard deviation; SE, standard error.

4.3.3 Adverse effects

The Summary of Product Characteristics (SPC) for ivabradine[(25)] states that the most common adverse effects associated with ivabradine use are luminous phenomena (phosphenes; an ocular condition in which the patient sees "light flashes") and bradycardia, both of which are dose dependent and related to the pharmacological effect of ivabradine. Other adverse effects listed in the SPC as commonly (≥1/100 to <1/10) occurring in clinical trials of ivabradine are uncontrolled blood pressure and blurred vision.

The manufacturer reported adverse effects in the "on treatment" population, which is defined as patients taking one dose of study drug and all adverse events occurring between the first study drug intake and the last intake plus two days. For the licensed subgroup of the SHIfT trial, of the adverse events presented in the MS, ivabradine use was associated with a statistically significant increased risk of recognised adverse effects – that is, bradycardia and phosphenes (Table 16). Compared with the placebo group, patients in the ivabradine group were: 6 times more likely to experience symptomatic bradycardia (Relative Risk [RR] 6.14; 95% CI: 3.50 to 10.78); 4 times more likely to experience asymptomatic bradycardia (RR 4.01; 95% CI: 2.60 to 6.20); and 5 times more likely to experience phosphenes (RR 5.31; 95% CI: 2.79 to 10.09).

The manufacturer did not present data on inadequately controlled blood pressure in the subgroup of the licensed population. Data for the on-treatment population of the SHIfT trial indicate that a larger proportion of patients experienced uncontrolled blood pressure in the ivabradine group compared with

the placebo group (228/3,232 [7.1%] with ivabradine vs 198/3,260 [6.1%]).[36] The SPC states that patients most frequently experienced uncontrolled blood pressure shortly after modification of their blood pressure treatment. Episodes of uncontrolled blood pressure were transient, and did not affect the treatment effect of ivabradine.

In the full trial population of SHIfT, treatment-related adverse events occurred more frequently in the ivabradine group compared with the placebo group (574/3,232 [17.8%] in the ivabradine group vs 271/3,260 [8.3%] in the placebo group). The manufacturer indicates that the difference between the two groups was predominantly due to the listed adverse effects recognised as being associated with ivabradine treatment (i.e., asymptomatic bradycardia, symptomatic bradycardia, phosphenes, dizziness and blurred vision). The manufacturer did not present equivalent data for the licensed population of the SHIfT trial, but the ERG considers that, because the adverse effects most commonly occurring in the licensed population are analogous to the full population, it is likely that the proportion of patients experiencing a treatment-emergent adverse effect will be larger in the ivabradine group compared with the placebo group.

The manufacturer presents data on cardiac failure as an adverse effect. The ERG considers that cardiac failure could include adverse effects due to heart failure. As aspects of heart failure are assessed as clinical effectiveness outcomes in the SHIfT trial, the ERG speculates that data on cardiac failure as an adverse effect are potentially confounded and should be interpreted with caution.

The ERG notes that there was no statistically significant difference between ivabradine and placebo in all emergent adverse effects (RR 0.99; 95% CI 0.96 to 1.02), or emergent adverse effects leading to withdrawal (RR 1.04; 95% CI 0.90 to 1.21) in the licensed population of the SHIfT trial (Table 16). Ivabradine was associated with a statistically significant reduction in risk of serious emergent adverse effect (RR 0.90; 95% CI: 0.84 to 0.96).

The ERG notes that the reported adverse effects (Table 16), other than inadequate blood pressure control, are similar to those reported in BEAUTIFUL,[68] which was a large RCT (10,917 patients randomised) assessing the effects of adding ivabradine to standard care in patients with coronary artery disease and LVSD.

Table 16. Adverse events in 'on treatment' group of licensed population (resting heart rate ≥75 bpm)

Adverse event	Ivabradine (N = 2,046)	Placebo (N = 2,095)	RR (95% CI)
All emergent adverse events	1,554 (76.0%)	1,607 (76.7%)	0.99 (0.96 to 1.02)
All serious emergent adverse[a] events	892 (43.6%)	1,020 (48.7%)	0.90 (0.84 to 0.96)
All emergent adverse events leading to drug withdrawal	300 (14.7%)	295 (14.1%)	1.04 (0.90 to 1.21)
Emergent adverse events (reported in MS; Table 24, pg 90)			
Cardiac failure	487 (23.8%)	609 (29.1%)	0.82 (0.74 to 0.91)
Symptomatic bradycardia	84 (4.1%)	14 (0.7%)	6.14 (3.50 to 10.78)
Asymptomatic bradycardia	98 (4.8%)	25 (1.2%)	4.01 (2.60 to 6.20)
Atrial fibrillation	161 (7.9%)	143 (6.8%)	1.15 (0.93 to 1.43)
Phosphenes	57 (2.8%)	11 (0.5%)	5.31 (2.79 to 10.09)
Blurred vision	11 (0.5%)	7 (0.3%)	1.61 (0.62 to 4.14)

[a] Serious emergent adverse effects listed in the MS (pg 118) as heart failure hospitalisations, other cardiovascular hospitalisations and non-cardiovascular hospitalisations.

Abbreviations used in table: RR, relative risk.

4.3.4 Subgroup analysis

No subgroups of interest were specified in the final scope issued by NICE.[35] However, the manufacturer specified *a priori* subgroup analyses to investigate further the clinical effect of ivabradine. Pre-specified subgroup analyses in the full population of SHIfT were:

- age: <65/≥65 years;
- gender: male/female;
- beta-blocker intake at randomisation: yes/no;
- primary cause of heart failure: ischaemic cause/non ischaemic cause;
- NYHA class: II/III or IV;
- diabetes: yes/no;
- hypertension: yes/no;
- heart rate above and below the median, for patients in sinus rhythm: (<77 bpm/≥77 bpm).

In addition, the manufacturer carried out *post hoc* subgroup analyses of: patients with a baseline heart rate ≥75 bpm (the subgroup identified within the licensing process); age ≥70 years; and age ≥75 years.

As part of the clarification process, after discussion with the ERG's clinical expert, the ERG requested data for subgroups of the licensed population based on: age ≥70 years; NYHA classification; and baseline beta-blocker dose achieved.

As noted in Section 4.3.1, a pre-specified secondary outcome in the SHIfT trial[33] was evaluation of the primary outcome in the RS_{BBDOSE} subgroup. Data were not provided in the MS for this subgroup in the licensed population. As part of the clarification process, the ERG requested data for the RS_{BBDOSE} subgroup of the licensed population, in addition to the data listed above.

Potential effect of beta-blocker dose achieved on clinical effectiveness of ivabradine

The clinical effectiveness of beta-blockers in reducing mortality and morbidity in patients with heart failure is well-established. Beta-blockers bind to the receptors for, and thus block the action of, the hormones adrenaline and noradrenaline: release of adrenaline and noradrenaline during times of stress leads to an increase in heart rate.[69] Thus, beta-blockers are thought to primarily exert beneficial effects in heart failure through reduction in heart rate. However, beta-blockers are also thought to exert additional beneficial effects on cardiac function through pathways and mechanisms that are independent of beta-blockade, having antihypertensive, antiarrhythmic and antioxidant activities that vary among the class.[70] As a result, the importance of the contribution of heart rate reduction alone to the clinical effectiveness of beta-blockers in the treatment of heart failure is unclear.

As discussed in Section 2.2, despite recommendations that ACE inhibitors and beta-blockers be used concomitantly as first-line treatments in the management of heart failure due to LVSD,[19;58] unless contraindicated or not tolerated, data indicate that prescription of beta-blockers remains suboptimal.[1] It has been reported that 30–50% of patients for whom beta-blockers are indicated because of heart failure or previous MI do not receive a beta-blocker.[60] Reasons for underutilisation of this class of agent are complex, with potential factors cited as underestimation of the benefit received with beta-blockers, and reticence of clinicians to prescribe beta-blockers because of concerns over adverse effects of treatment and lack of tolerability for patients.[24;60] The Euro Heart Survey identified various factors that influence prescription of ACE inhibitors and beta-blockers, including age, aetiology of heart failure, co-morbidity, specialty at discharge and pathophysiology of heart failure. In the case of beta-blockers, presence of co-morbid conditions of asthma or chronic obstructive pulmonary disease (COPD) was associated with a reduction in prescription rate.

Data presented by the manufacturer from the National Heart Failure Audit (2010–2011)[1] and an audit of a community heart failure clinic[34] underscore the extent to which beta-blockers are currently underused. The National Heart Failure Audit[1] reported that only 65% of patients with a diagnosis of heart failure due to LVSD were prescribed this class of drug on discharge from hospital. In their audit

of a community heart failure clinic, Cullington *et al*.[34] report that, at the start of their audit, 42% of patients with heart failure due to LVSD (LVEF ≤50%) were not receiving a beta-blocker (2,211 people in cohort). Of those receiving a beta-blocker, only 7% were at target beta-blockade. Within a year of follow-up, only 14% of patients were not receiving a beta-blocker (910 people in cohort). Furthermore, the percentage of patients achieving target dose beta-blockade reached 19%. The authors of this study comment that they consider that initiation and titration of heart failure medication, including beta-blockers, is a priority and adequate time should be allowed for treatments to have an effect before considering the addition of ivabradine. The manufacturer also stresses that first line therapies should be assertively up-titrated to target, or maximum-tolerated dose in the case of intolerance, before considering treatment with ivabradine (MS; pg 94).

Absolute contraindications to beta-blockers have been reported to be rare,[60] with only 3–5% of patients being unable to tolerate beta-blockers due to hypotension or bradycardia, both of which are related to the pharmacological activity of beta-blockers. Moreover, it has been reported that beta-blockers are not contraindicated in COPD, and that patients with COPD also receive benefit because of their high cardiovascular risk. NICE guideline CG108[19] recommends beta-blockers for patients with heart failure due to LVSD and co-morbid COPD without reversibility. Because most adverse effects associated with beta-blockers are related to their pharmacological activity, and are therefore dose-dependent, the strategy recommended in NICE guideline of CG108 of "start low and go slow" can frequently avoid adverse effects, such as hypotension or bradycardia.[60]

In the MS, the manufacturer presents the results of a *post hoc* analysis based on various thresholds of beta-blocker dose achieved in the full population of the SHIfT trial. The manufacturer asserts that these data show that the clinical effect of ivabradine is independent of level of beta-blockade achieved and is determined by the patient's baseline resting heart rate. Patients receiving higher doses of beta-blocker at randomisation are likely to have lower resting heart rates at baseline and therefore receive less relative benefit from ivabradine. A meta-regression analysis of 23 RCTs evaluating beta-blocker treatment of patients with heart failure identified that for every 5 bpm reduction in heart rate with beta-blocker use there was a 18% reduction in all-cause mortality.[14] The authors of this study commented that it is unclear whether there is additional benefit to up-titrating beta-blocker dose to the doses achieved in clinical trials of beta-blockers if a substantial heart rate reduction has already been achieved with a lower dose, or, conversely, increasing beta-blocker dose above recommended doses if heart rate reduction is minimal.

During the evaluation process for the licence extension of ivabradine, the CHMP noted that benefit associated with ivabradine seemed to be inversely related to level of beta-blockade.[36] However, the CHMP also noted that, although the effect of ivabradine was attenuated in patients achieving target

daily beta-blocker dose, there was a trend towards benefit with ivabradine and subsequently issued a licence for ivabradine with no stipulation on beta-blocker dose.

To inform the decision problem that is the focus of this STA, the ERG considered it important to investigate the potential association between beta-blocker dose and clinical benefit of ivabradine for the licensed population of the SHIfT trial.

During clarification, the ERG requested data on the primary composite outcome and key secondary outcomes for subgroups of the licensed population receiving varying percentages of target beta-blocker dose at randomisation: 0%; <25%; 25–<50%; 50–<100%; and ≥100%. In addition, for the licensed population, the ERG requested data for the RS_{BBDOSE} subgroup, as well as the subgroup of patients classified as receiving optimised but not target dose of beta-blocker. Summary effect sizes for analyses are presented in Tables 17 and 18.

Analyses of results based on percentage dose of beta-blocker achieved (Table 17) suggest [redacted] benefit of ivabradine compared with placebo [redacted]. In Section 4.3.1, it is noted that ivabradine is associated with greatest relative benefit in the cause-specific endpoints of hospitalisation for heart failure and heart failure death. Results of the exploratory analysis based on beta-blocker dose [redacted]. Ivabradine is associated with [redacted] of hospitalisation for worsening heart failure and reduction in death from heart failure irrespective of category of beta-blocker dose assessed, although some of the differences between groups [redacted]. However, for all other outcomes, including the primary composite outcome, the benefit of ivabradine [redacted], and, in some analyses, [redacted], which suggests a [redacted]. Considering the primary composite outcome, the exploratory analyses suggest [redacted] of ivabradine on the primary outcome for patients achieving target dose of beta-blocker. The ERG considers it important to note that, at target beta-blocker dose, ivabradine was associated [redacted] for the outcome of cardiovascular mortality, and [redacted].

The ERG also carried out a simple linear regression analysis. Results of this analysis identified a [redacted] correlation between increasing level of beta-blockade and a [redacted] in benefit with ivabradine use for the endpoint of cardiovascular mortality [redacted]plot presented in Appendix 7).

Based on comparative analysis of the effect size based on category of beta-blocker dose achieved for the outcomes of hospitalisation due to heart failure (Figure 2), death from heart failure (Figure 3), cardiovascular death (Figure 4), and all-cause mortality (Figure 5), the ERG speculated that there was

a marked difference in benefit at a threshold of [redacted] target beta-blocker dose. To investigate this, the ERG grouped patients into two groups: no beta-blocker or low dose (<25%); and moderate/high dose (≥25%, including target dose). In the none/low dose analysis, ivabradine was associated with [redacted] in most outcomes compared with placebo (Table 18); the difference between groups in non-heart failure cardiovascular death [redacted]. By contrast, in the moderate/high group, with the exception of the primary composite outcome and hospitalisation due to heart failure, most differences between groups [redacted].

Although the ERG appreciates the manufacturer's comment that variation in clinical effect of ivabradine is linked with baseline resting heart rate and not baseline level of beta-blockade, the ERG considers it important to note that, in the licensed population, [redacted] across the groups assessed based on various thresholds of beta-blockade (Table 19). In addition, the ERG notes that, [redacted] in resting heart rate of [redacted] with ivabradine compared with placebo across beta-blocker categories, there [redacted]. Thus, the ERG speculates that variations in clinical effect noted in the ERG's exploratory analysis could be associated with level of beta-blockade.

The ERG speculates that the results of the exploratory analyses suggest that there is uncertainty around the benefit of adding ivabradine to standard care for patients with a resting heart rate of ≥75 bpm and who are [redacted]. The ERG considers it important to highlight that its analyses are speculative and are based on subgroups of subgroups, and thus should be interpreted with caution.

Table 17. Summary of outcome data for ivabradine versus placebo based on percentage beta-blocker dose at baseline

Outcome	RR[a] (95% CI) for analyses by % target beta-blocker dose at baseline					
	0%	<25%	25–<50%	50–<100%	≥100%	Licensed population of the SHIfT trial
Primary outcome (composite)						
Cardiovascular death or hospitalisation for worsening HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81 (0.74 to 0.89)
Secondary outcomes						
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85 (0.74 to 0.98)
Hospitalisation for	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.74

worsening HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(0.65 to 0.83)
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85 (0.75 to 0.97)
Death from HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.63 (0.48 to 0.83)
Additional outcome						
Cardiovascular death excluding death from HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97 (0.82 to 1.15)

Absolute data for all analyses are presented in Appendix 8.

[a] RR calculated by ERG (Ivabradine vs placebo: for outcomes listed, RR <1.0 favours ivabradine).

Abbreviations used in table: bpm, beats per minute; ERG, Evidence Review Group; HF, heart failure; RR, relative risk; SD, standard deviation.

Figure 2. Relative risk meta-analysis plot for the outcome of hospitalisation due to worsening heart failure based on percentage beta-blocker dose at baseline

Figure 3. Relative risk meta-analysis plot for the outcome of death from heart failure based on percentage beta-blocker dose at baseline

Figure 4. Relative risk meta-analysis plot for the outcome of cardiovascular death based on percentage beta-blocker dose at baseline

Figure 5. Relative risk meta-analysis plot for the outcome of death from any cause based on percentage beta-blocker dose at baseline

Table 18. Summary of outcome data for ivabradine versus placebo based on various categories of beta-blocker dose at baseline

Outcome	RR[a] (95% CI) for analyses by % target beta-blocker dose at baseline						
	0%	None or low dose[b]	Moderate/ high dose[c]	RS_{BBdose} (≥50%)	Optimised[d]	Target (≥100%)	Licensed population of the SHIfT trial
Primary outcome (composite)							
Cardiovascular death or hospitalisation for worsening HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81 (0.74 to 0.89)
Secondary outcomes							
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85 (0.74 to 0.98)
Hospitalisation for worsening HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.74 (0.65 to 0.83)
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85 (0.75 to 0.97)
Death from HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.63 (0.48 to 0.83)
Hospitalisation for any cause	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.87 (0.81 to 0.94)
Hospitalisation for cardiovascular reason	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.84 (0.77 to 0.91)

Additional outcome							
Cardiovascular death excluding death from HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97 (0.82 to 1.15)

Absolute data for all analyses are presented in Appendix 8.

[a] RR calculated by ERG (Ivabradine vs placebo: for outcomes listed, RR <1.0 favours ivabradine).

[b] Subgroup of patients achieving <25% target beta-blocker dose.

[c] Subgroup of patients achieving ≥25% target beta-blocker dose.

[d] Optimised dose denotes patients who received beta-blocker at randomisation but did not achieve target dose (i.e., >0%–<100%).

Abbreviations used in table: bpm, beats per minute; ERG, Evidence Review Group; HF, heart failure; RR, relative risk; RS_{BBDOSE}, patients achieving ≥50% of the target beta-blocker dose; SD, standard deviation.

Table 19. Mean resting heart rate in subgroups based on percentage of target beta-blocker dose at randomisation

Percentage target beta-blocker dose	**Ivabradine**			**Placebo**		
	Mean resting heart rate at baseline (bpm ± SD)	Mean change in heart rate at last visit (bpm ± SD)	No. in analysis	Mean resting heart rate at baseline (bpm ± SD)	Mean change in heart rate at last visit (bpm ± SD)	No. in analysis
No beta-blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25–<50%	[redacted]		[redacted]	[redacted]		[redacted]
50–<100%	[redacted]		[redacted]	[redacted]		[redacted]
≥100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Data presented for subgroup of patients achieving <100% target dose beta-blocker (i.e., >0%–<100%).

Abbreviations used in table: bpm, beats per minute; SD, standard deviation.

Age

For the full population of the SHIfT trial (i.e., resting heart rate ≥70 bpm), the CHMP requested that the manufacturer carry out a *post hoc* subgroup analysis in patients aged ≥70 years.[36] As part of the clarification process, the ERG requested that the manufacturer provide data for patients aged ≥70 years in the licensed population. As the manufacturer notes with respect to results in the overall population of the SHIfT trial, the incidence of primary composite and main secondary endpoints is higher in patients aged ≥70 years than in the overall licensed population. The ERG's analyses indicate that ivabradine use is associated with [redacted] for all outcomes assessed (data presented in Appendix 9). For the primary composite outcome, ivabradine [redacted] risk of cardiovascular death or hospitalisation for worsening heart failure by [redacted] compared with placebo. In this subgroup of patients, ivabradine has [redacted] of the cause-specific outcome of death from heart failure [redacted]. The ERG considers it important to highlight that its analyses are speculative and are based on subgroups of subgroups, and thus should be interpreted with caution.

NYHA class

The licensed indication for ivabradine in heart failure specifies severity of heart failure of NYHA classes II to IV.[26] The ERG's analyses suggest that benefit of ivabradine in the licensed population is [redacted]. Ivabradine was associated with [redacted] in the primary and pre-specified secondary outcomes across all the NYHA subgroups (results presented in Appendix 10), with most differences between groups [redacted]. [redacted]. The ERG considers it important to note that the analysis of effect of ivabradine in patients of NYHA IV class is based on [redacted].

4.4 Conclusions of the clinical effectiveness section

4.4.1 Summary of results

- The submitted evidence is derived from the SHIfT trial.[33]
- The SHIfT trial assessed the effects of adding ivabradine versus adding placebo to optimised standard care for heart failure in patients in sinus rhythm with symptomatic heart failure (NYHA class II to IV) due to LVSD (LVEF ≤35%).
- The European licence for the use of ivabradine stipulates a resting heart rate of ≥75 bpm. In the SHIfT trial, 4,150 patients (63.8% of the overall trial population) had a resting heart rate of ≥75 bpm.
- Ivabradine is recommended as an adjuvant treatment to standard care.
- In the licensed population, addition of ivabradine was associated with a statistically significant reduction in the primary composite outcome of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure (HR 0.76; 95% CI: 0.68 to 0.85).
- Analyses of the individual components of the primary composite outcome indicate that reduction in hospitalisation for worsening heart failure is the key driver in the clinical effect of ivabradine observed for the primary composite outcome, with a statistically significant risk reduction of 30% for this endpoint relative to placebo (HR 0.70; 95% CI: 0.61 to 0.80; p <0.0001).
- The greatest relative benefit of ivabradine was associated with the cause-specific outcomes of hospitalisation due to worsening heart failure and death from heart failure (HR 0.61; 95% CI: 0.46 to 0.81).
- In the licensed population of the SHIfT trial, adverse effects associated with ivabradine treatment were bradycardia and phosphenes, both of which are recognised adverse effects of treatment. Compared with the placebo group, patients in the ivabradine group were: 6 times more likely to experience symptomatic bradycardia (Relative Risk [RR] 6.14; 95% CI: 3.50 to 10.78); 4 times more likely to experience asymptomatic bradycardia (RR 4.01; 95% CI: 2.60 to 6.20); and 5 times more likely to experience phosphenes (RR 5.31; 95% CI: 2.79 to 10.09).
- Exploratory subgroup analyses based on beta-blocker dose achieved suggest that the effect of ivabradine is [redacted] in patients who are able to [redacted].

- Additional subgroup analyses suggest that ivabradine effect is [redacted] of age and of severity of heart failure based on NYHA class.

4.4.2 Clinical issues

- Only one RCT is available for the comparison of adding ivabradine versus adding placebo to optimised standard care in the treatment of heart failure.
- Due to the limitation of a licence to patients with resting heart rate ≥75 bpm, submitted evidence is based on a subgroup of the overall population of the SHIfT trial.
- The ERG considers that there is limited evidence on the effectiveness of adding ivabradine to standard care for patients with NYHA class IV severity of heart failure. In addition, the ERG considers that the evidence base is limited for the addition of ivabradine for patients who have had a device implanted or who may be considered for CRT.
- Patients enrolled in the SHIfT trial have more severe heart failure than patients seen in general practice in the UK. However, patients in SHIfT have similar characteristics to those of other key heart failure trials.
- The ERG considers that there is uncertainty around the benefit of adding ivabradine to optimised standard care where patients are able to achieve at least 25% of target beta-blocker dose. Although a trend to [redacted] of ivabradine is observed, benefit seems to [redacted] with increasing beta-blocker dose and [redacted] achieved for all outcomes assessed in the ERG's exploratory analyses.

5 COST EFFECTIVENESS

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the manufacturer. The manufacturer provided a written submission of the economic evidence together with an electronic version of the Microsoft© EXCEL-based economic model. The location of the key economic information within the manufacturer's submission (MS) is summarised in Table 20.

Table 20. Summary of key information within the manufacturer's submission

Information	Section (MS)
Details of the systematic review of the economic literature	6.1
Model structure	6.2.2 to 6.2.6
Technology	6.2.7 to 6.2.8
Clinical parameters and variables	6.3
Measurement and valuation of health effects and adverse events	6.4
Resource identification, valuation and measurement	6.5
Sensitivity analysis	6.6
Results	6.7
Validation	6.8
Subgroup analysis	6.9
Interpretation of economic evidence	6.10
Strengths and weaknesses of economic evaluation	6.10.3 to 6.10.4
Abbreviations used in table: MS, manufacturer's submission.	

5.1 Summary and critique of the manufacturer's review of cost-effectiveness evidence

The manufacturer stated *a priori* that they did not expect to find evidence within published literature of the cost-effectiveness of ivabradine in patients with heart failure. Therefore, the manufacturer developed a wider search for economic evaluations in heart failure that could be used to inform modelling methods of a *de novo* cost-utility analysis. The manufacturer initially carried out a systematic search in 2011 of: MEDLINE; MEDLINE(R) In-Process; EMBASE; NHS-EED; EconLit; and Cochrane databases. In addition, the following Centre for Reviews and Dissemination (CRD) database were searched:

- Health Economic Evaluation Database;
- Database of Abstracts of Reviews and Effects;
- Health Technology Assessment Database.

To ensure that all publications relevant to the decision problem were captured, the manufacturer updated the search to 2012, limiting the period of the search from 2006 to 2012. The restriction applied was intended to exclude all but the most recent and relevant cost-effectiveness studies.

The final cost-effectiveness review identified 20 economic evaluations in heart failure, nine of which considered cardiac devices[71-79] and 11 considered pharmaceutical interventions.[80-90] Studies assessing pharmaceutical interventions were considered to be the most relevant to inform modelling methods used in the assessment of the relative cost-effectiveness of ivabradine. The studies considering pharmaceutical interventions: three used Markov models,[80-82] two used patient-level simulations[83;84] and six were reported as unclear but were presumed to be simple area under the curve models (or 2-state Markov cohort models).[85-90] Angiotensin-converting enzyme (ACE) inhibitors were evaluated in 5 of the studies considering pharmaceutical interventions,[81;84;85;87;89] and aldosterone antagonists were evaluated in 3.[80;88;90] The remaining 3 studies evaluated beta-blockers,[83] amiodarone,[86] and statins.[82]

Following the identification of studies that met the manufacturer's initial inclusion criteria, the manufacturer further limited the scope of the review to consider only Markov models using a lifetime time horizon.[80;82;86] Patient-level simulations were "not considered necessary for the ivabradine cost-effectiveness analysis". The manufacturer stated that all but two of the Markov cohort studies compared the intervention of interest with standard care; it should be noted that the definition of standard care varied across studies. The most common outcomes modelled were all-cause mortality, fatal and non-fatal cardiovascular events, hospitalisation and quality of life. Three of the Markov models used a lifetime time horizon,[80;82;86] one used a 10-year time horizon[81] and the remainder[85;87-90] adopted a "within trial" duration. Extrapolation in the models considering a lifetime time horizon used either parametric survival analysis based on randomised controlled trial (RCT) data or population epidemiological data (to extrapolate RCT data).

Table 21 summarises the pharmacological studies included in the manufacturer's review, which used a Markov framework, and a lifetime (or 10-year) time horizon. The manufacturer reported that these studies were used to inform the methods used to develop the *de novo* model that was implemented to assess the relative cost-effectiveness of ivabradine. Details of all the studies assessing pharmacological interventions that were identified by the manufacturer's review of the cost-effectiveness literature are provided in Appendix 11. The Evidence Review Group (ERG) is confident that all relevant databases were searched and appropriate search terms were used. Furthermore, the ERG is confident that no relevant studies have been missed. In addition, the ERG notes that the manufacturer's economic model was influenced by the economic studies identified from the systematic literature search, particularly regarding model structure and the extrapolation methods used.

Table 21. Summary of cost-effectiveness studies of pharmaceutical interventions in heart failure that used a Markov framework and a lifetime (or 10 year) time horizon

Author, year Country	Model framework and time horizon	Population	Data source clinical evidence	Intervention and comparators	Outcomes	Treatment effect
Mark,[86] 2006 USA	Area under the curve (2-state Markov cohort model) Lifetime	Patients aged >18 with NYHA class II, III chronic stable heart failure and LVEF <35%	SCH-HEFT (Sudden Cardiac Death in Heart Failure Trial)	Amiodarone, placebo or implantable ICD	All-cause mortality. Extrapolation Cox regression model	The treatment was modelled as a hazard ratio, which was a function of age and was assumed to remain constant over time
McKenna,[80] 2010 UK	State transition model: Markov cohort model Lifetime	Patients with post-MI heart failure	EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)	Spironolactone plus standard care, eplerenone plus standard care vs standard care	Death from cardiovascular events, death from any cause (all-cause mortality). Parametric Weibull regressions were used for extrapolation of cardiovascular death	Bayesian meta-analysis (indirect comparison) Non-cardiovascular mortality was estimated from UK age/sex-specific mortality rates.
Rosen,[82] 2010 USA	State transition model: Markov cohort model Lifetime	Patients with a history of both coronary heart disease and heart failure	Patient level data from Treating to New Targets (TNT) trial	Atorvastatin 80 mg/day (A80) vs atorvastatin 10 mg/day (A10)	Event specific all-cause mortality Mortality estimates were derived from literature from TNT trial	Treatment effects/events rate were derived from the TNT trial and extrapolated

Taylor,[81] 2009 UK	State transition model: Markov cohort model 10 years	Post-MI patients with LVSD, heart failure or both who are not suitable for ACE inhibitors	VALIANT (Valsartan Acute Myocardial Infarction)	Valsartan vs placebo	All-cause mortality. For placebo, event rates were estimated from a meta-analysis of clinical trials. Methods used to extrapolate data to 10 years not reported	Valsartan event rates were obtained from the VALIANT trial
Abbreviations used in table: ACE, angiotensin-converting enzyme; ICD, implantable cardioverter defibrillator; LVEF, left-ventricular ejection fraction; LVSD, left-ventricular systolic dysfunction; MI, myocardial infarction; NYHA, New York Heart Association; UK, United Kingdom; vs, versus.						

5.2 Summary and critique of manufacturer's submitted economic evaluation

The manufacturer developed a *de novo* model to evaluate the clinical and economic consequences of adding ivabradine to standard care. The model was constructed in Microsoft© EXCEL and was a two-state Markov cohort model. The manufacturer described this approach as "simple, flexible and consistent with previous approaches taken in cost-effectiveness studies of pharmaceutical interventions in heart failure". The ERG agrees that the modelling approach taken by the manufacturer is reasonable and is consistent with other published economic studies evaluating interventions used in the treatment of heart failure.[80;86;88] Furthermore, the ERG notes that the model was well constructed and largely transparent and that patient-level rather than cohort data have been used to improve the accuracy of the model's base case results. However, the ERG considers it important to highlight that an excessive use of coding made it difficult to stress test the model. In addition, the base case and subgroup results took an average of two hours to update.

5.2.1 NICE reference case checklist

Tables 22 and 23 summarise the ERG's quality assessment of the manufacturer's economic evaluation. The manufacturer's base case economic evaluation satisfies the requirements set out in the reference case 'Guide to the Methods of Technology Appraisal'[91] (Table 22) and the Philips[92] checklist (Table 23).

Table 22. NICE reference case[91]

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	Yes, however, the only trial identified was the SHIfT trial
Outcome measure	QALYs	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes QoL data were obtained from a sub-study of the main trial which used 5D was used in accordance with NICE guidance
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes The manufacturer carried out sensitivity analysis, scenario analysis and probabilistic sensitivity analysis
Abbreviations used in table: EQ-5D, EuroQol 5 dimensions questionnaire; NICE, National Institute for Health and Clinical Excellence; NHS, National Health Service; QoL; quality of life; QALY, quality adjusted life year.		

Table 23. Philips[92] checklist

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated
S2:Statement of scope/perspective	NICE scope was followed and addressed adequately; the manufacturer was requested to model the licensed population with ≥75 bpm. The ERG notes that the manufacturer has also assessed cost-effectiveness in a variety of relevant patient subgroups including beta-blocker usage.
S3: Rationale for structure	The ERG notes that the manufacturer justified the structure of the model they adopted based on previous publications of related technology appraisals. The ERG considers the model structure to be appropriate and well constructed. However, the use of individual patient level data whilst improving accuracy also impedes running time.
S4: Structural assumptions	The structural assumptions were transparent, and any bias was likely to be against ivabradine. In addition, a number of scenario and sensitivity analysis were undertaken to test the robustness of the different assumptions
S5: Strategies/comparators	All relevant comparators were evaluated and the optimisation of standard care was emphasised.
S6: Model type	Correct, cost-utility analysis
S7: Time horizon	Lifetime is in accordance with NICE methods guide.[91] Shorter time horizons have been used in sensitivity analysis
S8: Disease states/pathways	The ERG agrees with the pathways/health states modelled
S9: Cycle length	The ERG considers one month to be a reasonable cycle length to capture the consequences of model events. Half-cycle correction was included for only on-going costs
Data	
D1: Data identification	Data were taken from the whole population of the SHIfT trial. Where external data were used, it was systematically sourced, clearly described and justified by the manufacturer
D2: Premodel data analysis	Pre-model data analysis predominantly consisted of regression analyses which were systematically developed and rigorously assessed by experts in the disease area.
D2a: Baseline data	Baseline data were taken from the SHIfT trial. Conversion of yearly rates to quarterly probabilities was conducted using standard formulae. A half cycle correction was not included because of the short cycle length (one month) used
D2b: Treatment effects	Treatment effects for each outcome were estimated from the regression equations for that outcome, data from both treatment arms were used to develop the relative treatment effect inline with current guidance.[93] Extrapolation of treatment effects is clearly described and justified. Alternative assumptions on extrapolating methods and treatment effect generated from the SHIfT trial analysis were used in sensitivity analysis
D2d: Quality of life weights (utilities)	Derived from a SHIfT sub-study – PRO-SHIfT, which is well described. The PRO-SHIfT study report and the PRO-SHIfT full publication were provided

D3: Data incorporation	The manufacturer clearly described how data were used in the model, all sources are referenced and hard copies of referenced papers were provided. Standard distributions were used for different outcomes (e.g. the gamma distribution for costs).
D4: Assessment of uncertainty	The assessment of sensitivity was thorough and robust. Probabilistic, one-way sensitivity analysis and various scenario analysis were reported satisfactorily
D4a: Methodological	Appropriate analytical methods were used, and were supported with sensitivity and scenario analyses to test the robustness of the chosen base case approach
D4b: Structural	The manufacturer described deterministic sensitivity analysis and scenario analysis in detail
D4c: Heterogeneity	Heterogeneity was partially addressed by the analysis of different subgroups of patients
D4d: Parameter	Probabilistic sensitivity analysis was done to the satisfaction of the ERG
Consistency	
C1: Internal consistency	The model seems to be mathematically sound with no obvious inconsistencies. The manufacturer reported that the model was validated by experienced economists and biostatisticians
C2: External consistency	The model results are intuitive and conclusions are valid given the data presented. Both internal (SHIfT) and external data sources have been utilised and yielded consistent results
Abbreviations used in table: bpm, beats per minute; CSR, clinical study report; ERG, Evidence Review Group; MS, manufacturer's submission; NICE, National Institute for Health and Clinical Excellence; OR, odds ratio.	

5.2.2 Model structure

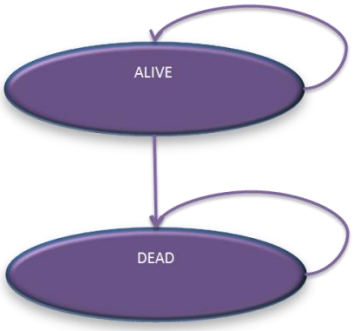
The manufacturer's *de novo* Markov cohort model included the health states of "alive" or "dead" (structure depicted in Figure 6). All patients in the "alive" health state are categorised into one of four New York Heart Association (NYHA) classes (I, II, III or IV). The NYHA system categorises patients based on the severity of their heart failure and consequently each class is associated with a different level of quality of life and resource use. NYHA class is not a health state *per se* as patients do not explicitly transition between NYHA classes. Instead a proportion of patients within the "alive" health state are assumed to be in each NYHA class. Similarly, the amount and type of hospitalisation experienced by patients in each treatment arm is captured not as a separate health state but as a proportion within the "alive" health state. The model uses a series of regression equations to capture the following outcomes:

- mortality: mortality is categorised as cardiovascular and non-cardiovascular mortality. Cardiovascular mortality is further categorised as heart failure-related or non-heart failure-related and includes death from unknown cause;
- NYHA distribution: patients were distributed across NYHA classes I, II, III and IV;
- hospitalisation: hospitalisation is grouped into hospitalisations resulting from heart failure, cardiovascular causes and all cause;
- health-related quality of life (HRQoL); HRQoL was estimated to vary according to NYHA class, amount of hospitalisation experienced and treatment received.

Adverse events were not explicitly modelled as the manufacturer considered that any costs associated with adverse events would be captured in the outcome of hospitalisation. Similarly, any decrements in quality of life, as a result of an adverse event, were assumed to be captured by the treatment covariate of the HRQoL regression equation.

The mean age of patients entering the model was 60 years and a lifetime time horizon was employed using a cycle length of 1 month. The model is largely driven by utility, which in turn is driven by the distribution of patients across NYHA class and the amount of hospitalisation experienced.

Figure 6. Model structure (reproduced from MS; pg 117)



The ERG considers that the manufacturer's model captures all the relevant outcomes associated with the treatment of heart failure.

5.2.3 Population

The manufacturer's base case analysis considers the licensed population (baseline resting heart rate ≥75 bpm). However, the manufacturer's model is constructed around regression equations developed from the entire patient population of the SHIfT trial. The manufacturer stated that the full dataset from SHIfT was used in order to avoid:

- breaking randomisation;
- reducing the predictive power of the risk equations (due to the smaller sample size).

However, the regression equations used to estimate mortality, hospitalisation and quality of life adjust for baseline resting heart rate (baseline resting heart rate is included as a covariate). Therefore, the model is able to estimate cost-effectiveness results in the licensed population by running the regression equations using patient-level data from only the licensed population. The ERG notes that the regression equations used to inform the distribution of patients across NYHA class do not adjust for baseline resting heart rate (this is discussed in Section 5.2.6).

The generalisability of the licensed population of the SHIfT trial to the UK is discussed in Section 4.2.1. To summarise, the ERG considers that the patients enrolled in SHIfT are younger, predominantly male, and have more severe heart failure than would be expected in UK clinical practice. Furthermore, patients in the SHIfT trial were hospitalised for worsening heart failure in the 12 months prior to enrolment and have a left-ventricular ejection fraction (LVEF) of ≤35% (LVEF ≤40% is typically used as a threshold for heart failure). Therefore, the population of SHIfT may represent a more severe patient population than routinely seen in clinical practice. The manufacturer has acknowledged the differences between SHIfT and the UK heart failure patient population. Furthermore, the manufacturer highlights that the characteristics of patients in the SHIfT trial are comparable with those in other key heart failure trials (see Appendix 1). The ERG's clinical advisors agreed that the population in SHIfT is more severe than would be seen in routine UK clinical practice but are comparable to other key heart failure trials.

In addition to the licensed population, the manufacturer's model considers the following populations:

- UK representative licensed population: the characteristics of patients in this analysis were similar to patients in the licensed population of SHIfT, with the exception of region (which was assumed to be Western Europe only), beta-blocker dose achieved (assumed to be at least half target dose) and age (median age 78 years);
- low risk licensed population: patients in this population had similar characteristics to the licensed population of SHIfT with the exception of smoking status (all patients were assumed to be non-smokers), beta-blocker dose achieved (all patients were assumed to achieve target dose), LVEF (patients were assumed to have an LVEF ≥33%) and duration of heart failure (assumed to be less than 0.6 years).

The relative cost-effectiveness of ivabradine in the UK representative and low-risk licensed populations are considered as part of the manufacturer's sensitivity analysis (see section 5.2.11). The ERG notes that the manufacturer has not carried out an analysis in a patient population with a disease severity reflective of the UK population. However, the ERG accepts the manufacturer's rationale that "values for patients characteristics which are beyond the SHIFT population range may generate unreliable results."(Manufacturer's model, user notes).

5.2.4 Interventions and comparators

The focus of the manufacturer's submission is the clinical and cost-effectiveness of adding ivabradine to standard care. Standard care was the only comparator defined as relevant in the NICE final scope.[35] The manufacturer highlights that standard care, particularly the use of beta-blockers and ACE inhibitors, should be optimised before treatment with ivabradine is considered. For the purposes of this submission, standard care includes all heart failure medications stipulated in NICE guideline CG108[19] on the management of heart failure.

The ERG is satisfied that the drugs constituting standard care in the SHIfT trial and those used in the economic model, are appropriate and relevant to UK clinical practice. Furthermore, based on expert clinical advice, and evidence from SHIfT (discussed in Section 4.3.4), the ERG supports the manufacturer's assertion that standard therapy should be optimised ahead of ivabradine treatment.

5.2.5 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and Personal Social Services (PSS). In accordance with the NICE reference case,[91] the model considered a lifetime time horizon and both costs and benefits were discounted at 3.5% per annum.

5.2.6 Estimated treatment effectiveness

The manufacturer's model captures the effect of treatment (ivabradine plus standard care versus standard care alone) on: mortality; the distribution of patients across NYHA classes; and the rate of hospitalisation. In the base case, the effectiveness of each treatment is derived from a series of regression equations based on the whole population of the SHIfT trial.[33] The differential effect of treatment with ivabradine plus standard care versus standard care alone is accounted for in each regression equation by a treatment-specific covariate(s). This section provides an overview of the regression analysis techniques employed by the manufacturer. Followed by details of the development and implementation of the regression equations for each of the following outcomes:

- mortality;
- the distribution of patients across NYHA class;
- hospitalisation.

Extrapolation is discussed in Section 5.2.7.

Regression analysis techniques

Regression analysis is frequently used to investigate the relationship between a particular outcome (e.g. mortality), known as the dependant variable and potential predictors of this outcome (e.g. patient's age, heart rate, etc.), known as the independent variables. Regression analysis techniques can be used to develop a regression equation from observed data, in which each independent variable is associated with a coefficient; this coefficient serves to predict the value of the dependant variable based on unilateral changes in the independent variable. The manufacturer uses the following forms of regression analysis in their submission:

- parametric regression analysis;
- generalised ordered logistic regression;
- Poisson regression;

- mixed regression.

Parametric regression involves fitting a parametric distribution to the observed data (e.g. the exponential) and developing a regression equation with covariates that predict the parameter values of the chosen distribution.

Logistic regression models (proportional odds models) are a technique used to assess the impact of covariates on categorical data. Essentially, a separate regression equation is developed assessing the impact of covariates on each category and the results of each analysis pooled to give the overall result. This model relies on the assumption that the relationship between any two outcome categorisations is the same (the proportional odds assumption).

Poisson regression is a regression methodology used to estimate count data (e.g. number of hospitalisations). The logarithm of the count data is modelled with a standard linear regression equation.

Mixed regression is a technique capable of accounting for datasets of repeated observations over time. A mixed regression model accounts for both fixed and random effects on the dependent variable. Fixed effects parameters (e.g. population characteristics) are the same each time they are collected, whereas, random effects parameters are sample dependent.

Further details of statistical terms and concepts are provided in the glossary on pg9.

Mortality

The manufacturer's model considered both cardiovascular and non-cardiovascular mortality. Estimates of non-cardiovascular mortality were taken from interim UK life tables[(94)] in preference to data from the SHIfT trial.[(33)] The manufacturer states that data from UK life tables, as opposed to data from the SHIfT trial, were used to inform non-cardiovascular mortality because UK life tables provided a larger UK-specific dataset. Furthermore, treatment with ivabradine plus standard care was assumed to have no effect on non-cardiovascular mortality. However, as part of the clarification process, the ERG requested that the manufacturer provide a sensitivity analysis that used non-cardiovascular mortality from the SHIfT trial. In response to this request, the manufacturer provided a univariate sensitivity analysis that used "a non-cardiovascular mortality endpoint adjusted for patient baseline characteristics" (Manufacturer's clarification response pg 21). The impact of this sensitivity analysis was to increase the base case ICER by £1,079. The ERG notes that the risk of non-cardiovascular death is higher in SHIfT than in UK life tables. Therefore, patients in each arm of the model are less likely to survive and experience the benefit of treatment, resulting in an increased ICER for ivabradine (the more effective treatment). However, the ERG accepts the manufacturer's

use of UK-specific data in the base case as this is standard practice in heart failure cost-effectiveness analyses.[80;87]

Cardiovascular mortality

Within the model, cardiovascular mortality was disaggregated into heart failure mortality and cardiovascular mortality excluding mortality due to heart failure (which included death from unknown cause corresponding to non-violent or traumatic deaths for which it was not possible to specify whether they were cardiovascular or not). This enabled the effect of treatment to be limited to heart failure mortality, as required for one of the manufacturer's sensitivity analyses (see Section 5.2.11). Therefore, two regression equations were developed to estimate the risk of cardiovascular mortality and the risk of heart failure mortality; the risk of non-heart failure cardiovascular mortality was calculated as the difference between the risk of cardiovascular and the risk of heart failure mortality. Parametric regression equations based on 29 months of observed data (from the entire patient population of SHIfT) were used to estimate the risk of cardiovascular and heart failure mortality.

The relative effect of treatment with ivabradine for each outcome (cardiovascular and heart failure mortality) was estimated from the parametric regression equation for that outcome. In line with recommendations from the NICE decision support unit (DSU),[93] each regression equation was based on data from both treatment arms (rather than a separate regression equation for each trial arm). Furthermore, each regression equation included heart rate as an independent variable, which enabled the model to predict the risk of cardiovascular outcomes for the licensed population (heart rate ≥75 bpm).

The manufacturer acknowledged that for the "within trial" period the most reliable estimate of patient survival may be obtained from the observed data. However, parametric regression was used in the base case for the "within trial" and extrapolated period. The manufacturer's rationale for using parametric regression in the base case is displayed in Box 7.

Box 7. Manufacturer's rationale for using parametric regressions to estimate cardiovascular and heart failure mortality risks in the "within trial" period

It is recognised that in general the most reliable estimate of the patient survival in the "within-trial" period may be obtained from the observed data, a parametric regression has been used in this study to:

- Provide the relative treatment effect of ivabradine and permit specific exploration of the interaction between treatment and baseline heart rate evidenced in SHIfT;
- Provide cost-effectiveness results relevant to the licensed indication (patients with a baseline heart rate ≥75 bpm);
- Provide an estimate of the natural history of heart failure (underlying baseline risk of mortality without ivabradine) and explore differences in the underlying baseline mortality risk due to patient heterogeneity and to permit subgroup analyses;
- Extrapolate SHIfT estimates beyond the SHIfT study period.

The ERG notes that the incremental cost-effectiveness ratio (ICER) obtained using the observed Kaplan-Meier data for the "within trial" period was £794 more than the base case ICER. Therefore, the ERG considers the use of parametric equations for the "within trial" period to favour the ivabradine model arm. However, the difference is unlikely to affect any conclusions drawn from the model's cost-effectiveness results.

Cardiovascular regression equation

A full description of the process undertaken by the manufacturer to develop the cardiovascular regression equation is provided in Section 6.3.1 of the MS. To summarise, the manufacturer:

1. considered the fit of a range of parametric distributions (see below);
2. compiled a list of potential covariates based on the SHIfT trial protocol, a previously published heart failure risk equation[95] and expert clinical advice;
3. examined the relationship between continuous variables and cardiovascular mortality to ensure any relationship between these variables was accurately represented (i.e., checked whether the relationship was linear, quadratic, cubic and/or centred on the mean);
4. checked the categorisation of binary and categorical variables to ensure appropriate categorisation;
5. used a backwards selection process, validated by a forward selection process to develop the regression equation;
6. assessed the correlation of all included variables and tested any correlated variables for collinearity;
7. assessed the significance of the interaction between the treatment covariate and variables with prior clinical evidence of treatment effect modification;
8. refined the regression equation using steps 5 and 6 in conjunction with assessment of model fit (log likelihood test) and expert clinical opinion.

The choice of parametric distribution used to construct the regression equations was given careful consideration. The following distributions were considered:

- exponential;
- Weibull;
- log-logistic;
- lognormal;
- Gompertz;
- gamma.

The fit of each distribution to the observed data from the SHIfT trial was assessed using: visual plots of the resultant curves versus the Kaplan-Meier data; Akaike's information criterion (AIC), Bayesian information criterion (BIC); and the clinical plausibility of the tail of the survival curve. Following these assessments, the Gompertz distribution was selected for use in the base case because it provided conservative estimates of long-term survival: curves from the exponential and Weibull distributions were used in sensitivity analyses.

All the parametric distributions implemented in the manufacturer's model were based on the assumption of proportional hazards (PH). That is, the relative effect of ivabradine treatment was assumed to remain constant over time. The assumption of a constant relative treatment effect over time is pivotal to the manner in which the parametric distributions have been implemented. Therefore, any violation of this assumption affects the validity of any outcomes estimated by the manufacturer's model. The manufacturer proposed that evidence to support the assumption of PH was available from SHIfT and a 7-year extension study of ivabradine in patients with angina.[12;68] Furthermore, the assumption of PH was tested using plots of the Schoenfeld residuals and log cumulative hazards; these showed no evidence of the violation of the PH assumption. In addition, sensitivity analysis was carried out to investigate the impact of assuming a reduction in the effect of treatment over time (this is discussed further in Sections 5.2.7 and 5.2.11). The ERG notes that the manufacturer has submitted relatively robust evidence that the PH assumption is upheld and considers the assumption of a constant relative treatment effect to be reasonable. The ERG notes that the manufacturer has adhered to the recommendations of the NICE DSU technical report in the development and implementation of the parametric regression equations.[93] Furthermore, the ERG notes that the use of the Gompertz distribution results in higher ICERs than the exponential and Weibull distributions and therefore may be considered conservative (Table 24).

Table 24. Comparison of ICERs from the lifetime time horizon obtained with the different parametric distributions used in the manufacturer's model

Parametric distribution	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)[a]
Gompertz	2,376	0.280	8,498
Exponential	3,004	0.363	8,267
Weibull	2,955	0.359	8,237

[a] ICERs have been calculated individually for each patient and then averaged to give an overall ICER value.

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

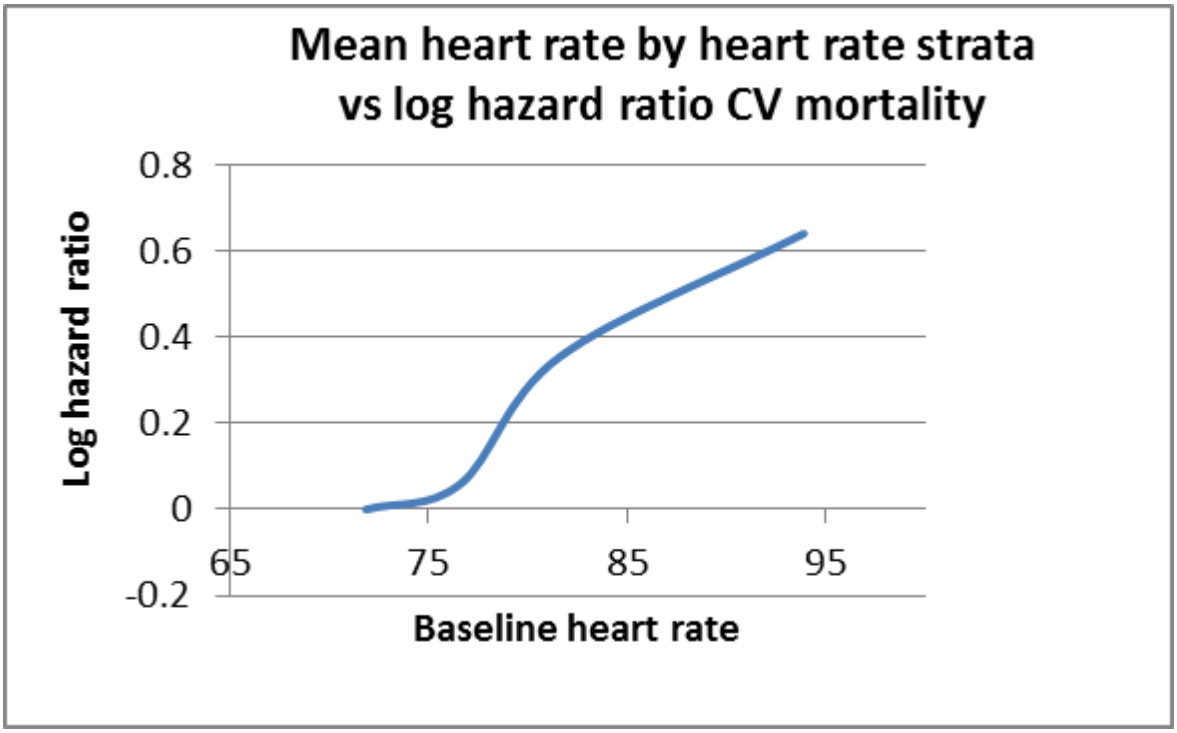
The variables assessed for inclusion in the manufacturer's regression analysis are displayed in Box 8.

Box 8. Potential variables considered by the manufacturer for inclusion in the cardiovascular regression equation (reproduced from MS; pg 125)

- Baseline socio demographic and clinical characteristics (age, sex, NYHA class, heart failure duration, LVEF, smoking status, alcohol use, diabetes, race, BMI);
- Baseline use of heart failure medications (beta-blockers, ACE inhibitors, aldosterone antagonists, loop diuretics (dose/kg/day), angiotensin receptor blocker, cardiac glycosides, allopurinol);
- Prior use of other cardiac therapies: cardiac resynchronisation, implantable cardiac device (ICD), conventional bradycardia-indicated pacemaker;
- Medical history: prior event (myocardial infarction, stroke, coronary artery disease, atrial fibrillation, renal disease, hypertension)
- Patient biological characteristics (serum sodium, potassium, creatinine clearance, cholesterol systolic blood pressure).

In the final regression equation, the continuous variables of age, body mass index, resting heart rate, systolic blood pressure and serum sodium were considered to be linear and centred on the mean. The manufacturer highlights that particular attention was given to the relationship between baseline resting heart rate and cardiovascular mortality. Following extensive examination of this relationship, the manufacturer concluded that (based on data from the whole trial population of SHIfT) the relationship between baseline resting heart rate and cardiovascular mortality was cubic (see Figure 7). However, to ease the implementation of this variable into the regression analysis (and following that into the manufacturer's economic model), the relationship between heart rate and cardiovascular mortality was assumed to be linear. The manufacturer asserts that this assumption is a conservative assumption, as the risk of cardiovascular mortality is underestimated in the licensed (heart rate ≥75 bpm) population.

Figure 7. Plot of mean baseline resting heart rate against log hazard ratio (cardiovascular mortality) in patients with baseline resting heart rate ≥75 bpm (reproduced from MS; Figure 13, pg 126)



The ERG considers that the manufacturer provided reasonable justification for assuming a linear relationship between heart rate and cardiovascular mortality. The ERG is also satisfied that the assumption of linearity is likely to underestimate the risk of cardiovascular mortality and therefore temper the potential for ivabradine to reduce this risk. Furthermore, the ERG notes that the manufacturer has carried out a sensitivity analysis using the assumption of a cubic relationship between baseline resting heart rate and cardiovascular mortality. The manufacturer reported that this sensitivity analysis resulted in an ICER of approximately £1,250 less than the base case. However, the manufacturer did not submit a version of the model that employed this sensitivity analysis. Therefore, the ERG has not been able to validate the results of this sensitivity analysis.

Of the binary and categorical variables included in the manufacturer's regression equation, the original categorisation used in the SHIfT trial was generally maintained. The exceptions to this were LVEF, heart rate, beta-blocker use and tobacco use. LVEF and heart rate were treated as continuous variables in the final regression equation. Tobacco use was re-categorised from the three categories of yes, stopped and never to two categories of yes or stopped and never. Beta-blocker use was re-categorised from the three groups used in the SHIfT trial analysis into the following four groups:

- no beta-blockade use;
- beta-blockade use at less than half (<50%) target dose;

- beta-blockade use less than target dose but greater than or equal to half target dose (≥50%–<100%);
- beta-blockade use at at least target dose (≥100%).

The initial regression equation produced by the stepwise elimination process (backward selection validated by forward selection, see Glossary of statistical terms and concepts for more details) was refined by assessing variables for correlation, collinearity and face validity. In addition, the value of including variables of borderline significance ($0.05 < p < 0.1$) and the interaction effect of treatment was assessed.

The correlation matrix (produced as part of the regression analysis) was used to identify potentially correlated variables. Collinearity between variables was assessed by examining the regression equation with and without the inclusion of each potentially correlated variable. The impact of removing each correlated or borderline significant variable on overall model fit (using the log likelihood test) and on all other covariates (in terms of direction and magnitude of effect) was considered. Those variables that, when included, enhanced model fit or provided coefficients (particularly for treatment effect) of greater face validity were retained in the regression equation. In the case of collinearity, the variable with the strongest influence on cardiovascular mortality was retained in the regression equation.

Based on prior clinical evidence,[33] the interaction effect of treatment (or modification of treatment effect) was considered in relation to age, ischaemic heart failure, beta-blocker use and baseline resting heart rate. Examination of the regression equations indicated that ivabradine treatment effect was statistically significantly modified by baseline resting heart rate. However, the treatment effect of ivabradine was not significantly modified by age, presence of ischaemia or beta-blocker use. The manufacturer claimed that the absence of significant modification of ivabradine treatment effect with beta-blocker therapy (over and above that of heart rate) was consistent with the results of a clinical analysis (reported in Section 4.3.1). Although, the ERG notes that there is uncertainty around the effect of beta-blocker dose on the effect of ivabradine in the licensed population. This is discussed further in Section 4.3.4.

The final regression equation is displayed in Table 25. All the variables included in the model were checked by clinical experts to ascertain their internal and external validity. Furthermore, the overall model fit was evaluated by examining the Cox-Snell residuals for all included variables. Schoenfeld residuals were plotted to test the propriety of the PH assumption for all included variables and the model's predictive power was tested using the Harrell's concordance measure (Concordance was >70%; 95% confidence interval [CI]: 0.68 to 0.72). The ERG considers that the manufacturer's regression equation for the risk of cardiovascular mortality has been derived using systematic and

rigorous methodology. Furthermore, the ERG considers the assumptions used in the derivation of the regression equation to be reasonable and any bias is likely to be against treatment with ivabradine.

Table 25. The final regression equation for the risk of cardiovascular mortality (adapted from MS; Table 38, pg 133)

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment effect	0.94	–0.06	0.07	0.38	–0.19	0.07
Female	0.69	–0.37	0.08	0.00	–0.54	–0.21
Aldosterone antagonists	1.28	0.25	0.07	0.00	0.10	0.39
Digitalis use	1.32	0.28	0.07	0.00	0.13	0.43
Loop diuretic (dose/kg/day)	1.12	0.11	0.03	0.00	0.06	0.17
Lipid medications	0.79	–0.23	0.07	0.00	–0.36	–0.10
Systolic BP[a]	0.99	–0.01	0.00	0.00	–0.01	–0.01
NYHA III (vs II)	1.30	0.26	0.07	0.00	0.13	0.40
NYHA III (vs II)	2.76	1.02	0.16	0.00	0.69	1.34
HF duration ≥0.6<2 years vs <0.6 years	1.51	0.41	0.11	0.00	0.20	0.62
HF duration ≥2<4.8 years vs <0.6 years	1.73	0.55	0.11	0.00	0.34	0.76
HF duration >+4.8 years vs <0.6 years	1.98	0.68	0.10	0.00	0.48	0.89
LVEF ≥26%<30% vs <26%	0.86	–0.15	0.09	0.12	–0.33	0.04
LVEF ≥30%<33% vs <26%	0.71	–0.34	0.09	0.00	–0.51	–0.16
LVEF ≥33% vs <26%	0.59	–0.53	0.09	0.00	–0.71	–0.35
Heart rate bpm[a]	1.02	0.02	0.00	0.00	0.01	0.03
Beta-blocker use <half td	0.99	–0.01	0.10	0.93	–0.20	0.18
Beta-blocker use ≥half td<td	0.71	–0.34	0.11	0.00	–0.56	–0.11
Beta-blocker use ≥td	0.69	–0.37	0.12	0.00	–0.61	–0.13
Age (years)[a]	1.02	0.02	0.00	0.00	0.01	0.03
Prior stroke	1.28	0.24	0.11	0.02	0.04	0.45
Sodium[a]	0.98	–0.02	0.01	0.04	–0.04	–0.001
Potassium	1.20	0.19	0.08	0.02	0.03	0.34
Treatment and heart rate interaction	0.99	–0.01	0.01	0.07	–0.03	0.001
_cons	0.00	–5.53	0.16	0.00	–5.85	–5.21
_gamma	1.01	0.01	0.00	0.01	0.002	0.02

[a] Variables centred on the mean.

Abbreviations used in table: BP, blood pressure; bpm, beats per minute; cons, constant; HF, heart failure; HR, hazard ratio; kg, kilogramme; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; MS, manufacturer's submission; NYHA, New York Heart Association; SE, standard error; td, target dose; UCI, upper confidence interval.

The final cardiovascular regression equation indicates that female gender, treatment with lipid medications, lower systolic blood pressure, an increase in LVEF of at least 4% (from a baseline LVEF of 26%), beta-blockade at ≥50% target dose and an increase in serum sodium levels (an increase in serum sodium levels indicates the reduction of fluid retention) are individually associated with a statistically significant ($p < 0.05$) reduction in the risk of cardiovascular mortality. Whereas, treatment with ivabradine, an increase in LVEF of less than 4% (from a baseline of 26%) and beta-blockade at <50% target dose are associated with a statistically non-significant ($p > 0.1$) reduction in the risk of cardiovascular mortality. Furthermore, there is evidence that the interaction of treatment and resting heart rate is associated with further reduction in the risk of cardiovascular mortality ($0.05 < p < 0.1$).

Regarding variables that are associated with an increase in the risk of cardiovascular mortality (i.e., those with positive coefficients), the following covariates exhibited a statistically significant ($p < 0.05$) effect on the overall risk of cardiovascular mortality:

- treatment with aldosterone;
- digitalis use;
- loop diuretics (dose/kg/day);
- worsening disease (as classified by NYHA class);
- heart failure of longer duration;
- increasing heart rate (bpm),
- increasing age (years);
- history of stroke;
- decrease in serum potassium (a decrease in serum potassium is a common consequence of the use of diuretics for fluid retention).

In the MS, the manufacturer noted that the use of particular heart failure medications was associated with poorer outcomes, which was contrary to clinical expectations. A particular example was the use of aldosterone antagonists. However, the manufacturer proposed that as "aldosterone was not recommended in a heart failure indication at the time of the SHIfT trial it is likely that patients taking these medications were of poorer health than the average SHIfT patient, and this effect, rather than the true effect of aldosterone use, was captured". Following consultation with clinical experts, the ERG agrees with the manufacturer that this finding may be because aldosterone was not recommended in heart failure during recruitment for the SHIfT trial.

The ERG considers it important to note that the manufacturer's regression analysis suggests that beta-blocker therapy of at least 50% of target dose is associated with a statistically significant reduction in the risk of CV mortality. Whereas, contrary to the clinical analysis of SHIfT, the manufacturer's regression analysis suggests that treatment with ivabradine is associated with a non-significant reduction in the risk of cardiovascular mortality (Table 25). The absence of a significant treatment

effect for ivabradine in the regression analysis may be a result of the adjustment for patient characteristics not accounted for in the clinical analysis. However, the ERG notes that the absence of a significant treatment effect for ivabradine may also be because the regression equation is likely to under-predict the risk of cardiovascular mortality. Consequently, the potential for ivabradine to reduce the risk of cardiovascular mortality is restricted; as can be seen in the comparison of hazard ratios predicted from the economic model with hazard ratios estimated from the clinical trial data (Table 26). However, the under-prediction of cardiovascular mortality risk could also be expected to affect the statistical significance of the optimisation of beta-blocker therapy. Therefore, the ERG considers that evidence from the manufacturer's regression analysis further supports the manufacturer's assertion of the importance of optimising beta-blocker therapy ahead of treatment with ivabradine.

Table 26. The relative effect of treatment with ivabradine plus standard care versus standard care on the risk of cardiovascular mortality

Analysis	HR
Parametric regression analysis carried out for the manufacturer's model	0.90
Clinical analysis[33]	0.83
Abbreviation used in table: HR, hazard ratio.	

Heart failure mortality regression equation

As discussed above, cardiovascular mortality was disaggregated into heart failure mortality and non-heart failure cardiovascular mortality. Therefore, a separate regression equation was developed for heart failure mortality based on the patient population of the SHIfT trial.[33] The development details of the parametric regression equation for heart failure mortality and the final heart failure mortality regression equation are not provided in the MS. However, the manufacturer does indicate that the development of the regression equation for heart failure mortality was undertaken using the same methodology as for the cardiovascular mortality regression equation. The final regression equation for total heart failure mortality and the covariates that were included are presented in Table 27.

Table 27. The final regression equation for heart failure mortality (reproduced from the manufacturer's model)

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment effect	0.7798	–0.2487	0.1304	0.0560	–0.50	0.01
Digitalis use	1.5609	0.4453	0.1341	0.0010	0.18	0.71
Loop diuretic (dose/kg/day)	1.1836	0.1685	0.0449	0.0000	0.08	0.26
Lipid medications	0.7610	–0.2731	0.1274	0.0320	–0.52	–0.02
Systolic BP[a]	0.9747	–0.0256	0.0044	0.0000	–0.03	–0.02
NYHA III (vs II)	1.3166	0.2751	0.1351	0.0420	0.01	0.54
NYHA IV (vs II)	2.4133	0.8810	0.2961	0.0030	0.30	1.46

HF duration >=0.6<2 yrs vs <0.6 yrs	1.4001	0.3365	0.2161	0.1190	–0.09	0.76
HF duration ≥2<4.8 yrs vs <0.6 yrs	2.1387	0.7602	0.2045	0.0000	0.36	1.16
HF duration >4.8 yrs vs <0.6 yrs	2.3380	0.8493	0.1998	0.0000	0.46	1.24
LVEF ≥26%<30% vs <26%	0.6580	–0.4185	0.1701	0.0140	–0.75	–0.09
LVEF ≥30%<33% vs <26%	0.4462	–0.8071	0.1768	0.0000	–1.15	–0.46
LVEF ≥33% vs <26%	0.4110	–0.8892	0.1772	0.0000	–1.24	–0.54
Heart rate bpm[a]	1.0291	0.0287	0.0068	0.0000	0.02	0.04
Beta-blocker use <half td	0.7226	–0.3249	0.1647	0.0490	–0.65	–0.002
Beta-blocker use ≥half td<td	0.5481	–0.6013	0.1980	0.0020	–0.99	–0.21
Beta-blocker use >=td	0.4283	–0.8480	0.2330	0.0000	–1.30	–0.39
Sodium[a]	0.9442	–0.0574	0.0173	0.0010	–0.09	–0.02
ACE inhibitor or ARB	0.7600	–0.2744	0.1844	0.1370	–0.64	0.09
Age (years)[a]	1.0257	0.0253	0.0058	0.0000	0.01	0.04
Treatment and heart rate interaction	0.9811	–0.0191	0.0110	0.0830	–0.04	0.002
Cons	0.0018	–6.3020	0.3215	0.0000	–6.93	–5.67
Gamma	1.0220	0.0218	0.0076	0.0040	0.01	0.04

[a] Variables centred on the mean.

Abbreviations used in table: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats per minute; Cons, constant; HF, heart failure; HR, hazard ratio; kg, kilogramme; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; SE, standard error; td, target dose; UCI, upper confidence interval.

The final heart failure regression equation indicates that treatment with lipid medications, lower systolic BP, an increase in LVEF of at least 4% (from a baseline LVEF of 26%), beta-blocker use (at any dose) and an increase in serum sodium levels are individually associated with a statistically significant ($p < 0.05$) reduction in the risk of heart failure mortality. Treatment with ACE inhibitor or ARB is associated with a non-significant ($p > 0.1$) reduction in heart failure mortality. Furthermore, treatment with ivabradine and the interaction effect of heart rate and treatment are associated with a reduction in the risk of heart failure mortality of borderline significance ($0.05 < p < 0.1$).

Regarding variables that are associated with an increase in the risk of heart failure mortality (i.e., those with positive coefficients), the following covariates exhibited a statistically significant ($p < 0.05$) effect on the overall risk of heart failure mortality:

- digitalis use;
- loop diuretics (dose/kg/day);
- worsening disease (as classified by NYHA class);
- heart failure duration of ≥2 years (compared with <0.6 years);

- increasing heart rate (bpm);
- increasing age (years).

Based on advice from clinical advisors, the ERG considers that the regression equation for heart failure mortality is clinically plausible.

The ERG considers it important to highlight that the manufacturer's regression analysis suggests that beta-blocker therapy of any level is associated with a statistically significant reduction in the risk of heart failure mortality. Moreover, the statistical significance of the ivabradine treatment effect is lower in the regression equation compared with the clinical analysis (Table 27). This reduction in statistical significance may be a result of the adjustment for patient characteristics in the regression equation not accounted for in the clinical analysis. However, the ERG notes that the reduction in the significance of the treatment effect for ivabradine may also be because the regression equation is likely to under-predict the risk of heart failure mortality. Consequently, the potential for ivabradine to reduce the risk of heart failure mortality is restricted; as can be seen in the comparison of the hazard ratio estimated from the clinical analysis with the hazard ratio estimated from the economic model (Table 28). However, the under-prediction of heart failure mortality risk could also be expected to affect the statistical significance of beta-blocker therapy. Therefore, the ERG wishes to highlight the importance of the manufacturer's assertion that beta-blocker therapy should be optimisation ahead of treatment with ivabradine.

Table 28. The relative effect of treatment with ivabradine plus standard care versus standard care on the risk of heart failure mortality

Analysis	HR
Parametric regression analysis carried out for the manufacturer's model	0.78
Clinical analysis[33]	0.61
Abbreviation used in table: HR, hazard ratio.	

Implementation of the risk of cardiovascular mortality into the economic model

In order to implement the estimates of cardiovascular (or heart failure) mortality risk, the manufacturer calculated the survival function S(t) for each of the parametric regression equations implemented in the model as follows:

- Gompertz: S(t) = exp{(-λt)p^-1(exp(pt)-1)};
- Weibull: S(t) = exp{(-λt)p};
- exponential: S(t) = exp{-λt}.

Where: t = time; λ = location parameter; p = shape parameter. For details of how the location and shape parameters were calculated from the regression equations, see Appendix 12.

Thereafter, transition probabilities were estimated using standard formulae:

$$tp(t) = \frac{S(t)}{S(t-1)}$$

NYHA class

The distribution of patients by NYHA class within the "alive" health state was estimated with a generalised ordered logistic regression model (Table 29). The regression model was based on the entire patient population of the SHIfT trial and included covariates for time and treatment. Time was included as a covariate based on the clinical expectation that disease severity would worsen over time; a reasonable assumption given the progressive nature of heart failure. Treatment was included as a covariate based on evidence from SHIfT that ivabradine has a disease-modifying effect (see Section 4.3.1). The ordered logistic regression model used in the manufacturer's base case model is presented in Table 29.

Table 29. Ordered logistic regression model to estimate the distribution of patients in each NYHA class (reproduced from MS; Table 39, pg 134)

Description	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment NYHA II	–0.1681	0.0922	0.0680	–0.35	0.01
Logmonths NYHA II	–0.6288	0.0270	0.0000	–0.68	–0.58
Cons NYHA II	4.5662	0.0931	0.0000	4.38	4.75
Treatment NYHA III	–0.0933	0.0473	0.0480	–0.19	–0.0006
Logmonths NYHA III	–0.2106	0.0091	0.0000	–0.22	–0.19
Cons NYHA III	0.0305	0.0346	0.3780	–0.04	0.10
Treatment NYHA IV	–0.3666	0.1571	0.0200	–0.67	–0.06
Logmonths NYHA IV	–0.0476	0.0420	0.2570	–0.13	0.03
Cons NYHA IV	–3.9546	0.1248	0.0000	–4.20	–3.71
Abbreviations used in table: Cons, constant; LCI, lower confidence interval; NYHA, New York Heart Association; SE, standard error; UCI, upper confidence interval.					

Implementation of estimated NYHA distribution into the economic model

The treatment and time (logmonths) coefficients of NYHA classes II to IV relate to the likelihood of a patient moving into that particular NYHA class from the previous NYHA class (e.g. from NYHA class I to NYHA class II). These coefficients are used in standard formulae to calculate the cumulative odds of moving into each class as follows:

$$CO_{NYHA} = \exp(\lambda_{NYHA} + \ln(t).\log mths_{NYHA} + t.Treat_{NYHA})$$

Where CO_{NYHA} is the cumulative odds of moving into a particular NYHA class, t is time in months, λ_{NYHA}, $logmths_{NYHA}$, and $Treat_{NYHA}$ are the constant, time coefficient, and treatment coefficient associated with that particular NYHA class (estimated from the regression).

The cumulative odds of moving into NYHA class II, III or IV are subsequently converted into cumulative probabilities as follows:

$$CP_{NYHA} = \frac{CO_{NYHA}}{1 + CO_{NYHA}}$$

Where CP_{NYHA} is the cumulative probability of moving into a particular NYHA class.

For example, the cumulative odds of patient classified as NYHA II moving into NYHA class III after 10 months of treatment with ivabradine in addition to standard care would be:

$$CO_{NYHA\_III} = \exp(0.0305 + \ln(10).-0.2106 + 10.-0.093) = 0.2497$$

Thence, the cumulative probability of moving into NYHA class III from NYHA class II would be:

$$CP_{NYHA\_III} = \frac{CO_{NYHA\_III}}{1 + CO_{NYHA\_III}} = \frac{0.2497}{1 + 0.2497} = 0.1998$$

The cumulative probabilities calculated for each NYHA class are then applied to the proportion of patients currently in each NYHA class to determine the proportion of patients remaining in that class for the following cycle.

The ERG considers the manufacturer's approach to estimating the distribution of patients by NYHA to be reasonable. The distribution of patients across NYHA class estimated in the manufacturer's base case model is summarised in Tables 30 and 31.

Table 30. Predicted proportion of patients by NYHA class in the standard care treatment arm (reproduced from MS; Table 40, pg 134)

Year	NYHA I	NYHA II	NYHA III	NYHA IV
0[a]	0.01	0.48	0.49	0.02
1	0.05	0.57	0.36	0.02
2	0.07	0.58	0.33	0.02
3	0.08	0.58	0.32	0.02

[a] These proportions represent the distribution over the course of the first modelled year rather than at baseline.
Abbreviation used in table: NYHA; New York Heart Association.

Table 31. Predicted proportion of patients by NYHA class in the Ivabradine plus standard care treatment arm (reproduced from MS; Table 41, pg 134)

Year	NYHA I	NYHA II	NYHA III	NYHA IV
0*	0.01	0.50	0.47	0.01
1	0.06	0.59	0.35	0.01
2	0.08	0.59	0.31	0.01
3	0.09	0.59	0.30	0.01
[a] These proportions represent the distribution over the course of the first modelled year rather than at baseline. Abbreviation used in table: NYHA; New York Heart Association.				

The ERG notes that the regression model for the distribution of patients across NYHA class was not adjusted for patient baseline characteristics. The manufacturer's rationale for using a regression model unadjusted for patient baseline characteristics was that this would ease the implementation of the regression into the economic model. As part of the clarification process, the ERG requested a regression model that included adjustment for patient baseline characteristics, particularly baseline heart rate. The manufacturer provided two updated regression models that included and excluded interaction terms, respectively (see Appendix 13 and Appendix 14). The manufacturer also provided an overview of the development process. The identification and selection of covariates was similar to that used in the development of the cardiovascular risk equation. However, only age and heart rate were considered as modifiers of treatment effect, as the presence of ischaemia and beta-blocker therapy were statistically non-significant predictors of NYHA distribution (and therefore were excluded from the regression analysis). Furthermore, the regression model indicated that neither age nor heart rate significantly modified the effect of treatment ($p > 0.5$ in all NYHA categories).

In addition to providing the updated regression models, the manufacturer also provided an updated economic model using the regression model excluding interaction terms. The distribution of patients across NYHA classes estimated in the manufacturer's updated model is displayed in Tables 32 and 33.

Table 32. Predicted proportion of patients distributed in each NYHA class in the standard care arm of the manufacturer's updated model

Year	Month	NYHA I	NYHA II	NYHA III	NYHA IV
0	0	0.01	0.55	0.43	0.01
1	12	0.01	0.57	0.41	0.01
2	24	0.01	0.58	0.40	0.01
3	36	0.01	0.58	0.40	0.01
4	48	0.01	0.58	0.40	0.01
5	60	0.01	0.58	0.40	0.01
Abbreviation used in table: NYHA, New York Heart Association.					

Table 33. Predicted proportion of patients distributed in each NYHA class in the ivabradine plus standard care treatment arm of the manufacturer's updated model

Year	Month	NYHA I	NYHA II	NYHA III	NYHA IV
0	0	0.01	0.58	0.40	0.004
1	12	0.02	0.61	0.37	0.004
2	24	0.02	0.61	0.37	0.004
3	36	0.02	0.61	0.37	0.004
4	48	0.02	0.61	0.37	0.004
5	60	0.02	0.61	0.37	0.004
Abbreviations used in table: NYHA, New York Heart Association.					

The manufacturer's updated model also included costs from the British National Formulary (BNF) 62,[96] as opposed to costs from BNF 59,[97] as included in the manufacturer's original analysis. The updated model resulted in an incremental quality adjusted life year (QALY) gain for treatment with ivabradine of 0.01 (0.29 vs 0.28) more than the manufacturer's base case model. Therefore, the ERG considers the manufacturer's base case model to be marginally conservative regarding the distribution of patients across NYHA class.

Hospitalisation

The manufacturer's base case model considered the effect of treatment on all-cause hospitalisation. All-cause hospitalisation was disaggregated into non-cardiovascular and cardiovascular hospitalisation, and cardiovascular hospitalisation was further disaggregated into heart failure and non-heart failure hospitalisation. This enabled the effect of treatment to be limited to heart failure hospitalisation, as required for one of the manufacturer's sensitivity analyses (see Section 5.2.12). Therefore, 3 regression equations were developed to estimate the rate of all-cause hospitalisation, cardiovascular hospitalisation and heart failure hospitalisation; non-heart failure cardiovascular hospitalisation was calculated as the difference between cardiovascular hospitalisation and heart failure hospitalisation, and non-cardiovascular hospitalisation was calculated as the difference between all-cause and cardiovascular hospitalisation.

Poisson regression equations based on observed data from the entire population of the SHIfT trial were used to estimate the rate of each type of hospitalisation. The variance associated with each patient was accounted for using clustering (data was grouped by patient ID). Each regression equation was based on data from both treatment arms which was used to estimate the relative effect of treatment with ivabradine. Furthermore, each regression equation included heart rate as an independent variable, which enabled the model to predict the rate of hospitalisation for the licensed population (heart rate ≥75 bpm).

The process used to develop each regression equation was similar to that used in the development of the cardiovascular risk equation, namely:

- a list of potential covariates based on the SHIfT trial protocol was compiled (geographical regions were also included);
- the relationship between continuous variables and cardiovascular mortality was examined to ensure any relationship between these variables was accurately represented;
- the categorisation of binary and categorical variables was checked to ensure appropriate categorisation;
- a backwards selection process, validated by a forward selection process, was used to develop the regression equation;
- all included variables were assessed for correlation and any correlated variables were tested for collinearity;
- the significance of the interaction between the treatment covariate and variables with prior clinical evidence of treatment effect modification was assessed (only heart rate showed a significant interaction effect);
- the regression equation was refined in conjunction with expert clinical opinion.

The final regression equations for each type of hospitalisation are displayed in Appendix 15, Appendix 16, and Appendix 17. The following variables were associated with a statistically significant reduction in the rate of each type of hospitalisation:

- treatment with ivabradine;
- other regions compared with Western Europe;
- an increase in LVEF (from a baseline of 26%);
- optimisation of beta-blockade;
- increase in serum sodium levels;
- decrease in systolic blood pressure.

In addition, the regression equations for cardiovascular and heart failure hospitalisation indicated that for a reduction in hospitalisation due to cardiovascular or heart failure causes to reach statistical significance, beta-blockade had to be above 50% of target dose. Furthermore, an increase in LVEF of at least 4% (from a baseline of 26%) was required for a statistically significant reduction in the rate of hospitalisation for heart failure. Rates of hospitalisation for most categories assessed were higher in Western Europe than in other regions, with the exception of heart failure hospitalisations which were only higher in Western Europe compared with Asia.

The following variables were associated with a statistically significant increase in the rate of each type of hospitalisation:

- increase in heart rate;
- a history of renal disease;
- worsening disease (as classified by NYHA class);
- use of digitalis, loop diuretics or allopurinol;

- presence of diabetes;
- current tobacco use;
- longer duration of heart failure;
- increase in age.

However, the regression equation for cardiovascular and heart failure hospitalisation indicated that aldosterone antagonist use was also associated with a statistically significant increase in the rate of each type of hospitalisation. In addition, the threshold of increase in the duration of heart failure (required to have a statistically significant effect on the rate of hospitalisation) decreased from all-cause hospitalisation to cardiovascular hospitalisation and then again to heart failure hospitalisation. Furthermore, a history of atrial fibrillation, a history of stroke or the presence of coronary artery disease were significant predictors of an increase in the rate of all-cause and cardiovascular hospitalisation, but not of an increase in heart failure hospitalisation.

Based on expert clinical opinion, the ERG considers the manufacturer's regression equations to be reasonable predictors of hospitalisation rate. Furthermore, the ERG notes that, compared with the relative rates of hospitalisation estimated in the SHIfT trial, the relative rate of hospitalisation estimated by the Poisson regression equations is conservative (Table 34).

Table 34. Treatment effect of ivabradine on hospitalisation

Outcome	Poisson regression model		Clinical analysis	
	RR	p-value	HR	p-value
All cause-hospitalisation	0.87	0.0020	0.82	<0.001
Cardiovascular hospitalisation	0.87	0.0030	0.79	<0.001
HF hospitalisation	0.77	0.0000	0.70	<0.001
Abbreviations used in table: HF, heart failure; HR, hazard ratio; RR, relative risk.				

Implementation of estimated rate of hospitalisation in the economic model

The rate of hospitalisation estimated from each regression equation was converted into a monthly probability for use in the economic model as follows:

$$\exp(\frac{Y}{t}) = \alpha + \beta X$$

Where Y = number of hospitalisations, and t = time (person months). Hospitalisation was not modelled as a health state *per se*. Therefore, the monthly probability of each type of hospitalisation is applied to all patients within the "alive" health state to calculate the proportion of patients experiencing each type of hospitalisation. These proportions are then used in the cost and QALY calculations.

5.2.7 Extrapolation

The manufacturer's base case model uses a lifetime time horizon, which is in line with NICE methods guidance[91] on interventions that affect overall survival. However, median follow-up in the SHIfT trial was 23 months and the economic model runs for a maximum of 30 years. Therefore, to inform the economic model, it was necessary to extrapolate the baseline and relative probability of each outcome. This section describes the methods used to extrapolate the baseline probability of:

- mortality;
- NYHA distribution;
- hospitalisation.

In addition, this section discusses the extrapolation of the treatment effect of ivabradine.

Mortality

Mortality is disaggregated into cardiovascular and non-cardiovascular mortality (with cardiovascular mortality further disaggregated into heart failure and non-heart failure mortality). The manufacturer's base case model uses non-cardiovascular mortality estimates from UK interim life tables[94] and these are implemented for the full model time horizon.

In the base case, the risk of cardiovascular mortality is estimated from parametric regression equations based on 29 months of observed data from the SHIfT trial. The observed data used to inform the parametric regression equations was truncated at 29 months (from the full trial period of 36 months) as following this time point <20% of patients were available for follow-up. The manufacturer acknowledged the high level of uncertainty associated with using data from the SHIfT trial to inform the risk of cardiovascular mortality for a lifetime time horizon. Therefore, sensitivity analyses using long-term follow-up data from the CARE-HF trial[98] and the Western Australian 5-year Hospital Morbidity database[99] were carried out. The CARE-HF[27] trial was an "RCT conducted in heart failure patients (NYHA class III or IV) with a prior hospitalisation event, on pharmacologic therapy with a left ventricular ejection fraction (LVEF) ≤35% and QRS interval ≥120 ms". The manufacturer obtained a crude mortality estimate of 50% at 65 months (estimated from Kaplan-Meier data), and assumed a constant hazard to calculate the monthly probability of death (cardiovascular and non-cardiovascular). The crude estimate of mortality was then age and gender adjusted using data from UK interim life tables.[94] The probability of death used in the manufacturer's sensitivity analysis is summarised in Table 35. No further details of the Western Australia data were provided in the manufacturer's submission. However, the data used has been extracted from the manufacturer's model and is displayed in Table 35.

Table 35. Probability of death estimated from CARE-HF and UK interim life tables

Age group	CARE-HF mortality rate male	CARE-HF mortality rate female	UK annual probability of death (gender adjusted)	Age multiplier based on UK data	Probability of death per month (age and gender adjusted)
Age 20–24	0.0035	0.0013	0.0030	0.0279	0.00029
Age 25–29	0.0041	0.0017	0.0035	0.0327	0.00034
Age 30–34	0.0053	0.0024	0.0046	0.0432	0.00045
Age 35–39	0.0068	0.0037	0.0061	0.0569	0.00060
Age 40–44	0.0093	0.0058	0.0085	0.0792	0.00083
Age 45–49	0.0140	0.0091	0.0128	0.1197	0.00125
Age 50–54	0.0218	0.0146	0.0201	0.1876	0.00197
Age 55–59	0.0329	0.0218	0.0303	0.2827	0.00296
Age 60–64	0.0510	0.0342	0.0471	0.4389	0.00460
Age 65–69	0.0772	0.0532	0.0716	0.6675	0.00698
Age 70–74	0.1139	0.0855	0.1073	1.0000	0.01044
Age 75–79	0.1679	0.1397	0.1614	1.5039	0.01566
Age 80–84	0.2223	0.2158	0.2208	2.0573	0.02136
Age 85–89	0.2265	0.2764	0.2381	2.2188	0.02301
Age 90–94	0.1705	0.2651	0.1924	1.7935	0.01864
Age 95 and over	0.0790	0.1576	0.0972	0.9060	0.00946
Western Australia data					
<75 years	-	-	-	-	0.003977
≥75 years	-	-	-	-	0.008908
Abbreviations: CARE-HF, Cardiac Resynchronization on Morbidity and Mortality in Heart Failure; UK, United Kingdom.					

The ERG notes that the ICERs obtained using CARE-HF and the Western Australia data as the source of long-term mortality are £676 lower and £196 higher than the manufacturer's base case ICER, respectively. This suggests that the parametric equations used in the manufacturer's base case are conservative (favour standard care) when compared with data from CARE-HF. However, as the manufacturer highlights, the patient population of CARE-HF is more severe than those recruited to the SHIfT trial. Therefore, the long-term mortality of patients from CARE-HF may be expected to be unduly pessimistic compared with that likely to be experienced by patients recruited to the SHIfT trial. Furthermore, an increase in the long-term risk of death is likely to favour the less effective treatment as the potential for the more effective treatment (ivabradine) to benefit patients will be limited. However, the fact that the ICER falls when the mortality of a more severe population is used suggests that the parametric regression equations (used in the manufacturer's base case) are themselves unduly pessimistic; the estimates of mortality obtained from the parametric equations used in the manufacturer's base case appear to estimate a baseline risk of death that is higher than that observed in a more severe population.

NYHA distribution

In the manufacturer's base case the proportion of patients in each NYHA class at 29 months (the end of the "within trial" period) is carried forward for the remaining time horizon of the model. Therefore, 7%, 58%, 32% and 2% of patients in the standard care arm are assumed to be in NYHA class I, II, III and IV, respectively. Similarly, 9%, 59%, 30% and 1% of patients in the ivabradine arm are assumed to be in NYHA class I, II, III and IV, respectively. However, the manufacturer has assessed the robustness of the model to this assumption by carrying out a sensitivity analysis. This analysis assumed no difference in the proportion of patients by NYHA class in the extrapolated period of the model. In addition, this sensitivity analysis assumed that an arbitrary 5% of class I and II patients would be moved annually into classes II and III, respectively. The sensitivity analysis around NYHA extrapolation resulted in a £485 increase in the ICER, suggesting that the manufacturer's base case assumption favours ivabradine.

Hospitalisation

In the extrapolated period of the manufacturer's base case model, the rate of hospitalisation is assumed to be equivalent to that estimated for the "within trial" period (based on the Poisson regression equations). However, the manufacturer highlights that this may be conservative as there is evidence from the Poisson regression equations developed from SHIfT that increasing age is associated with an increased rate of hospitalisation (7% increase in rate of hospitalisation for every 10-year increase in age). The ERG agrees with the manufacturer that the assumption of constant hospitalisation rates is likely to be conservative compared with assuming that hospitalisation rates increase over time. However, the ERG notes that this assumption is only valid if the treatment effect of ivabradine is also assumed to be constant over time. The consistency of effect of ivabradine has not been assessed as the Poisson regression equations are not used for extrapolation.

Treatment effect

In the manufacturer's base case model, the treatment effect of ivabradine is assumed to remain constant over the full model time horizon. Consequently, the relative reduction in cardiovascular and heart failure mortality risk is maintained over the full time horizon. In addition, the distribution of patients by NYHA class at the end of the "within trial" period is maintained for the duration of the model (i.e., the improvement in NYHA classification achieved with ivabradine treatment is assumed to be maintained over time). Furthermore, the rate of hospitalisation estimated from the Poisson regression models (see Appendix 15, Appendix 16, and Appendix 17) is assumed to be constant over time. However, the manufacturer has carried out several sensitivity analyses to assess the robustness of the economic model to alternative assumptions around the extrapolation of treatment effect. The ERG notes that the sensitivity analyses carried out by the manufacturer are in concordance with those recommended by NICE.[91] These were:

- assuming a maximum duration of treatment with ivabradine of 5 years, after which costs and benefits of ivabradine treatment ceased instantaneously;
- assuming lifetime continuation of ivabradine therapy with gradual decline in the effects of treatment (5-10 year range was considered).

The results of these sensitivity analyses are discussed in Section 5.2.11. However, the ERG notes that none of these analyses led to substantial increases in the ICER.

5.2.8 Health-related quality of life

HRQoL was estimated to vary according to a patient's NYHA classification. Consequently, utility values specific to NYHA class are used within the manufacturer's model. In addition, a utility benefit is applied to patients treated with ivabradine plus standard care versus patients treated with standard care alone, and a utility decrement (specific to NYHA class) is applied to patients who are hospitalised for any reason.

In the base case analysis, the manufacturer uses EQ-5D data derived from a patient-reported outcome sub-study of SHIfT (PRO-SHIfT).[48] The PRO-SHIfT sub-study was carried out in 5,038 of the 6,505 patients recruited to the SHIfT trial. HRQoL was evaluated using the generic EuroQoL questionnaire and the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ).[16] Data from the EuroQoL questionnaires were used to calculate EQ-5D index scores (EQ-5D data) using UK population tariff values as per the NICE reference case.[91]

A mixed regression model was developed based on EQ-5D data from the PRO-SHIfT sub-study to predict patients' quality of life. The manufacturer stated that potential covariates were consistent with those considered in the development of the cardiovascular mortality and hospitalisation regression equations. In addition, the manufacturer stated that NYHA class and hospitalisation (±30 days from an EQ-5D visit) were treated as time-varying covariates. Furthermore, the manufacturer assessed the interaction of the treatment covariate with baseline resting heart rate and age; only variables with prior clinical evidence of the modification of treatment effect and that were significant predictors of patients' quality of life were considered as modifiers of treatment effect. In addition, based on prior clinical expectation, the interaction between hospitalisation and NYHA class was considered. The mixed regression model used in the manufacturer's economic model to predict patients' quality of life is presented in Table 36.

Table 36. The mixed regression model for quality of life (reproduced from MS; Table 53, pg 157)

Description	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation within 30 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration >=0.6<2 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration >=2<4.8 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration >+4.8 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allopurinol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI kg/m^2*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate bpm*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loop diuretics dose/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potassium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hosp30*NYHA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hosp30*NYHA II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hosp30*NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment*heart rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: BMI, body mass index; bpm, beats per minute; Cons, constant; HF, heart failure; Hosp30, hospitalisation within 30 days of an EQ-5D visit; kg, kilogramme; LCI, lower confidence interval; NYHA, New York Heart Association; SE, standard error; UCI, upper confidence interval; vs, versus; yrs, years.

*Variables centred on the mean

The mixed regression model for quality of life indicates that a statistically significant ($p < 0.05$) reduction in HRQoL is associated with the following covariates:

- increasing age;
- female gender;
- hospitalisation within 30 days of an EQ-5D visit;
- worsening disease (as classified by NYHA class);
- a history of ischaemia or stroke;
- longer duration of HF;
- increase in BMI (kg/m^2)
- increase in resting heart rate;
- the use of loop diuretics;
- increase in potassium serum levels.

However, the effect of hospitalisation and worsening disease severity (NYHA class) is mediated somewhat by the interaction of hospitalisation and NYHA class.

Treatment with ivabradine and treatment with allopurinol are associated with a statistically significant ($p < 0.05$) improvement in HRQoL. In the MS, the manufacturer highlighted that the treatment effect of ivabradine on quality of life was not significantly modified by baseline resting heart rate ($p = 0.133$). However, the interaction term was retained in the final regression model as there was evidence of a potential trend towards interaction. The ERG notes that the manufacturer provided a regression equation without interaction terms and that the exclusion of this interaction effect did not noticeably alter the covariate estimate of treatment effect.

Furthermore, adverse events were not explicitly considered as predictors of quality of life and the manufacturer stated that "any utility loss associated with treatment-related adverse events is assumed to be captured by the treatment covariate included in the mixed regression model".

Following consultation with expert clinical advisors, the ERG is satisfied that the manufacturer's regression model for quality of life is clinically plausible. Furthermore, the ERG notes that the utility decrement associated with hospitalisation is likely to capture any serious repercussions of adverse events on quality of life; clinical experts advised that hospitalisation would be the main consequence of serious adverse events, such as bradycardia.

Implementation of quality of life data into the economic model

The utility values derived from the mixed regression model and used in the manufacturer's base case are displayed in Table 37.

Table 37. Quality of life (utility) values used in the manufacturer's base case analysis (adapted from MS; Table 49, pg 156)

NYHA class	Utility for NYHA class (standard care arm)	NYHA-specific utility decrement for hospitalisation	Treatment benefit for patients treated with ivabradine
I	0.823	–0.071	[redacted]
II	0.738	–0.032	
III	0.643	–0.084	
IV	0.457	–0.212	
Abbreviation used in table: NYHA, New York Heart Association.			

The values in Table 37 are obtained by applying the patient characteristics of the licensed population (heart rate ≥75 bpm) to the regression equation displayed in Table 36. The covariates for NYHA class II vs I, NYHA class III vs I and NYHA class IV vs I are only active in the calculation of the utility value associated with patients in NYHA classes II, III and IV, respectively (e.g. the covariate of NYHA class II vs I is only used in the calculation of the utility value for NYHA class II). Similarly,

the hospitalisation and hospitalisation/NYHA class interaction terms are only used in the calculation of each NYHA-specific hospitalisation decrement.

In addition to developing a regression model to estimate quality of life data, the manufacturer carried out a systematic review of the quality of life literature. This review aimed to identify studies reporting utility values by NYHA class. Explicit inclusion and exclusion criteria limited the included studies to those considering generic measures of utility obtained using the time-trade off or standard gamble methods. The review identified nine studies reporting utility data by NYHA class (summarised in Appendix 18). The largest of the identified studies, a study by Gohler *et al*.[100] in 1,359 patients with heart failure, reported EQ-5D data for NYHA classes I to IV. Gohler *et al*.[100] estimated utility scores of 0.86, 0.77, 0.67 and 0.53 for NYHA classes I, II, III and IV, respectively. The manufacturer stated that these values were consistent with the utility scores for NYHA classes I to IV (without hospitalisation) estimated from the regression analysis. Moreover, the manufacturer has used these data in a sensitivity analysis, which resulted in an ICER approximately £204 lower than the manufacturer's base case (see Section 5.2.11). The similarity between the ICER obtained using external quality of life data and the manufacturer's base case suggests that the manufacturer's model is relatively robust to changes in quality of life data. Furthermore, the ERG considers that data estimated from the SHIfT trial may be more reliable because of its larger sample size.

Extrapolation of quality of life data

The mixed regression model used in the manufacturer's base case includes NYHA class and hospitalisation as time-varying covariates. That is, the quality of life accrued by individual patients will vary as patients move between NYHA classes over time; disutility associated with hospitalisation will also vary over time as a result of movement between NYHA classes. However, the manufacturer assumed that over and above the movement between NYHA classes, patients' quality of life remains constant over time; no adjustment for age beyond patients' baseline age is applied.

The assumptions surrounding the extrapolation of patient distribution across NYHA classes over time are discussed in Section 5.2.7. However, it is important to note that the assumptions surrounding NYHA distribution over time have a direct impact on estimates of quality of life. The manufacturer carried out a sensitivity analysis to assess the impact of adjusting for age throughout the modelled time horizon (see Section 5.2.11). This sensitivity analysis resulted in an ICER that was £216 higher than the manufacturer's base case, suggesting that the absence of ongoing age adjustment may be biased towards ivabradine. However, the difference between the ICERs is unlikely to influence any conclusions around the cost effectiveness of ivabradine.

Extrapolation of treatment effect on quality of life

Treatment is a significant covariate in the mixed regression model and in the manufacturer's base case analysis treatment effect is assumed to remain constant over the full model time horizon. However, sensitivity analyses around the long-term effects of treatment with ivabradine have been carried out by the manufacturer (see Section 5.2.11) and are applied to the treatment effect on quality of life.

5.2.9 Resources and costs

The manufacturer used UK-specific unit cost data for the valuation of resources used in the economic model. Three key types of cost were identified as follows: intervention and comparator costs; costs of serious adverse events; and heart failure management costs. Non-serious adverse events were excluded from the analysis and the costs of serious adverse events were captured as hospitalisations. All costs were obtained from published sources and referenced. The main sources used to obtain cost data were: NHS Reference Costs (2010–2011);[101] the University of Kent Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2011;[102] and the BNF 59.[97] With the exception of length of hospital stay, type of hospital ward admitted to and ivabradine administration, all resource use data were taken from the SHIfT trial. The manufacturer stated that based on expert clinical advice, UK-specific data on the length of hospital stay and type of ward admitted to were used to inform the model. This is because the SHIfT trial was carried out in various countries and it was thought that this would be reflected in hospital admission data generated from the SHIfT trial. In addition, the administration costs associated with ivabradine were based on assumptions made by the manufacturer.

Ivabradine costs

The cost of ivabradine listed in the BNF 59 (the most current BNF at the time of the manufacturer's submission) was £40.17 per 56 tab pack (5 mg or 7.5 mg). This cost was used in the model in conjunction with estimates of the proportion of patients on different doses taken from SHIfT. The manufacturer stated that, as per clinical practice, the cost of a 2.5 mg dose of ivabradine was assumed to be half the cost of a 5 mg dose; standard clinical practice is to halve the scored tablets. The overall monthly cost of the ivabradine tablet was calculated as a weighted average of the different doses, with the cost of each dose weighted by the proportion of patients receiving that dose in SHIfT (Table 38).

In the MS, the manufacturer stated that no additional administration costs were anticipated with ivabradine treatment. This is because it is expected that ivabradine titration will take place in primary care. Furthermore, the manufacturer stated that any electrocardiogram (ECG) assessment undertaken is likely to be part of standard care as recommended by NICE,[19] rather than for the purpose of prescribing ivabradine. However, the manufacturer has included two initiation costs for ivabradine,

these are: a face-to-face outpatient visit with a cardiology specialist; and an ECG. The unit and monthly costs associated with ivabradine therapy are summarised in Table 38.

Table 38. Costs associated with ivabradine therapy

Description	Ivabradine 2.5 mg	Ivabradine 5 mg/7.5mg	Source
Price per tablet (£)	0.36	0.72	Calculated from BNF list price
No. of tablets required per month	60.88	60.88	SPC
Total dose-related cost per month (£)	21.83	43.67	Calculated
Proportion of patients per dose	7%	93%	SHIfT
Total weighted drug cost per month (£)	= 0.07*21.83 + 0.93*43.67 = 42.10		Calculated
Face-to-face outpatient visit with cardiology specialist (NHS ref code 320)	118.81		NHS reference costs (2010–11)
ECG (NHS reference cost code DA01)	31.28		NHS reference costs (2010–11)
Total cost (£) of ivabradine (month 1)	**201.73**		Calculated
Total cost (£) of ivabradine (subsequent months)	**42.10**		Calculated
Abbreviations used in table: BNF, British National Formulary; ECG, electrocardiogram; NHS, National Health Service; SPC, Summary of Product Characteristics.			

Comparator costs (usual care)

The manufacturer stated that drugs currently recommended in a recent update of the European Society of Cardiology (ESC) guidelines[47] were used in the calculation of cost of standard care. In addition, the manufacturer stated that other cardiovascular drugs were included in the analysis if more than 10% of patients in SHIfT had received them (MS; pg 162). The overall cost of standard care is calculated using the proportion of patients on each therapy based on data from the SHIfT trial. The proportion of patients on each therapy is multiplied by the average cost of that particular therapy. The average cost of each therapy is in turn calculated using an assumed average dose (based on expert clinical advice) applied to the lowest generic list price reported in the BNF 59. The calculation of therapy costs for standard care is summarised in Table 39. No initiation or administration costs were assumed to be incurred by patients receiving standard care alone.

Table 39. Costs of standard care treatments (adapted from manufacturer's response to clarification questions; Table 11)

Drug class	Most common drug	SHIfT % of cohort	UK dose (mg)	Price per pack (£)	Tablets per pack	mg per tablet	Price per mg (£)	Total cost per month (£)
ACE inhibitors	Ramipril	78.9	5.00	1.25	28.00	5.00	0.0089	1.0720
ARBs	Candesartan	14.3	16.00	12.72	28.00	16.00	0.0284	1.9790
Aldosterone antagonists	Spironolactone	62.4	34.79	2.11	28.00	50.00	0.0015	0.9954
Digitalis	Digoxin	21.9	0.13	2.03	28.00	0.06	1.1600	0.9648
Loop diuretics	Furosemide	74.2	59.36	0.84	28.00	40.00	0.0008	1.0051
Beta-blockers[a]	Bisoprolol	89.7	5.00	1.08	28.00	5.00	0.0077	1.0531
Statins	Simvastatin	60.8	23.39	0.90	28.00	10.00	0.0032	1.3917
Antiarrhythmics	Bendroflumethiazide	14.1	5.00	0.86	28.00	5.00	0.0061	0.1319
Anticoagulants	Clopidogrel	12.2	74.71	3.17	28.00	75.00	0.0015	0.4184
	Warfarin	16.3	3.00	0.95	28.00	3.00	0.0113	0.1683
Nitrates	Isosorbide mononitrate	35.4	53.24	1.40	56.00	40.00	0.0006	0.3590
Total cost (£)								**9.54**

[a] The price of beta-blockade is simplified to an average dose and does not vary according to proportion of patients undertaking therapy in subgroup analyses.

Abbreviations used in the table: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

As part of the clarification process, the ERG requested that the manufacturer provide an updated analysis using the more up-to-date costs from the BNF 62. The manufacturer implemented the change and supplied an updated model (also including updated regression equations for NYHA distribution). The changes had a minimal impact on the cost of usual care, changing the total monthly cost from £9.54 to £8.60. The ERG considers the approach taken by the manufacturer in costing usual care drugs to be appropriate.

Adverse events costs

The costs of serious adverse events were captured in the economic model through the cost of hospitalisation. The different hospitalisation costs used in the manufacturer's model are summarised in Table 40.

Table 40. Summary of hospitalisation costs

Type of hospitalisation	Mean cost per event (£)	Weighted cost used in the model (£)
HF diagnosis (general ward)	2,307.98	2,801.55
HF diagnosis (cardiac ward)	3,295.12	
Other cardiovascular diagnosis (general ward)	1,942.44	1,836.02
Other cardiovascular diagnosis (cardiac ward)	1,729.60	
Non-cardiovascular diagnosis (general ward)	2,643.56	2,643.56
Abbreviation used in table: HF, heart failure.		

The proportion of patients admitted for cardiovascular reasons (heart failure or non-heart failure) to a general ward (50%) rather than an acute coronary care ward (50%) was estimated from National Heart Failure Audit (2009–2010) data.[103] All patients hospitalised for non-cardiovascular reasons were assumed to be admitted to a general ward. The cost of each hospitalisation event was calculated from the unit cost and length of stay associated with that particular hospitalisation event. The unit cost of admission to a cardiac ward was obtained from NHS reference costs[101] (code CC7: coronary care unit). However, the unit cost of admission to a general ward was dependent on the type of admission (heart failure, non-heart failure cardiovascular or non-cardiovascular). For each type of admission, a weighted average of all relevant Healthcare Resource Group (HRG) codes was used to calculate the unit cost associated with that type of hospital admission; unit costs of each relevant HRG code were weighted by the level of activity reported. Similarly, the length of stay for each type of admission (heart failure, non-heart failure cardiovascular or non-cardiovascular) was calculated as a weighted average of the length of stay associated with each HRG code relevant to that type of admission. The calculation of each hospitalisation event is summarised in Table 41.

Table 41. Calculation of the cost of each type of hospitalisation event

Type of hospitalisation	Mean cost per day (£)	Source	Mean length of stay (days)	Source	Mean cost per event (£)
HF diagnosis (general ward)	305.06	NHS reference costs codes: EB03H-EB03I	7.57	NHS reference costs codes: EB03H-EB03I	2,307.98
HF diagnosis (cardiac ward)	435.53	NHS reference costs code: CC7	7.57	NHS reference costs codes: EB03H-EB03I	3,295.12
Other cardiovascular diagnosis (general ward)	489.13	NHS reference costs codes: EA03Z-EB10Z	3.97	NHS reference costs codes: EA03Z-EB10Z	1,942.44
Other cardiovascular diagnosis (cardiac ward)	435.53	NHS reference costs code: CC7	3.97	NHS reference costs codes: EA03Z-EB10Z	1,729.60
Non-cardiovascular diagnosis (general ward)	515.06	NHS reference costs codes: AA02Z-WA23Y (cardiovascular codes and codes associated with pregnancy and delivery removed)	5.13	NHS reference costs codes: AA02Z-WA23Y (cardiovascular codes and codes associated with pregnancy and delivery removed)	2,643.56
Abbreviation used in table: HF, heart failure; NHS, National Health Service.					

The ERG is satisfied that appropriate HRG codes were used in the calculation of each type of hospital admission. Furthermore, the ERG notes that the manufacturer carried out sensitivity analysis around the length of stay, using hospital episode statistics[104] or National Heart Failure Audit (2009–

2010)[103] data. Moreover, the ERG notes that both of these sensitivity analysis resulted in lower ICERs than the manufacturer's base case. However, the ERG notes that the manufacturer assumed no patients will be seen in intensive care units (ICUs). Based on expert clinical opinion, the ERG requested a scenario analysis (during the clarification process) applying the cost of ICU care to patients with symptomatic bradycardia or atrial fibrillation. The manufacturer provided a scenario analysis in which the proportion of patients with bradycardia or atrial fibrillation admitted to ICU in SHIfT ([redacted] both arms combined) was assumed to require ICU care. A cost per day of £1,213 for ICU treatment was calculated from a weighted average of ICU admission costs reported in the 2010–2011 NHS reference costs.[101] In addition, the average length of stay reported in SHIfT was used to inform cost calculations. The length of stay reported in SHIfT differed between treatment arms ([redacted] days for ivabradine plus standard care vs [redacted] days for standard care alone). The scenario analysis resulted in an ICER that was less than £500 higher than the manufacturer's base case.

Heart failure management costs

Ongoing management of heart failure, for example physician visits, outpatient procedures and diagnostic tests, is required for all patients regardless of treatment arm. The costs associated with the ongoing management of heart failure included in the manufacturer's model were estimated from British Heart Foundation statistics.[105] The British Heart Foundation statistics for 2005 reported that heart failure costs the NHS £192.5 million per annum (excluding drug costs and inpatient hospitalisations). This is equivalent to £242 per patient per annum. Using UK health price index values from the ONS,[94] the manufacturer inflated this cost to a 2011 cost. This resulted in an inflated cost of £321 per patient per annum, which is equivalent to a monthly cost of £26.77 per patient. The manufacturer highlights that this method of cost calculation is consistent with the methods used in an National Institute for Health Research assessment of aldosterone antagonists in heart failure patients.[80]

5.2.10 Cost effectiveness results

The base case cost-effectiveness results of ivabradine plus standard care versus standard care alone in the licensed population (baseline heart rate ≥75 bpm) are presented in Table 42.

Table 42. Base case cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/LYG)	ICER (£/QALY)
Standard care	9,445.74	5.61	3.99	–	–	–	–	–
Ivabradine plus standard care	11,821.96	5.86	4.27	2,376	0.25	0.28	9,363	8,498
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life-years gained; QALY, quality adjusted life year.								

The result presented in Table 42 has been calculated by the sequential application of each individual patient profile from the licensed population of SHIfT in the manufacturer's economic model. The individual characteristics of each patient in the licensed population are applied to the regression equations around which the manufacturer's model is structured. For each patient, the potential incremental costs, incremental life-years gained (LYG), incremental QALYs and ICER are estimated. Next, the estimates generated from each iteration are averaged to estimate the overall ICER. In the MS, the manufacturer provided a rationale for using individual rather than average patient characteristics to inform the base case cost-effectiveness results. The manufacturer stated that the use of individual rather than average characteristics would provide a more accurate assessment of the ICER (MS; pg 139). The ERG agrees with the manufacturer that the use of individual patient characteristics is likely to produce a more accurate estimation of the cost-effectiveness results. Moreover, the ERG notes that the use of individual patient characteristics produces a less favourable ICER for ivabradine than the use of average patient characteristics (£8,498 vs £7,742). A full breakdown of the LYG, QALYs and costs accrued with each therapy disaggregated into NYHA class and hospitalisation are provided in Table 43. A summary of the model results compared with the clinical results of the SHIfT trial for the licensed population (baseline heart rate ≥75 bpm) for the outcomes of mortality and hospitalisation is presented in Table 44.

Table 43. Summary of LYG and QALYs gained by clinical outcome for standard care and ivabradine plus standard care (reproduced from MS; Table 61, pg 171)

	Outcome	**LYG**	**QALY**	**Cost (£)**
Standard care	NYHA I	0.38	0.32	166.16
	NYHA II	3.23	2.41	1,409.26
	NYHA III	1.90	1.23	829.37
	NYHA IV	0.09	0.04	40.01
	Hospitalisation	–	–0.01	7,000.94
	Total	**5.61**	**3.99**	**9,445.74**
Ivabradine plus standard care	**Outcome**	**LYG**	**QALY**	**Cost (£)**
	NYHA I	0.47	0.39	443.38
	NYHA II	3.44	2.60	3,365.75
	NYHA III	1.89	1.25	1,909.14
	NYHA IV	0.07	0.03	67.36
	Hospitalisation	–	–0.01	6,036.32
	Total	**5.86**	**4.27**	**11,821.96**
Abbreviations used in table: LYG, life-years gained; NYHA, New York Heart Association; QALY, quality adjusted life year.				

Table 44. Summary of model results compared with clinical data: number of events in the licensed population, baseline heart rate ≥75 bpm (reproduced from MS; Table 57, pg 167)

Outcome	Trial result standard care	Model result standard care	% error prediction	Trial result ivabradine	Model result ivabradine	% error prediction
Heart failure mortality	126.00	107.66	–14.56%	78.00	74.56	–4.40%
Cardiovascular mortality	364.00	325.70	–10.52%	304.00	291.15	–4.23%
All-cause mortality	407.00	401.59	–1.33%	340.00	367.81	8.18%
Hospitalisations	2,213.00	1,814.00	–18.03%	1,754.00	1,629.75	–7.08%

The number of events (cardiovascular death and hospitalisation) estimated by the model is lower than the number of events observed in the licensed population of SHIfT; with the exception of all-cause mortality, which is overestimated by the model in the ivabradine arm. Moreover, the relative difference in the number of events occurring in patients treated with ivabradine plus standard care versus patients treated with standard care alone is underestimated. That is, the model is biased against ivabradine therapy. The manufacturer stated that some discrepancy between observed and predicted event rates is to be expected as the model predominantly uses regression analysis to predict the number of events. Regression analysis is constrained by the clinical covariates included and "it is possible that some predictors may not have been captured by the available clinical data" (MS; pg 168). Furthermore, the manufacturer highlighted that the relationship between baseline heart rate and cardiovascular mortality was in essence cubic. However, the regression analysis used to predict cardiovascular mortality assumed a linear relationship. This assumption may have contributed to the underestimation of cardiovascular mortality in the manufacturer's model.

Overall, the ERG considers the manufacturer's base case model to be conservative, that is, likely to be biased against ivabradine.

5.2.11 Sensitivity analyses

In support of the ivabradine submission, the manufacturer carried out several sensitivity analyses including probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (parameter and structural). All sensitivity analyses have been carried out using average patient characteristics to inform the regression equations, rather than the method of averaging the results obtained from individual patient profiles used in the base case. The use of average patient characteristics was a pragmatic approach used to limit the time demands of each analysis (each analysis would take ≥2 hours to run using the base case method). The manufacturer highlighted that this approach resulted in some loss of accuracy in the ICER estimates; the base case ICER decreases by £756. However, the ERG notes that the level of accuracy foregone is unlikely to alter any conclusions drawn from the evidence presented by the manufacturer. Therefore, the ERG accepts the manufacturer's pragmatic

approach to the sensitivity analyses. The following sections summarise the methods, results and findings of the manufacturer's various sensitivity analyses.

Probabilistic sensitivity analysis

The sensitivity of the model to parameter uncertainty has been assessed using probabilistic analysis. All costs, with the exception of drug costs, are sampled from lognormal distributions; drug costs are not assumed to be subject to uncertainty. In addition, each covariate in the regression equations for mortality, hospitalisation and NYHA distribution are sampled from multivariate normal distributions, using the Cholesky decomposition method. However, the Cholesky decomposition matrix for the mixed regression analysis used to estimate quality of life weights could not be derived (as the variance-covariance matrix was not positive definite). Therefore, in the PSA, the covariates in the regression analysis used to estimate quality of life weights are assumed to be independent. The ERG notes that the assumption of independent covariates is a strong assumption, particularly in a regression model with interaction terms (interaction terms suggest a high level of correlation between certain covariates). However, the impact of this assumption on the estimated quality of life weights (and subsequent cost-effectiveness results) is unclear, as an assessment of the impact of each correlation was not feasible within the manufacturer's model. The results of the PSA are presented in Figures 8 and 9.

Figure 8. Cost-effectiveness plane for ivabradine plus standard care compared with standard care alone (1,000 runs; adapted from MS; Figure 17, pg 176)

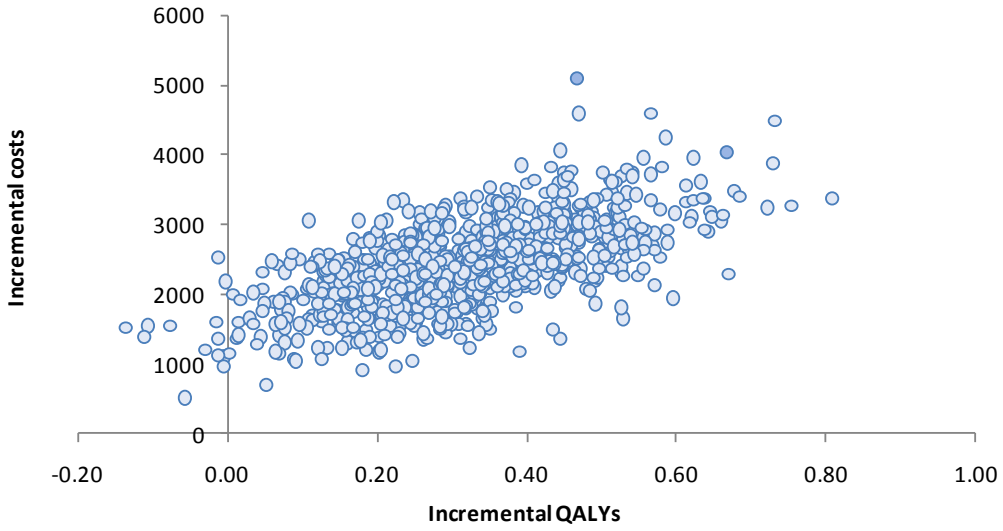
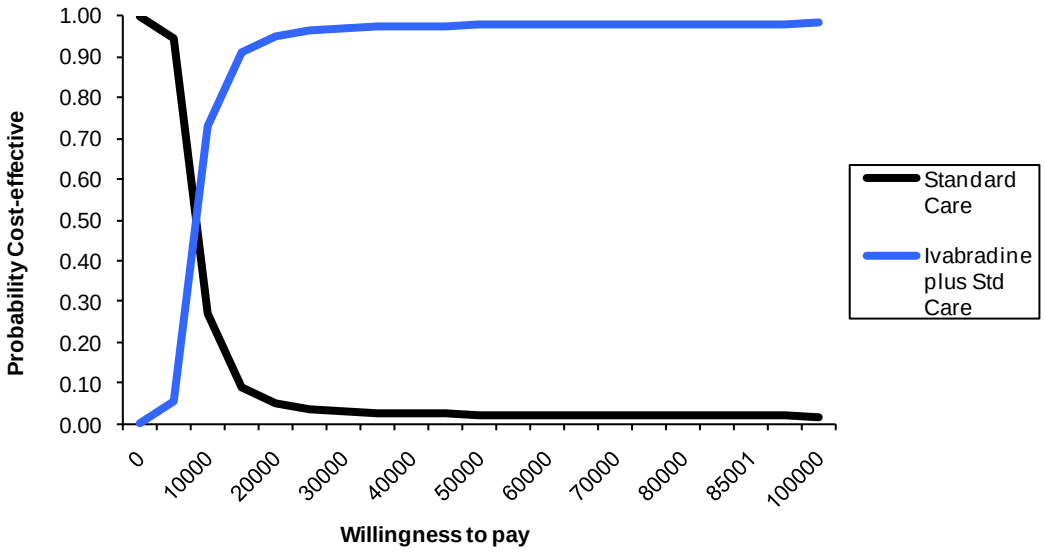


Figure 9. Cost-effectiveness acceptability curve for ivabradine plus standard care compared with standard care alone (1,000 runs; adapted from MS; pg 176)



Based on the manufacturer's PSA, it appears there is little uncertainty surrounding the superior clinical efficacy of ivabradine plus standard care versus standard care alone; ivabradine resulted in more QALYs in 98.7% of runs. Furthermore, at a willingness to pay threshold of £20,000 per QALY, there is a 95% probability of ivabradine plus standard care being the optimal therapy compared with standard care alone. However, it is important to note that the impact of correlation in the covariates used to inform the estimation of quality of life weights has not been captured.

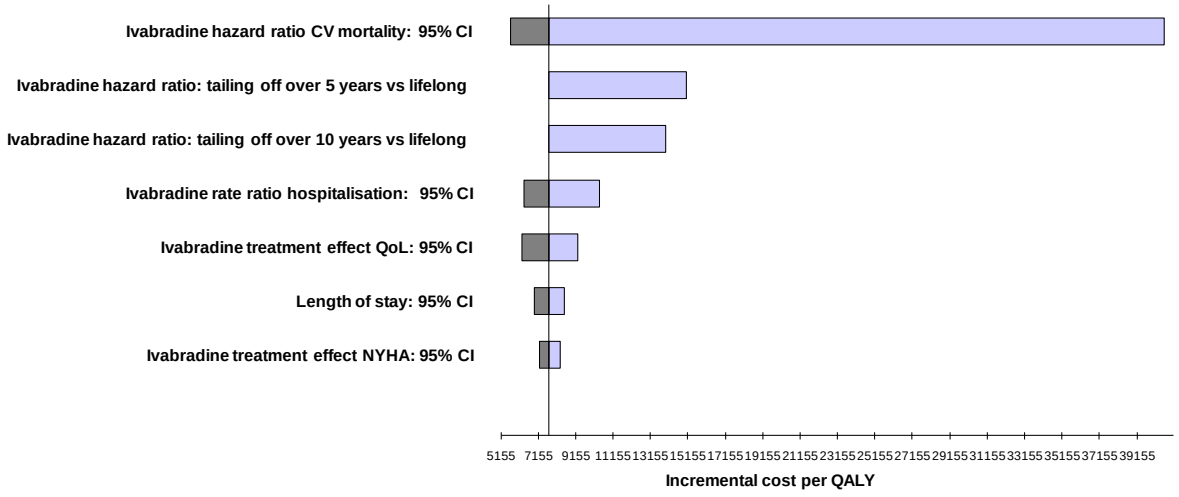
Deterministic sensitivity analysis

The manufacturer carried out several deterministic sensitivity analyses to assess the univariate sensitivity of the model to uncertainty around key parameters and structural assumptions. Each key parameter was alternately assigned a low and high value estimated from the 95% confidence intervals associated with that parameter; structural assumptions were assessed by implementing alternative assumptions. The parameter values and alternative structural assumptions around the duration of treatment effect are presented in Table 45, together with the resultant ICERs. The impact on the ICER (£/QALY) of each variation (either parameter or structural) is further summarised in the tornado diagram presented in Figure 10.

Table 45. Deterministic sensitivity analysis around key parameters and structural assumptions surrounding treatment effect

Parameter		Base case value	95% LCI	95% UCI	ICER for 95% LCI (£/QALY)	ICER for 95% UCI (£/QALY)
Ivabradine hazard ratio cardiovascular mortality		0.94	0.83	1.07	5,655	40,638
Ivabradine rate ratio hospitalisation		0.87	0.80	0.95	6,384	10,424
Ivabradine treatment effect quality of life:		0.010	0.001	0.020	9,253	6,283
Length of stay		7.57	5.67	9.46	6,938	8,549
Ivabradine treatment effect NYHA	NYHA II	–0.168	–0.349	0.013	7,232	8,349
	NYHA III	–0.093	–0.186	–0.001		
	NYHA IV	–0.367	–0.675	–0.059		
Structural assumptions surrounding treatment effect						
Base case assumption		**Alternative assumption**			**Base case ICER (£/QALY)**	**Alternative ICER (£/QALY)**
Ivabradine treatment effect remaining constant over lifetime time horizon		Ivabradine treatment effect tailing off over 5 years			7,742	15,078
Ivabradine treatment effect remaining constant over lifetime time horizon		Ivabradine treatment effect tailing off over 10 years			7,742	13,964
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LCI, lower confidence interval; NYHA, New York Heart Association; QALY, quality adjusted life year; UCI, upper confidence interval.						

Figure 10. Tornado diagram for one-way sensitivity analysis of key parameters and structural assumptions around treatment effect (adapted from MS; Figure 16, pg 174)



Overall, the manufacturer's model was robust to changes in key parameter estimates; the ICERs obtained using the 95% upper CI for rate ratio of hospitalisation, quality of life benefit with ivabradine treatment, length of hospitalisation stay and treatment effect of ivabradine on NYHA distribution all remained below £11,000 per QALY gained (an increase of less than 33%). However, when the 95% upper CI for the hazard ratio (HR) of cardiovascular mortality is used in the analysis (1.07; i.e., ivabradine increases the risk of cardiovascular mortality) the ICER increases to

approximately £40,000 per QALY gained, which suggests that the manufacturer's model is most sensitive to changes in the treatment-related risk of cardiovascular mortality. In addition, one-way sensitivity analysis of the structural assumptions around treatment effect demonstrated some sensitivity in the model to the assumed duration of treatment effect; the ICER increased to £15,078 and £13,964 when treatment effect is assumed to continue for 5 and 10 years, respectively. However, the ERG notes that the alternative assumptions used in the assessment of the model's sensitivity to the duration of treatment effect are pessimistic. That is, the effect of treatment is assumed to gradually decline and cease over 5 to 10 years, yet the cost of therapy is maintained.

In addition to assessment of the model's sensitivity to structural assumptions around the duration of treatment effect, the manufacturer carried out several structural sensitivity analyses, which are summarised in Table 46. The impact on the ICER (£/QALY) of each structural sensitivity analysis is summarised in the tornado diagram presented in Figure 11.

Table 46. Structural deterministic analysis

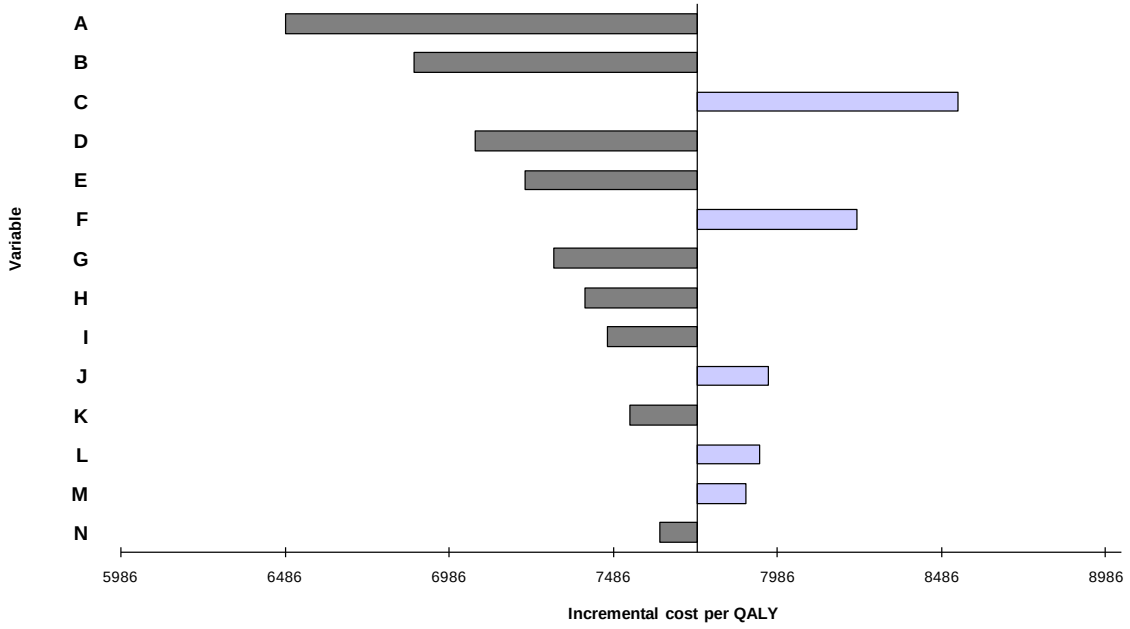
Scenario	Description of scenario	Base case assumption	Sensitivity analysis assumption	Alternative ICER (£/QALY)
A	Hospitalisation length of stay	NHS reference cost	HES data	6,486
B	Titration visit and ECG costs	Included	Excluded	6,881
C	Data used to estimate the within trial risk of cardiovascular mortality	Parametric regression (Gompertz)	Kaplan-Meier	8,536
D	Data used to extrapolate cardiovascular mortality risk	SHIfT predicted (Gompertz)	External data from CARE-HF	7,066
E	Ivabradine treatment duration	Lifelong	5 years	7,218
F	Method of extrapolation of NYHA distribution	LoCF	Assumption based[a]	8,227
G	Hospitalisation length of stay	NHS ref cost	NHF audit	7,305
H	Parametric regression used to estimate risk of cardiovascular mortality	Gompertz	Weibull	7,400
I	Parametric regression used to estimate risk of cardiovascular mortality	Gompertz	Exponential	7,468
J	Age adjustment of quality of life weights	Excluded	Included	7,959

K	Data used for quality of life weights	SHIfT predicted	External literature	7,538
L	Data used to extrapolate cardiovascular mortality risk	SHIfT predicted (Gompertz)	External data from Western Australian	7,934
M	Ivabradine treatment effect	All cardiovascular mortality and all-cause hospitalisation	Heart failure mortality and hospitalisation only	7,889
N	Method of extrapolation of NYHA distribution	LoCF	SHIfT predicted	7,630

[a] The distribution of patients across NYHA classes is assumed to be the same for both arms at the end of the "within trial" period and 5% of patients from NYHA classes I and II will move into NYHA classes II and II, respectively.

Abbreviations used in table: ECG, electrocardiogram; HES, hospital episode statistics; HF, heart failure; ICER, incremental cost-effectiveness ratio; LoCF, last observation carried forward; NHF, National Heart Failure; NHS, National Health Service; NYHA, New York Heart Association; QALY, quality adjusted life year.

Figure 11. Tornado diagram of structural deterministic analysis (adapted from MS; Figure 19 pg178)



The manufacturer's model showed little sensitivity to any of the structural sensitivity analyses; the ICERs obtained all remained below £9,000 per QALY gained (an increase of less than 16%).

5.2.12 Subgroup analysis

The manufacturer carried out extensive subgroup analysis using the method of sequential application of individual patient characteristics as per the base case analysis. The subgroups were pre-specified in the SHIfT trial protocol or from previous SHIfT study publications.[33;57], with an additional post-hoc subgroup of patient age (<75 years and ≥ 75 years). The subgroups considered were:

- patient age (<75 years and ≥75 years);
- NYHA classification (II, III and IV);
- beta-blocker use (no beta-blocker use, <50% target dose, ≥ 50% of target dose and < 100% target dose, and ≥ 100% target dose);
- heart failure duration (<0.6 years, ≥ 0.6 years and <2 years, ≥2 years and <4.8 years, ≥4.8 years);
- LVEF (<26%, ≥26% and<30%, ≥30% and <33%, ≥33%);
- prior medical history (coronary artery disease, diabetes);
- ischaemic aetiology (yes/no).

The ICER for each of these subgroups was calculated using the manufacturer's base case model. In addition, the ICERs were calculated using an alternative model with regression equations developed from the licensed population rather than the entire population of the SHIfT trial. The ICER results of these subgroup analyses are presented in Table 47 (full results are given in Appendix 19 and Appendix 20).

Table 47. Subgroup results for ivabradine plus standard care versus standard care alone using the base case and alternative models

Subgroup	ICER (£/QALY) (Base case model)	ICER (£/QALY) (Alternative model)
Licensed population	8,498	6,307
Age <75 years	8,464	6,286
Age ≥75 years	9,101	6,666
NYHA II	9,712	6,945
NYHA III	7,467	5,731
NYHA IV	5,197	4,625
Heart failure duration <0.6 years	8,886	6,585
Heart failure duration ≥0.6 years and <2 years	8,489	6,291
Heart failure duration ≥2 years and <4.8 years	8,901	6,492
Heart failure duration ≥4.8 years	7,573	5,786
No beta-blocker	5,361	4,700
Beta-blockade <50% target dose	7,726	5,919
Beta-blockade ≥50% target dose and< 100% target dose	9,689	6,855

Beta-blocker ≥100% target dose	10,374	7,169
LVEF <26%	6,258	5,025
LVEF ≥26% and <30%	8,030	6,093
LVEF ≥30% and <33%	9,090	6,595
LVEF ≥33%	10,427	7,369
Non-diabetic	8,883	6,485
Diabetic	7,654	5,909
No prior CAD	7,785	5,814
Prior CAD	8,851	6,542
Abbreviations used in the table: CAD, coronary artery disease; ICER, incremental cost-effectiveness ratio; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; QALY, quality adjusted life year.		

The results of the manufacturer's subgroup analyses indicate that the cost-effectiveness results are robust to changes in patient characteristics. Furthermore, the ERG notes that the results of the alternative model (based on regression equations developed using the licensed population rather than the entire SHIfT patient population) were more favourable for ivabradine than the results of the base case model. However, the manufacturer did not submit a version of the alternative model, therefore, the ERG has not been able to validate these results.

Based on evidence of the benefit of optimising beta-blocker therapy (discussed in Section 5.2.6), the cost-effectiveness results in the subgroups of patients at different levels of beta-blockade were of particular interest. The ICERs obtained from the manufacturer's base case and alternative models remained below £11,000 per QALY gained for all subgroups of the licensed population by beta-blocker dose. However, the ERG notes that the regression equations used to inform these subgroup analyses were based on the entire or licensed population of SHIfT, rather than the particular subgroup of patients considered. The ERG accepts that the issues of breaking randomisation and smaller patient numbers would compromise any analyses based on regression equations developed from subgroups. However, the ERG wishes to highlight that the HRs estimated from regression equations based on the entire or licensed population of SHIfT may over (or under) estimate the effect of treatment in particular patient populations; depending on the population considered.

In addition, two further subgroup analyses were considered using the manufacturer's base case model. These were:

- a typical UK heart failure population ≥75 bpm with beta blockade of ≥50% target dose beta-blockade and < 100% target dose;
- a typical UK heart failure population ≥75 bpm treated with ≥100% target dose beta-blockade.

A typical UK heart failure patient was considered to be a Western European male and aged 78 years. The results of these analyses are displayed in Table 48.

Table 48. Subgroup results for a typical UK heart failure population: heart rate ≥75 bpm (adapted from MS; Tables 67 and 68, pg 186)

Sub-group	ICER (£/QALY) (base case model)
Beta blockade ≥50% target dose and <100% target dose	8,735
Beta-blocker ≥100% target dose	9,185
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.	

5.2.13 Model validation and face validity check

The manufacturer stated that various measures (discussed below) were taken to validate and quality assure the model.

At the beginning of the model development, a clinical expert in heart failure reviewed the proposed economic model plan. In addition, the regression models developed from SHIfT data were reviewed by the clinical expert (for the validity of the covariates and derived estimates). Subsequently, an advisory board was convened that comprised two clinical experts in heart failure management and four health economists experienced in modelling this indication. The advisory board initially met twice to agree on the draft model and sense check model assumptions and at a later date to sign off the final model. All invited experts were asked to declare conflicts of interest at the start of the process.

In addition, internal quality assurance of the regression models was undertaken by a senior analyst and an independent biostatistician. Further validation of the Microsoft© EXCEL model was performed by a senior analyst and analysts not involved in the model development process (the Markov trace was independently rebuilt). The manufacturer stated that the model building was essentially iterative to ensure internal and external validity of the model. The model building was also informed by a systematic review of previous pharmaceutical interventions in heart failure.

Furthermore, a wide range of structural and parameter sensitivity analysis were undertaken to test the robustness of the model results. In addition, the outputs of the economic model were compared against the observed SHIfT trial outputs in order to evaluate the consistency of the model and trial estimates. As discussed in Section 5.2.10, the modelled results underestimate the risk of cardiovascular mortality and rate of hospitalisation. Moreover, the relative effect of treatment with ivabradine plus standard care versus standard care alone is underestimated. Consequently, the model results are relatively conservative, that is, any bias is likely to be against ivabradine.

The ERG notes that internal and external validity of the model has been robustly assessed and that good practice modelling guidance has been followed.[92]

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG was satisfied with the estimates obtained from the manufacturer's model. Moreover, the sensitivity and subgroup analyses carried out by the manufacturer provided sufficient assessment of any areas of uncertainty.

5.4 Conclusions of the cost effectiveness section

Overall, the ERG is satisfied that the model developed by the manufacturer to assess the relative cost-effectiveness of the addition of ivabradine to standard care is robust. Recommended methods for the estimation and extrapolation of survival have been followed.[93] In addition methodological recommendations for the assessment and extrapolation of relative treatment effect have been adhered to.[91;93] Furthermore, the ERG notes that all outcomes of interest have been captured either explicitly (e.g. cardiovascular mortality) or implicitly (e.g. adverse events).

The manufacturer carried out extensive sensitivity analysis on key parameters and structural assumptions which revealed that the model results are relatively insensitive to the use of alternative parameters and assumptions. Moreover, some of the manufacturer's key base case assumptions are conservative (i.e. favour treatment with standard care alone), particularly:

- the use of the entire SHIfT population to develop regression equations for the prediction of outcomes and relative treatment effects;
- the assumption of a linear relationship between baseline resting heart rate and cardiovascular mortality;
- the choice of a Gompertz distribution for parametric regression of cardiovascular mortality;
- the use of a regression equation unadjusted for patient baseline characteristics to predict the distribution of patients across NYHA classes.

Sensitivity analysis around the relative effect (hazard ratio [HR]) of treatment on the risk of cardiovascular mortality was the only analysis observed to have a large impact on model results. The variation of the HR between estimated 95% confidence intervals of 0.83 and 1.07 (mean estimate was 0.94) resulted in ICERs of £5,655 and £40,638, respectively. However, the ERG notes that the sensitivity of the model to this variation may be a reflection of the uncertainty around treatment effect on cardiovascular mortality risk; the regression analysis suggested that the effect of ivabradine treatment on the risk of cardiovascular mortality was statistically non-significant. Furthermore, the uncertainty around this treatment effect may be related to the conservative nature of the regression equations developed to predict the risk of cardiovascular mortality; the regression analysis underpredicts the risk of cardiovascular mortality and therefore limits the potential of ivabradine to reduce this risk.

The ERG notes that not all of the manufacturer's structural assumptions favoured treatment with standard care alone, particularly:

- the absence of age adjustment beyond baseline;
- the assumptions around the extrapolation of NYHA distribution;
- the use of parametric regression rather than Kaplan-Meier data in the "within-trial" period

The absence of age adjustment for health related quality of life (HRQoL) gains beyond baseline was a structural assumption that favoured ivabradine. However, the ERG notes that the impact of age adjustment was minimal (increased the ICER by £216). Furthermore, the ERG notes that the use of individual patient-level data to calculate the base case ICER, meant that the model had to be re-run each cycle to propagate the adjustment for age throughout the model time horizon. Therefore, the ERG accepts the exclusion of age adjustment from the base case analysis on the grounds of computational expediency.

The base case assumptions around the extrapolation of NYHA distribution favoured ivabradine. However, the ERG considers these assumptions to be reasonable based on evidence of improvement in NYHA classification from SHIfT (see Section 4.3.1). Similarly, the ERG considers the use of data from parametric regression analysis rather than Kaplan-Meier analysis for the "within-trial" period to be reasonable. This is because consistency of outcomes assessed is maintained throughout the model time horizon.

The ERG notes that the manufacturer constructed the economic model to enable examination of the relative cost-effectiveness of adding ivabradine to standard care in various subgroups. Following results from exploratory analysis carried out in the clinical section of this report (Section 4.3.4), the ERG were particularly interested in the results for patients grouped by different levels of beta-blocker dose. The ERG notes that the regression analyses carried out by the manufacturer of cardiovascular mortality (and heart failure mortality) suggest that ivabradine is associated with a statistically non-significant (or borderline significant in heart failure) risk reduction. In contrast, beta-blocker therapy of $\geq$ 50% of target dose (or any dose for heart failure mortality) is associated with a statistically significant risk reduction. However, the ICERs obtained from the manufacturer's base case model for these subgroups remained below £11,000 per QALY gained. The ERG notes that the maintenance of benefit for ivabradine (versus standard care alone) is likely to be a result of the reduction in hospitalisation; the significance of the effect of ivabradine on the reduction of hospitalisation is maintained across patients regardless of beta-blocker dose.

To conclude, the ERG considers that the manufacturer's base case ICER of £8,498 per quality adjusted life year (QALY) gained is likely to represent the expected cost-effectiveness of adding ivabradine to standard care. However, the ERG notes that the ICER is biased against ivabradine.

However, the ERG considers that evidence from the manufacturer's regression analyses suggests a level of uncertainty associated with the mortality benefit of ivabradine. Furthermore, the ERG notes that as the manufacturer's regression analyses adjust for heart rate, this uncertainty is over and above that observed in the clinical analysis (reported in Section 4.3.4).

6 OVERALL CONCLUSIONS

The manufacturer presents the case for the addition of ivabradine compared with addition of placebo to standard care for the treatment of heart failure based on data derived from the SHIfT randomised controlled trial (RCT).[33] The Evidence Review Group (ERG) considers the SHIfT trial to be a well-designed RCT evaluating a widely accepted primary outcome in heart failure (composite of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure). The SHIfT trial randomised patients with a baseline resting heart rate of ≥70 bpm. Subsequent to completion of the trial, the European Medicines Agency approved a licence extension for ivabradine to include use in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.[26] Consequently, the manufacturer submitted evidence to NICE based on the *post hoc* subgroup of patients in the SHIfT trial who had a resting heart rate of ≥75 bpm. The ERG notes that randomisation was not stratified by baseline resting heart rate and thus there is the potential for imbalance in unknown confounders between the groups. However, the reported baseline characteristics of the licensed population are well balanced for the ivabradine and placebo groups and the ERG considers the dataset to be of sufficient robustness to inform the decision problem.

Only 12 patients of 6,558 patients recruited to the full SHIfT trial were from the UK. Rationales proposed for the low level of recruitment from the UK are that the UK is a particularly poor recruiter for clinical trials and difficulties may have been encountered in identifying eligible patients. As patients from the UK contribute a negligible component to the overall trial population, and therefore the licensed population, for the results of the SHIfT trial to be generalisable to UK clinical practice one of the important considerations is that patients were receiving standard heart failure therapies comparable to UK clinical practice. The ERG considers that the manufacturer has provided evidence to demonstrate that patients received standard treatments at optimal doses and thus the results of the SHIfT trial for the licensed population are generalisable to a UK population. The ERG notes that, although patients in the licensed population of the SHIfT trial are younger and have more severe heart failure than patients typically seen in UK clinical practice, the baseline characteristics of the licensed population of the SHIfT trial are similar to those of patients recruited to other key heart failure clinical trials.[27;37-45]

In the licensed population of the SHIfT trial, addition of ivabradine to standard care was associated with a statistically significant reduction in the primary composite outcome of time to first event of cardiovascular mortality or hospitalisation for worsening heart failure (26.6% with ivabradine vs 32.8% with placebo; HR 0.76; 95% CI: 0.68 to 0.85). Analyses of the individual components of the primary composite outcome indicate that reduction in hospitalisation for worsening heart failure is the

key driver in the clinical effect of ivabradine observed for the primary composite outcome, with a statistically significant risk reduction of 30% for this endpoint relative to placebo (17.7% with ivabradine vs 24.0% with placebo; HR 0.70; 95% CI: 0.61 to 0.80; p <0.0001). However, ivabradine also reduced cardiovascular mortality (14.8% with ivabradine vs 17.4% with placebo; HR 0.83; 95% CI 0.71 to 0.97; p = 0.0166). The greatest relative benefit of ivabradine was associated with the cause-specific outcome of death from heart failure (3.8% with ivabradine vs 6.0% with placebo; HR 0.61; 95% CI: 0.46 to 0.81; p = 0.0006), which was assessed as a pre-specified secondary outcome.

The ERG considers that there is limited evidence on the effectiveness of adding ivabradine to standard care for patients with NYHA class IV severity of heart failure, and that the evidence base is limited for the addition of ivabradine for patients who have had a device implanted or who may be considered for CRT.

Ivabradine was generally well-tolerated. In the licensed population of the SHIfT trial, adverse effects associated with ivabradine treatment were bradycardia (symptomatic and asymptomatic) and phosphenes, both of which are recognised adverse effects of ivabradine.

Based on exploratory analyses, the ERG considers that the beneficial effect of ivabradine could be [redacted] in patients with a resting heart rate ≥75 bpm who achieve higher doses of beta-blocker therapy. The ERG carried out exploratory analyses based on various thresholds of beta-blockade. Results of the exploratory analysis based on beta-blocker dose achieved indicate that ivabradine was associated with [redacted] in the cause-specific endpoints of hospitalisation for heart failure and heart failure death, [redacted] of both endpoints irrespective of category of beta-blocker dose assessed; however, some of the differences between groups [redacted]. For all other outcomes, including the primary composite outcome, there was a trend towards [redacted] of ivabradine with increasing beta-blocker dose, and, in some analyses, [redacted], which suggests a [redacted] addition of ivabradine to standard care. In the case of the primary composite outcome, the exploratory analysis suggests [redacted] of ivabradine on the primary outcome for patients achieving ≥100% target dose of beta-blocker [redacted]. A meta-regression of 23 RCTs assessing the use of beta-blockers reported that for every 5 bpm reduction in heart rate with use of beta-blockers there was an 18% reduction in all-cause mortality.[14] The ERG notes that despite a consistent additional [redacted] in resting heart rate of [redacted] across beta-blocker categories there does not seem to be a consistent [redacted] in all-cause mortality.

Considering cardiovascular mortality, in patients achieving ≥100% target dose of beta-blockade, the ERG's analysis found that ivabradine was associated with [redacted].

The ERG speculates that the results of the exploratory analyses suggest that there is uncertainty around the benefit of adding ivabradine to standard care for patients with a resting heart rate of ≥75 bpm and who are achieving higher levels of beta-blockade. The ERG considers it important to highlight that its analyses are speculative and are based on subgroups of subgroups, and thus should be interpreted with caution.

The manufacturer's economic evaluation resulted in a base case ICER of £8,498 per quality adjusted life year (QALY) gained. The ERG considers that this is likely to represent the expected cost-effectiveness of adding ivabradine to standard care. However, the manufacturer's regression analyses suggests a level of uncertainty associated with the treatment effect of ivabradine on cardiovascular mortality; the treatment effect of ivabradine on cardiovascular mortality was statistically non-significant and the treatment effect of ivabradine on heart failure mortality was of borderline statistical significance. By contrast, beta-blockade of 50% of target dose or more was associated with a statistically significant reduction in the risk of cardiovascular mortality and beta-blockade of any level was associated with a statistically significant reduction in the risk of heart failure mortality. The ERG notes that the manufacturer's regression analyses are adjusted for baseline resting heart rate. Therefore, the risk reduction of ivabradine and beta-blockade is over and above the attenuating effect of heart rate.

The ERG considers that its exploratory clinical analyses reveal uncertainty around the benefit of adding ivabradine to standard care for patients with a resting heart rate of ≥75 bpm and who are achieving higher levels of beta-blockade. Although these analyses were not adjusted for baseline resting heart rate, baseline resting heart rate was similar across groups assessed. In addition, the ERG considers that the manufacturer's regression analyses, which do adjust for baseline resting heart rate, suggest that the treatment effect of ivabradine is uncertain compared with effect of beta-blockade.

6.1 Implications for research

Based on its exploratory analyses, the ERG considers up-titration of beta-blockade to be an important issue when considering the addition of ivabradine to standard care. As highlighted by the authors of a meta-regression analysis of RCTs evaluating treatment with beta-blockers, there is uncertainty around whether there is additional benefit to up-titrating beta-blocker dose to the recommended doses if a substantial heart rate reduction has already been achieved with a lower dose, or, conversely, increasing beta-blocker dose above recommended doses. The ERG considers that studies investigating this further would be informative for service provision within the NHS. The ERG considers that there is a need for further research into the clinical benefit of ivabradine for patients receiving optimised beta-blocker therapy.

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8 APPENDICES

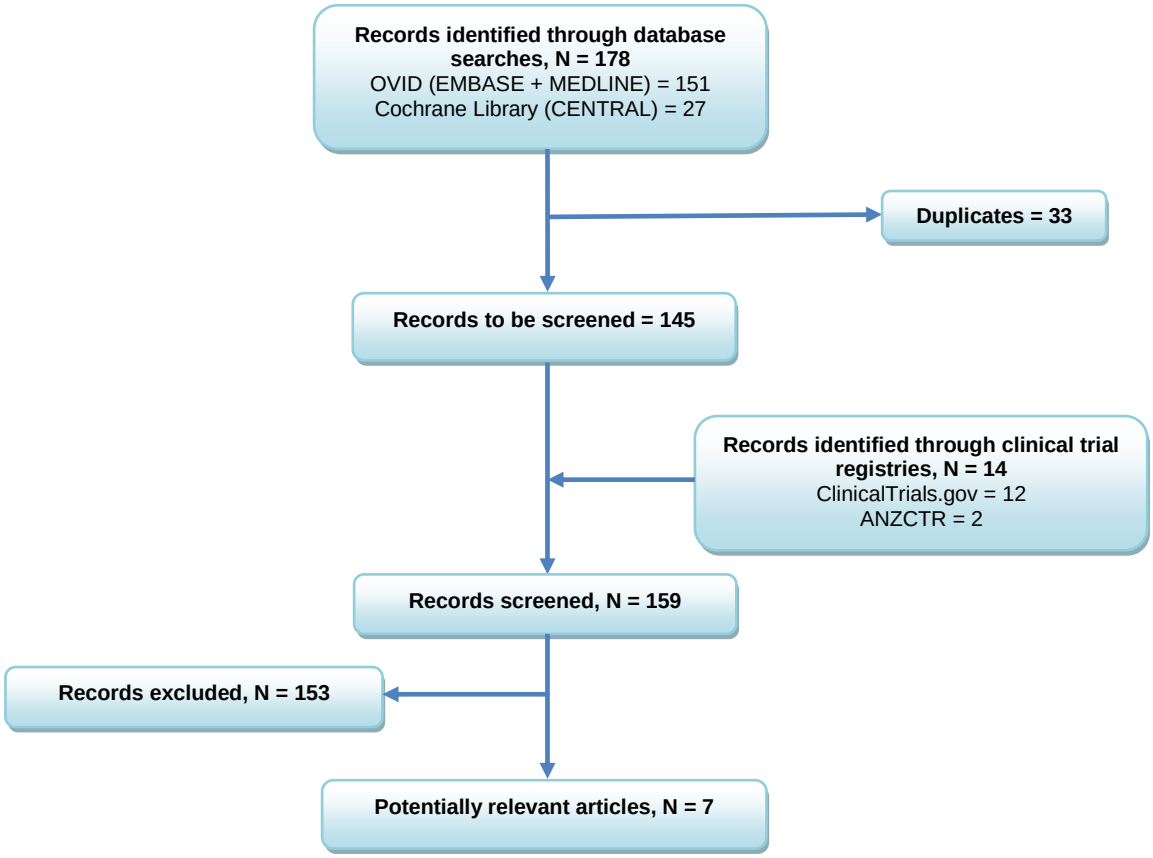
Appendix 1. Baseline characteristics of patients in key heart failure trials

Characteristic	SHIfT[33]	CONSENSUS[41]	CHARM[38]	MERIT[43]	COPERNICUS[42]	CIBIS II[39]
Treatment assessed (vs placebo unless stated)	Ivabradine	Enalapril (ACE inhibitor)	Candesartan (ARB)	Metoprolol (beta-blocker)	Carvedilol (beta-blocker)	Bisoprolol (beta-blocker)
Number of patients	6,505	253	2,548	3,991	2,289	2,647
Inclusion criteria	Age ≥18 years HR ≥70 bpm Sinus rhythm LVEF ≤35% NYHA class II–IV	NYHA class IV	Age ≥18 years LVEF ≤40% NYHA class II–IV	Age 40–80 years LVEF ≤40% NYHA class II–IV Optimised therapy for ≥2 weeks	LVEF ≤25%	Age ≥18 years LVEF ≤35% NYHA class III or IV Treated with diuretic and ACE inhibitor for at least 2 weeks
Mean age (years)	60	70–71	64	64	63	60–62
Male	76%	70–71% (baseline for full population not reported separately)	79%	77%	79%	81%
EF	29%	Not reported	28%	28%	20%	27%
NYHA class	NYHA II 49% NYHA III 50% NYHA IV 2%	NYHA 100%	NYHA II 24% NYHA III 73% NYHA IV 3%	NYHA II 41% NYHA III 55% NYHA IV 4%	Not reported	NYHA III 83% NYHA IV 17%
Baseline resting heart rate (bpm)	80	80	74	83	83	77–87 (baseline rate for full population not reported separately)

Beta-blocker dose achieved	26.2% achieved target dose 55.4% achieved ≥50% target dose (licensed population)	N/A	N/A	64% achieved target dose of 200 mg once daily	65.1% achieved target dose of 25 mg twice daily	42.6% achieved target dose of 10 mg once daily
Characteristic	**BEST[37]**	**SENIORS[45]**	**CARE HF[27]**	**RALES[44]**	**COMET[40]**	
Treatment assessed (vs placebo unless stated)	Bucindolol (beta-blocker)	Nebivolol (beta-blocker)	Cardiac resynchronization (without a defibrillator) added to standard care	Spironolactone	Carvedilol vs metoprolol (both beta-blockers)	
Number of patients	2,708	2,128	813	1,663	3,029	
Inclusion criteria	Age ≥18 years LVEF ≤35% NYHA class III or IV Optimised therapy for ≥4 weeks	Age ≥70 years	Age ≥18 years LVEF ≤35% NYHA class III or IV	LVEF ≤35% NYHA class III or IV at enrollment	NYHA class II–IV Optimised therapy for ≥4 weeks	
Mean age, years	60	76	66–67 (median) (baseline for full population not reported separately)	65	62	
Male	78%	63%	73%	73%	80%	
EF	23%	36% (some patients has preserved EF)	25%	25%	26%	
NYHA class	NYHA III 92% NYHA IV 8%	NYHA III / IV 42% (data not reported separately for individual NYHA classes)	NYHA III 94% NYHA IV 6%	NYHA II 0.5% NYHA III 70.5% NYHA IV 29%	NYHA II 48% NYHA III 48% NYHA IV 4%	

Baseline resting heart rate (bpm)	82	72.8–81.0 (baseline for full population not reported separately)	69–70 (median) (baseline for full population not reported separately)	81	81	
Beta-blocker dose achieved	Not reported	67% achieved target dose of 10 mg once daily	N/A	N/A	Carvedilol: 75% achieved target dose of 25 mg twice daily, 85% achieved ≥50% target dose Metoprolol: 78% achieved target dose of 50 mg twice daily, 87% achieved ≥50% target dose	
Abbreviations used in table: ACE, angiotensin-converting enzyme; bpm, beats per minute; EF, ejection fraction; HR, heart rate; LVEF, left-ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association.						

Appendix 2. Flow diagram for Evidence Review Group's validation of manufacturer's systematic review



Appendix 3. Quality assessment of SHIfT

Question	Description in MS[a]	Manufacturer's assessment	ERG's assessment
Was randomisation carried out appropriately?	Randomisation was via a central telephone randomisation service. The randomisation was balanced, non-adaptive, stratified on centre and beta-blocker intake at randomisation	Yes	Agree
Was the concealment of treatment allocation adequate?	The allocation sequence was generated at the sponsor level through validated in-house application software; access was restricted to people responsible for study therapeutic unit's production until database lock. These people had no involvement in the rest of the trial	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The randomisation was balanced, non-adaptive, stratified on centre and beta-blocker intake at randomisation. Eligible patients were allocated to receive ivabradine or placebo in addition to treatments appropriate to their HF, with particular emphasis on background treatment with a beta-blocker. Randomisation blocks (of size 4) were randomly and dynamically assigned to the centres in order to respect the stratification on the two pre-defined factors	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was double blind; patients and investigators were masked to treatment allocation. The DMC was the only committee authorised to have access to comparative results on safety and efficacy data. All PSE (leading to study endpoint if adjudicated) were reviewed by the EVC who confirmed or rejected the diagnoses attached to the PSEs. This committee was blinded to the allocated study treatments as well as to baseline heart rate	Yes	Agree
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A total of 1287 patients (19.8% of the RS) prematurely discontinued the study treatment (SHIfT CSR pg 81 and Table (10.1) 5 pg 82). A slightly higher rate of study treatment withdrawal was observed in the ivabradine group: 682 patients (21.0%) in the ivabradine group vs 605 patients (18.5%) in the placebo group. The treatment withdrawals were mainly due to adverse events (64.0% of withdrawals) or non-medical reason (31.0% of withdrawals). The main between-group differences were: Events related to the mechanism of action	No	Agree

	of ivabradine – i.e., slowing of the heart rate (including the category 'heart rate <50 bpm at the 2.5 mg bd dose'; and the adverse events, bradycardia and heart rate decreased) which led to treatment withdrawal in a total of 70 patients in the ivabradine group (2.2% of RS; 10.3% of withdrawals) vs13 in the placebo group (0.4% of RS; 2.1% of withdrawals); and Episodes of 'cardiac failure' i.e. acute decompensation, which led to treatment withdrawal in 56 patients (8.2% of withdrawals) in the ivabradine group vs 65 patients (10.7% of withdrawals) in the placebo group. The use of a prohibited concomitant treatment was the main reason for permanent study drug withdrawal in a total of 39 patients (3.0% of withdrawals): 18 patients (2.6%) in the ivabradine group vs 21 patients (3.5%) in the placebo group. Non-medical reasons were mostly consent withdrawals		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Full details of the study (outcomes etc.) are provided within the CSR	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	In the SHIfT study, all survival analyses based on time-to-first event were performed for all outcomes on an intention-to-treat (ITT) basis. The safety analyses were carried out on patients of the safety set; i.e., patients having taken at least one dose of study medication	Yes	Agree

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

[a] Description taken from Table 8 (pg 60) of the MS.

Abbreviations used in table: bd., twice daily; bpm, beats per minute; CSR, Clinical Study Report; DMC, Data Monitoring Committee; ERG, Evidence Review Group; EVC, Endpoint Validation Committee; HF, heart failure; MS, manufacturer's submission; PSE, pre-specified events; RS, randomised set.

Appendix 4. Results from the SHIfT trial for the full population (resting heart rate ≥70 bpm)

Outcome	Ivabradine N = 3,241	Placebo N = 3,264	HR[a] (95% CI)	p-value
Primary outcome				
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	793 (24.5)	937 (28.7)	0.82 (0.75 to 0.90)	<0.0001
Secondary outcomes				
Cardiovascular death, n (%)	449 (13.9)	491 (15.0)	0.91 (0.80 to 1.03)	0.128
Hospitalisation for worsening HF, n (%)[c]	514 (15.9)	672 (20.6)	0.74 (0.66 to 0.83)	<0.0001
Death from any cause, n (%)	503 (15.5)	552 (16.9)	0.90 (0.80 to 1.02)	0.092
Death from HF, n (%)	113 (3.5)	151 (4.6)	0.74 (0.58 to 0.94)	0.014
Hospitalisation for any cause, n (%)[c]	1,231 (38.0)	1,356 (41.5)	0.89 (0.82 to 0.96)	0.0027
Hospitalisation for cardiovascular reason, n (%)[c]	977 (30.2)	1,122 (34.4)	0.85 (0.78 to 0.92)	0.0002
Primary outcome in population on ≥50% target dose beta-blockade				
	N = 1,581	**N = 1,600**		
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	330 (20.9)	362 (22.6)	0.90[b] (0.77 to 1.04)	0.155

[a] For the primary outcome, HR is an estimate of the HR between treatment groups based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate.

[b] Estimate of the HR between treatment groups based on an unadjusted Cox proportional hazards model.

[c] Patients were often hospitalised on more than one occasion and for different reasons: the first admission for each analysed reason is counted in this analysis.

Abbreviations used in table: HF, heart failure; HR, hazard ratio.

Appendix 5. Concomitant treatments for heart failure at randomisation in the licensed population

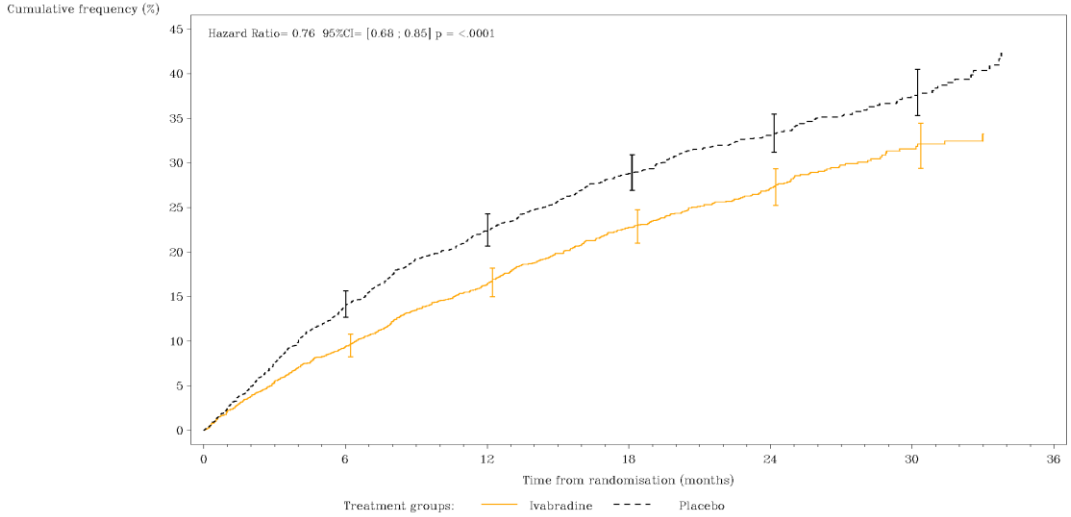
Background therapy	Heart rate ≥75 bpm at baseline (N = 4,150)	
	Ivabradine N = 2,052	Placebo N = 2,098
Beta-blocker intake		
Beta-blocker intake at randomisation, n (%)	1,794 (87.4)	1,845 (87.9)
ESC recommended beta-blocker or metoprolol tartrate[a] (N)	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
At least half of the target daily dose (N)	1,767	1,818
Yes, n (%)	974 (55.1)	1,012 (55.7)
No, n (%)	793 (44.9)	806 (44.3)
Target daily dose (N)	1,767	1,818
Yes, n (%)	467 (26.4)	471 (25.9)
No, n (%)	1,300 (73.6)	1,347 (74.1)
Reasons why not at target daily dose (N)	[redacted]	[redacted]
Hypotension, n (%)	[redacted]	[redacted]
Fatigue, n (%)	[redacted]	[redacted]
Pulmonary dyspnoea, n (%)	[redacted]	[redacted]
Dizziness, n (%)	[redacted]	[redacted]
Cardiac decompensation, n (%)	[redacted]	[redacted]
Bradycardia, n (%)	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]
Concomitant treatments (other than beta-blockers)		
ACE inhibitor and/or ARB, n (%)	1,852 (90.3)	1,896 (90.4)
Diuretics (excluding aldosterone antagonist), n (%)	1,743 (85.0)	1,741 (84.0)
ACE inhibitor, n (%)	[redacted]	[redacted]
Aldosterone antagonist (potassium-sparing diuretic), n (%)	1,286 (62.7)	1,271 (60.6)
Digitalis/digoxin, n (%)	478 (23.3)	512 (24.4)
ARB, n (%)	[redacted]	[redacted]

Cardiac devices at baseline		
At least one device: pacemaker and/or CRT and/or ICD	66 (3.2)	94 (4.5)
ICD	[redacted]	[redacted]
Device with pacemaker function	[redacted]	[redacted]
Conventional pacemaker only	[redacted]	[redacted]
CRT	[redacted]	[redacted]
CRT and ICD	[redacted]	[redacted]

[a] Concerning the 107 patients who were not taking one of the recommended beta-blockers, 59 were taking atenolol, 33 were taking betaxolol and the remaining patients were taking other types of beta-blocker. None of these patients was eligible for inclusion in the RS_{BBDOSE}.

Abbreviations used in table: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; ESC, European Society of Cardiology; ICD, implantable cardioverter defibrillator; RS_{BBDOSE}, patients of the randomised set (full trial population) receiving at least half of target daily dose of beta-blockers at randomisation.

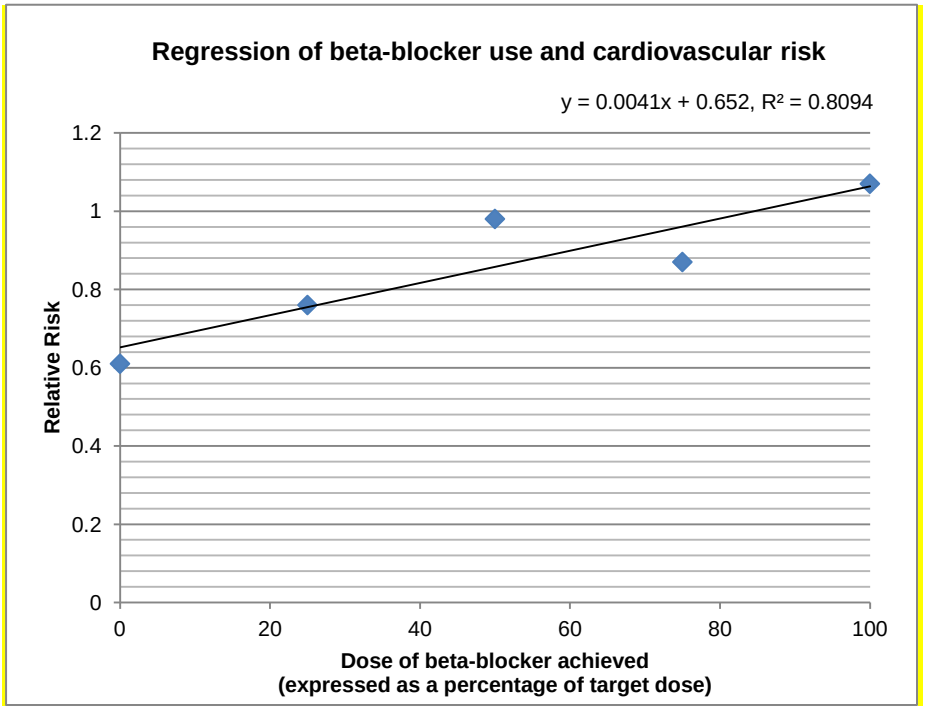
Appendix 6. Kaplan-Meier analysis for time to first event of primary composite endpoint: licensed population (≥75 bpm) (reproduced from MS; Figure 8, pg 70)



Nber of patients at risk*	2052/2098	1837/1785	1614/1521	1318/1227	715/657	261/257	8/9
Cumul. nber of endpoints*	0/0	191/290	331/463	449/583	510/646	541/677	545/688
Cumul. frequency (%)*	0/0	9.37/13.9	16.37/22.37	22.74/28.8	27.11/33.08	31.57/37.59	33.23/42.42

*:Ivabradine/Placebo

Appendix 7. Linear regression plot based on threshold of beta-blocker dose achieved for the outcome of cardiovascular mortality



Appendix 8. Results for licensed population based on percentage target beta-blocker dose at randomisation

Outcome	Ivabradine % (n/N)	Placebo % (n/N)	RR[a] (95% CI)	p-value
Patients not receiving a beta-blocker at baseline				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for cardiovascular reason	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving <25% target beta-blocker dose at baseline				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving 25–<50% target beta-blocker dose at baseline				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]

Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving 50–<100% target beta-blocker dose at baseline				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving ≥100% target beta-blocker dose at baseline				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for cardiovascular reason	[redacted]	[redacted]	[redacted]	[redacted]

Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Patients optimised for beta-blocker but not achieving target dose (>0%–<100%)				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for cardiovascular reason	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Patients achieving ≥50% of target dose				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
ERG analysis: subgroup of patients achieving <25% beta-blocker dose				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]

Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
ERG analysis: subgroup of patients achieving ≥25% beta-blocker dose				
Primary outcome (composite)				
Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]	[redacted]
Death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]

[a] RR calculated by ERG.

Abbreviations used in table: bpm, beats per minute; ERG, Evidence Review Group; RR, relative risk; SD, standard deviation.

Appendix 9. Results for subgroup of licensed population aged ≥70 years

Outcome	Ivabradine n (%) [redacted]	Placebo n (%) [redacted]	RR[a] (95% CI)	p-value
Primary outcome				
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for cardiovascular reason, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate				
Mean change in heart rate at last visit, bpm (SD)	[redacted]	[redacted]	–	–

[a] RR calculated by ERG.

Abbreviations used in table: CI, confidence interval; ERG, Evidence Review Group; HF, heart failure; HR, Hazard ratio.

Appendix 10. Results for subgroups of licensed population based on NYHA classification

Outcome	Ivabradine n (%)	Placebo n (%)	RR[a] (95% CI)	p-value
NYHA II	[redacted]	[redacted]		
Primary outcome				
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for cardiovascular reason, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate				
Mean change in heart rate at last visit, bpm (SD)	[redacted]	[redacted]	–	–
NYHA III	[redacted]	[redacted]		
Primary outcome				
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Hospitalisation for cardiovascular reason, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate				
Mean change in heart rate at last visit, bpm (SD)	[redacted]	[redacted]	–	–
NYHA class IV	[redacted]	[redacted]		
Primary outcome				
Composite of first event of cardiovascular death or hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for worsening HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death from HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for any cause, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation for cardiovascular reason, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate				
Mean change in heart rate at last visit, bpm (SD)	[redacted]	[redacted]	–	–

[a] RR calculated by ERG.

Abbreviations used in table: CI, confidence interval; ERG, Evidence Review Group; HF, heart failure; NYHA, New York Heart Association; RR, Relative risk.

Appendix 11. Details of pharmaceutical economic evaluations studies identified by the manufacturer (adapted from MS; Table 84)

Author and year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Boersma, 2006	The Netherlands	Incremental cost analysis	Mean age 62.7	Not stated	Total inpatient and outpatient cost Valsartan = €8,810 Placebo = €8,442	Valsartan provided cost saving of €368 per person with heart failure in The Netherlands
Colombo, 2008	Italy	Within trial analysis conducted based on three CHARM trials	Not stated	QALY not reported. Life year gain CHARM – alternative: 0.078 CHARM – Added: 0.061 Reduced LVEF: 0.068	Total or incremental cost not reported	Cost per LYG CHARM – alternative: €713 LYG CHARM – Added: dominant Reduced LVEF: Dominant
Mark, 2006	US, Canada and New Zealand (SCD-HeFT study)	Cumulative within-trial 5-year medical costs estimated using non-parametric partitioned estimator. Post-trial long-term costs estimated using 2 covariate-specific regression models. Life expectancy estimated using extrapolated trial data. Two separate Cox proportional hazards models used with the hazard rate modelled as a function of patient's age	Median age 60.1	**1 year follow-up (utilities)**: ICD arm = 0.85 Placebo = 0.85	Amiodarone = $49,338* Placebo = $42,971* ICD = $61,938* **cumulative 5-year estimates.*	ICER per life-year saved (base case): ICD vs medical therapy = $38,389 ICER (1 year follow-up): $41,530 per QALY

McKenna, 2010	RALES trial conducted in 15 countries, EPHESUS conducted in 37 countries. AREA IN-CHF study also used	Two-part Markov model used: Part I is a short term model that captures costs and outcomes in first 3 months post-MI; Part II is a long term model that captures long-term costs and outcomes after 3 months	Median age 64 (AREA IN-CHF trials)	Eplerenone = 4.8486 Spironolactone = 4.5551 Standard care = 4.5972	Eplerenone = £5,249 Spironolactone = £4,191 Standard care = £4,129	Eplerenone vs standard care = £4,457 Spironolactone vs standard care = Dominated
McMurray, 2006	France, Germany, and UK	Within trial analysis conducted based on three CHARM trials	Not stated	QALY not reported. Life year gain CHARM – alternative: 0.078 CHARM – Added: 0.061 Reduced LVEF: 0.068	Total or incremental cost not reported	**France** Cost per LYG CHARM – alternative: dominant CHARM – Added: dominant Reduced LVEF: Dominant **Germany** Cost per LYG CHARM – alternative: €3,881 CHARM – Added: €1,427 Reduced LVEF: €2,997 **UK** Cost per LYG CHARM – alternative: €2,547 CHARM – Added: dominant Reduced LVEF: €1,348

de Pourvourville, 2008	EPHESUS study conducted in 37 countries	Within-trial study designed, piecewise regression model produced survival gains and death rates adjusted for patients' characteristics. Comparable patients extracted from Saskatchewan database. Long-term survival predicted using piecewise regression and Cox proportional hazards models.	Not stated	∆ life-years gained: **Saskatchewan model**: Eplerenone = 0.066 (no discount) **Framingham model**: Eplerenone = 0.108 (no discount)	∆ cost: **Saskatchewan model**: Eplerenone = €970 (no discount) **Framingham model**: Eplerenone = €970 (no discount)	ICER per life-year saved: **Saskatchewan model**: €15,382 **Framingham model**: €8,954
Pradelli, 2009	Val-HeFT study included patients from 16 countries	Markov model with patient-level simulation. Four health states were used corresponding with NYHA classes	Mean age 62.7	Valsartan = 1.674 Placebo = 1.659	Valsartan = €6,289* Placebo = €6,843* **2007 €'s*	Valsartan was dominant vs placebo across the total patient population
Rosen, 2010	USA	Lifetime cohort Markov model used to assess cost-effectiveness of A80 vs A10 by predicting likelihood of major and minor cardiovascular events. Model composed of several health states according to major CVD event status, minor events and survival	64	Life-years gained (base case): A80 = 8.85 A10 (comparator) = 8.64	Total discounted costs estimated to be $2,000 higher per patient for those receiving A80 (base case).	Base case: A80 vs A10 = $13,600 ($9,600 per life-year saved)

Szucs, 2006	Clinical trial carried in Europe, Latin America, USA and Canada. The data were assumed to transferred to Switzerland	Cost-effectiveness analysis; No model description reported. The majority of data in this study were taken from the EPHESUS study. Survival estimates obtained from other sources	Patients with acute MI complicated by left ventricular dysfunction and heart failure Mean age: Eplerenone group = 64.2 (SD 11.3); Placebo group = 64.7(SD 11.7)	No individual QALYs reported. However, incremental gains in QALYs were: **Framingham study** 0.0722 **Saskatchewan study** 0.0446 **Worcester study** 0.1029	Costs (over 1.3 years or 16 months) in Swiss Francs: Eplerenone = 16,969.78 Placebo = 5,941.29	Incremental costs per QALY gained: **Framingham study** CHF15,219 **Saskatchewan study** CHF23,965 **Worcester study** CHF11,337
Taylor, 2009	*Not stated*	Markov model consisting of 5 health states, data taken from VALIANT and other trials developed to predict future health pathways, resource use and costs.	Not stated	Valsartan = 5.021 Placebo = 4.519	Valsartan = £8,878 Placebo = £6,198	Valsartan vs placebo = £5,338
Yao, 2008	SENIORS trial carried out in 11 European countries	Individual simulation model based on Markov framework, health states defined by NYHA classes	Mean age 76	Nebivolol: 5.843 Standard care: 5.194	Nebivolol: €9,288* Standard care: €6,740* **2006 €'s*	Nebivolol vs standard care = €3,926*
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; LVEF, left-ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; QALY, quality adjusted life year; SD, standard deviation; vs, versus.						

Appendix 12. Implementation of the risk of cardiovascular mortality into the economic model

The survivor function for the Gompertz distribution was estimated as follows:

Gompertz: $S(t) = \exp\{(-\lambda t)p^{-1}(\exp(pt)-1)\}$

Where: t = time; λ = location parameter; p = shape parameter.

The location parameter shifts the distribution (shifts the graph left or right on the horizontal axis) as opposed to the shape parameter which affects the shape of the distribution. Inorder to derive the location and shape parameters, the manufacturer developed a multiple regression equation with 22 independent variables (X) including two additional variables for treatment and treatment/heart rate interaction variables. For example some of the variables included in the regression are sex, age, treatment with aldosterone and for the full list see the table A12.1 below. The simplified regression equation is presented below

$$Y = a + b_1*X_1 + b_2*X_2 + b_2*X_2 +... + b_{22}*X_{22}$$

Where:

- Y- is the dependant variable i.e. the variable to be explained or predicted in a multiple regression model (mortality);
- a - is the intercept the value of Y when all Xs are zero or the constant i.e. amount of mortality which is independent of the predictor variables;
- b1,2,3...22 - The change in the dependent variable associated with a 1-unit change in an explanatory variable X (slope). The dependant variable either increases or decreases depending on the sign of the coefficient;
- X1,2,3..22 - is any value of the independent variable that is selected that partially explains or predicts the movement of a dependent variable.

In the economic model the independent variables were estimated using the individual patient characteristics of all patients in the SHIfT trial and the average values were used. (X1, X2, X3,...X24). The manufacturer used STATA to estimate/predict the b1, b2, b3,...b22 coefficients. To calculate the location parameter (lambda) the b1, b2,b3,....b22 values estimated from the regression equation were multiplied by their corresponding values of X1, X2, X3, ...X22 and added together as illustrated with following formulation and table A12.1 below

b1*X1 + b2*X2 + b3*X3 + ... + b22*X22 giving the location parameter value of -5.1759

Shape parameters allow a distribution to take on a variety of shapes, depending on the value of the shape parameter. The shape parameter was estimated simultaneously with other parameters from the

SHIfT trial using individual patient characteristics (b1, b2,b3,....b22 coefficients and the shape/gamma coefficient were estimated from STATA by the manufacturer). The table below illustrates how the location and shape parameters were derived.

Table A12.1. Derivation of location and shape parameters used in the final regression equations for mortality (reproduced from the manufacturer's model)

Description	b (coefficient)	Xi	BiXi (b*X)
Sex	–0.3726	0.2321	–0.0865
Aldosterone	0.2486	0.6165	0.1533
Digitalis use	0.2795	0.2388	0.0668
Loop diuretic (dose/kg/day)	0.1147	0.6301	0.0723
Lipid medications	–0.2299	0.5643	–0.1297
Systolic BP *	–0.0099	–0.2895	0.0029
NYHA III (vs II)	0.2647	0.5091	0.1348
NYHA III (vs II)	1.0157	0.0209	0.0213
HF duration >=0.6<2 yrs vs <0.6 yrs	0.4120	0.2610	0.1075
HF duration >=2<4.8 yrs vs <0.6 yrs	0.5501	0.2468	0.1357
HF duration >+4.8 yrs vs <0.6 yrs	0.6848	0.2516	0.1723
LVEF >=26%<30% vs <26%	–0.1457	0.1755	–0.0256
LVEF >=30%<33% vs <26%	–0.3395	0.2631	–0.0893
LVEF >=33% vs <26%	–0.5285	0.2882	–0.1523
Heart rate bpm*	0.0226	4.5590	0.1032
Beta-blocker use < half target dose (td)	–0.0092	0.3982	–0.0037
Beta-blocker use >= half td< td	–0.3358	0.2530	–0.0850
Beta-blocker use >= td	–0.3684	0.2258	–0.0832
Age (years)*	0.0199	–0.8110	–0.0162
Prior stroke	0.2432	0.0799	0.0194
Sodium*	–0.0194	–0.1805	0.0035
Potassium	0.1855	0.1808	0.0335
Constant (a)	–5.5309	1.0000	–5.5309
Gamma-shape parameter	0.0101		
Lambda, location parameter			–5.1759

* Variables centred on the mean.

Abbreviations used in table: BP, blood pressure; bpm, beats per minute; cons, constant; HF, heart failure; kg, kilogramme; LVEF, left-ventricular ejection fraction; MS, manufacturer's submission; NYHA, New York Heart Association; SE, standard error; td, target dose.

Appendix 13. The final regression equation, NYHA generalised ordered logistic regression model adjusting for treatment, time and patient characteristics (no interaction terms – used in the manufacturer's clarification model)

Description	Coefficient	SE	P >z	95% LCI	95% UCI
Months NYHA II	–0.054	0.003	0	–0.06	–0.047
Treatment NYHA II	–0.191	0.1	0.057	–0.387	0.006
HF duration ≥0.6<2 yrs	0.364	0.126	0.004	0.117	0.612
HF duration ≥2<4.8 yrs	0.718	0.149	0	0.426	1.01
HF duration ≥4.8 yrs	0.54	0.142	0	0.262	0.818
Atrial fibrillation	0.526	0.246	0.033	0.043	1.008
LVEF ≥26%<30%	0.452	0.164	0.006	0.131	0.774
LVEF ≥30%<33%	0.303	0.134	0.024	0.039	0.566
LVEF ≥33%	0.422	0.135	0.002	0.157	0.687
NYHA III	1.99	0.141	0	1.713	2.267
NYHA IV	1.604	0.49	0.001	0.644	2.563
Aldosterone antagonist	–0.266	0.11	0.015	–0.481	–0.051
Age (years)[a]	0.017	0.004	0	0.008	0.025
Sodium mmol/L[a]	0.063	0.015	0	0.034	0.092
Heart rate bpm[a]	–0.001	0.006	0.861	–0.012	0.01
Constant NYHA II	2.783	0.152	0	2.485	3.082
Months NYHA III	–0.041	0.002	0	–0.046	–0.036
Treatment NYHA III	–0.153	0.058	0.009	–0.267	–0.038
HF duration ≥0.6<2 yrs	0.257	0.085	0.003	0.089	0.424
HF duration ≥2<4.8 yrs	0.374	0.084	0	0.21	0.539
HF duration ≥4.8 yrs	0.511	0.083	0	0.348	0.675
Atrial fibrillation	0.269	0.107	0.012	0.06	0.478
LVEF ≥26%<30%	–0.005	0.096	0.962	–0.193	0.184
LVEF ≥30%<33%	–0.024	0.082	0.767	–0.185	0.136
LVEF ≥33%	–0.003	0.081	0.968	–0.162	0.155
NYHA III	3.936	0.075	0	3.789	4.083
NYHA IV	5.12	0.305	0	4.522	5.718
Aldosterone	0.011	0.061	0.851	–0.108	0.131
Age (years)[a]	0.016	0.003	0	0.011	0.021
Sodium mmol/L[a]	0.043	0.008	0	0.027	0.058
Heart rate bpm[a]	0.013	0.003	0	0.006	0.019
Constant NYHA III	–2.784	0.107	0	–2.993	–2.575
Months NYHA IV	0.011	0.009	0.245	–0.007	0.028
Treatment NYHA IV	–0.365	0.167	0.029	–0.692	–0.038
HF duration ≥0.6<2 yrs	1.012	0.312	0.001	0.4	1.624
HF duration ≥2<4.8 yrs	0.58	0.307	0.059	–0.023	1.182
HF duration ≥4.8 yrs	0.938	0.297	0.002	0.355	1.52
Atrial fibrillation	–0.267	0.326	0.413	–0.906	0.372
LVEF ≥26%<30%	–0.475	0.237	0.045	–0.941	–0.01

LVEF ≥30%<33%	–0.349	0.243	0.151	–0.826	0.127
LVEF ≥33%	–0.444	0.22	0.044	–0.875	–0.013
NYHA III	1.693	0.25	0	1.203	2.183
NYHA IV	6.601	0.294	0	6.025	7.176
Aldosterone	0.688	0.191	0	0.314	1.063
Age (years)[a]	0.016	0.007	0.021	0.002	0.03
Sodium mmol/L[a]	0.031	0.023	0.176	–0.014	0.075
Heart rate bpm[a]	0.031	0.008	0	0.014	0.047
Constant NYHA IV	–7.234	0.427	0	–8.071	–6.397

[a] Variables centred on mean.

Abbreviations used in table: bpm, beats per minute; HF, heart failure; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; SE, standard error; UCI, upper confidence interval.

Appendix 14. The final regression equation, NYHA generalised ordered logistic regression model adjusting for treatment, time and patient characteristics (with interaction terms – not used in the manufacturer's clarification model)

Description	Coefficient	SE	P >z	95% LCI	95% UCI
Months NYHA II	–0.054	0.003	0	–0.06	–0.047
Treatment NYHA II	–0.191	0.1	0.057	–0.388	0.006
HF duration ≥0.6<2 years	0.365	0.126	0.004	0.117	0.612
HF duration ≥2<4.8 years	0.719	0.149	0	0.427	1.011
HF duration ≥4.8 years	0.54	0.142	0	0.262	0.818
Atrial fibrillation	0.525	0.246	0.033	0.043	1.008
LVEF ≥26%<30%	0.453	0.164	0.006	0.132	0.774
LVEF ≥30%<33%	0.303	0.134	0.024	0.04	0.567
LVEF ≥33%	0.423	0.135	0.002	0.158	0.687
NYHA III	1.99	0.141	0	1.713	2.267
NYHA IV	1.613	0.493	0.001	0.646	2.579
Aldosterone	–0.266	0.11	0.015	–0.482	–0.051
Age (years)[a]	0.017	0.004	0	0.008	0.025
Sodium mmol/L[a]	0.063	0.015	0	0.034	0.092
Heart rate bpm[a]	–0.002	0.008	0.817	–0.017	0.013
Treatment[a]heart rate	0.002	0.011	0.889	–0.02	0.023
Constant NYHA II	2.783	0.152	0	2.485	3.081
Months NYHA III	–0.041	0.002	0	-0.046	–0.036
Treatment NYHA III	–0.152	0.058	0.01	–0.266	–0.037
HF duration ≥0.6<2 years	0.256	0.086	0.003	0.089	0.423
HF duration ≥2<4.8 years	0.373	0.084	0	0.209	0.538
HF duration ≥4.8 years	0.511	0.083	0	0.348	0.674
Atrial fibrillation	0.269	0.107	0.012	0.059	0.478
LVEF ≥26%<30%	–0.005	0.096	0.96	–0.193	0.184
LVEF ≥30%<33%	–0.025	0.082	0.765	–0.185	0.136
LVEF ≥33%	–0.004	0.081	0.962	–0.162	0.155
NYHA III	3.936	0.075	0	3.789	4.083
NYHA IV	5.121	0.306	0	4.521	5.722
Aldosterone	0.011	0.061	0.857	–0.109	0.131
Age (years)[a]	0.016	0.003	0	0.011	0.021
Sodium mmol/L[a]	0.043	0.008	0	0.027	0.058
Heart rate bpm[a]	0.015	0.005	0.001	0.006	0.023
Treatment[a]heart rate	–0.004	0.006	0.531	–0.016	0.008
Constant NYHA III	–2.783	0.107	0	–2.993	–2.574
Months NYHA IV	0.011	0.009	0.242	-0.007	0.028
Treatment NYHA IV	–0.353	0.167	0.035	–0.681	–0.025
HF duration ≥0.6<2 years	1.008	0.311	0.001	0.398	1.617
HF duration ≥2<4.8 years	0.577	0.306	0.059	–0.022	1.176
HF duration ≥4.8 years	0.934	0.297	0.002	0.353	1.515

Atrial fibrillation	–0.269	0.325	0.408	–0.906	0.368
LVEF ≥26%<30%	–0.475	0.237	0.045	–0.939	–0.011
LVEF ≥30%<33%	–0.35	0.243	0.151	–0.827	0.127
LVEF ≥33%	–0.445	0.22	0.043	–0.877	–0.013
NYHA III	1.692	0.25	0	1.202	2.182
NYHA IV	6.602	0.295	0	6.025	7.18
Aldosterone	0.687	0.189	0	0.317	1.057
Age (years)[a]	0.016	0.007	0.022	0.002	0.03
Sodium mmol/L[a]	0.03	0.022	0.177	–0.014	0.074
Heart rate bpm[a]	0.033	0.011	0.004	0.01	0.055
Treatment[a]heart rate	–0.004	0.016	0.786	–0.035	0.027
Constant NYHA IV	–7.235	0.429	0	–8.076	–6.394

a Variable centred on mean.

Abbreviations used in table: bpm, beats per minute; HF, heart failure; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; SE, standard error; UCI, upper confidence interval.

Appendix 15. The final regression equation for all cause hospitalisations (reproduced from the manufacturer's model)

Description	RR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.8653	–0.1446	0.0494	0.0030	–0.2415	–0.0478
Heart rate bpm[a]	1.0148	0.0147	0.0031	0.0000	0.0086	0.0207
Eastern Europe vs Western Europe	0.8202	–0.1982	0.0755	0.0090	–0.3460	–0.0503
Latin America vs Western Europe	0.7155	–0.3348	0.1039	0.0010	–0.5385	–0.1311
Asia vs Western Europe	0.5694	–0.5631	0.1284	0.0000	–0.8147	–0.3115
LVEF >=26%<30% vs <26%	0.8284	–0.1883	0.0728	0.0100	–0.3309	–0.0456
LVEF >=30%<33% vs <26%	0.7339	–0.3094	0.0681	0.0000	–0.4428	–0.1760
LVEF >=33% vs <26%	0.6320	–0.4588	0.0700	0.0000	–0.5960	–0.3216
Prior atrial fibrillation	1.3243	0.2809	0.0762	0.0000	0.1316	0.4302
Prior stroke	1.3453	0.2966	0.0785	0.0000	0.1428	0.4504
Prior renal disease	1.3626	0.3094	0.0853	0.0000	0.1422	0.4766
Beta-blocker use <half target dose (td)	1.0363	0.0357	0.0791	0.6520	–0.1194	0.1907
Beta-blocker use >= half td <td	0.8417	–0.1723	0.0868	0.0470	–0.3424	–0.0023
Beta-blocker use >=td	0.7949	–0.2296	0.0910	0.0120	–0.4080	–0.0511
NYHA III (vs II)	1.2264	0.2041	0.0530	0.0000	0.1001	0.3081
NYHA IV (vs II)	1.6136	0.4785	0.1710	0.0050	0.1433	0.8136
Digitalis use	1.3252	0.2816	0.0604	0.0000	0.1632	0.3999
Loop diuretics dose/kg/day	1.1183	0.1118	0.0233	0.0000	0.0660	0.1575
Allopurinol	1.3917	0.3305	0.0866	0.0000	0.1608	0.5003
Diabetes	1.1476	0.1376	0.0510	0.0070	0.0376	0.2377
Tobacco use	1.1901	0.1740	0.0517	0.0010	0.0727	0.2753
Sodium[a]	0.9839	–0.0162	0.0069	0.0190	–0.0297	–0.0027
Age (years)[a]	1.0075	0.0075	0.0025	0.0030	0.0025	0.0124
HF duration >=0.6<2 yrs vs <0.6 yrs	1.1023	0.0974	0.0797	0.2220	–0.0588	0.2537
HF duration >=2<4.8 yrs vs <0.6 yrs	1.2153	0.1950	0.0792	0.0140	0.0397	0.3503
HF duration >+4.8 yrs vs <0.6 yrs	1.6659	0.5104	0.0727	0.0000	0.3679	0.6529
Aldosterone	1.1837	0.1687	0.0527	0.0010	0.0654	0.2719
Systollic BP[a]	0.9947	–0.0053	0.0016	0.0010	–0.0085	–0.0022
Coronary Artery Disease	1.2124	0.1926	0.0626	0.0020	0.0699	0.3154
Treat[a]heart rate	0.9905	–0.0095	0.0046	0.0390	–0.0185	–0.0005
Cons	0.0192	–3.9514	0.1270	0.0000	–4.2003	–3.7024

[a] Variable centred on mean.

Abbreviations used in table; bpm, beats per minute; Cons, constant; HF, heart failure; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; RR, relative risk; SE, standard error; td, target dose; UCI, upper confidence interval.

Appendix 16. The final regression equation for cardiovascular hospitalisations (reproduced from the manufacturer's model)

Description	RR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.8653	–0.1446	0.0494	0.0030	–0.2415	–0.0478
Heart rate bpm[a]	1.0148	0.0147	0.0031	0.0000	0.0086	0.0207
Eastern Europe vs Western Europe	0.8202	–0.1982	0.0755	0.0090	–0.3460	–0.0503
Latin America vs Western Europe	0.7155	–0.3348	0.1039	0.0010	–0.5385	–0.1311
Asia vs Western Europe	0.5694	–0.5631	0.1284	0.0000	–0.8147	–0.3115
LVEF >=26%<30% vs <26%	0.8284	–0.1883	0.0728	0.0100	–0.3309	–0.0456
LVEF >=30%<33% vs <26%	0.7339	–0.3094	0.0681	0.0000	–0.4428	–0.1760
LVEF >=33% vs <26%	0.6320	–0.4588	0.0700	0.0000	–0.5960	–0.3216
Prior atrial fibrillation	1.3243	0.2809	0.0762	0.0000	0.1316	0.4302
Prior stroke	1.3453	0.2966	0.0785	0.0000	0.1428	0.4504
Prior renal disease	1.3626	0.3094	0.0853	0.0000	0.1422	0.4766
Beta-blocker use <half target dose (td)	1.0363	0.0357	0.0791	0.6520	–0.1194	0.1907
Beta-blocker use >=half td <td	0.8417	–0.1723	0.0868	0.0470	–0.3424	–0.0023
Beta-blocker use >=td	0.7949	–0.2296	0.0910	0.0120	–0.4080	–0.0511
NYHA III (vs II)	1.2264	0.2041	0.0530	0.0000	0.1001	0.3081
NYHA IV (vs II)	1.6136	0.4785	0.1710	0.0050	0.1433	0.8136
Digitalis use	1.3252	0.2816	0.0604	0.0000	0.1632	0.3999
Loop diuretics dose/kg/day	1.1183	0.1118	0.0233	0.0000	0.0660	0.1575
Allopurinol	1.3917	0.3305	0.0866	0.0000	0.1608	0.5003
Diabetes	1.1476	0.1376	0.0510	0.0070	0.0376	0.2377
Tobacco use	1.1901	0.1740	0.0517	0.0010	0.0727	0.2753
Sodium[a]	0.9839	–0.0162	0.0069	0.0190	–0.0297	–0.0027
Age (years)[a]	1.0075	0.0075	0.0025	0.0030	0.0025	0.0124
HF duration >=0.6<2 yrs vs <0.6 yrs	1.1023	0.0974	0.0797	0.2220	–0.0588	0.2537
HF duration >=2<4.8 yrs vs <0.6 yrs	1.2153	0.1950	0.0792	0.0140	0.0397	0.3503
HF duration >+4.8 yrs vs <0.6 yrs	1.6659	0.5104	0.0727	0.0000	0.3679	0.6529
Aldosterone	1.1837	0.1687	0.0527	0.0010	0.0654	0.2719
Systollic BP[a]	0.9947	–0.0053	0.0016	0.0010	–0.0085	–0.0022
Coronary Artery Disease	1.2124	0.1926	0.0626	0.0020	0.0699	0.3154
Treat[a]heart rate	0.9905	–0.0095	0.0046	0.0390	–0.0185	–0.0005
Cons	0.0192	–3.9514	0.1270	0.0000	–4.2003	–3.7024

[a] Variable centred on mean

Abbreviations used in table: BP, blood pressure; bpm, beats per minute; Cons, constant; HF, heart failure; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; RR, relative risk; SE, standard error; td, target dose; UCI, upper confidence interval.

Appendix 17. The final regression equation for heart failure hospitalisations (reproduced from the manufacturer's model)

Description	RR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.7718	–0.2590	0.0652	0.0000	–0.3869	–0.1311
Heart rate bpm	1.0224	0.0222	0.0037	0.0000	0.0149	0.0294
Eastern Europe vs Western Europe	0.8582	–0.1529	0.0962	0.1120	–0.3415	0.0357
Latin America vs Western Europe	0.9579	–0.0430	0.1269	0.7350	–0.2918	0.2057
Asia vs Western	0.7787	–0.2501	0.1486	0.0920	–0.5415	0.0412
LVEF >=26%<30% vs <26%	0.8615	–0.1491	0.0894	0.0950	–0.3243	0.0261
LVEF >=30%<33% vs <26%	0.7090	–0.3440	0.0864	0.0000	–0.5132	–0.1747
LVEF >=33% vs <26%	0.5896	–0.5283	0.0931	0.0000	–0.7108	–0.3458
Prior stroke	1.3089	0.2692	0.1067	0.0120	0.0600	0.4783
Prior renal disease	1.4221	0.3521	0.1104	0.0010	0.1358	0.5685
Beta-blocker use <half target dose (td)	1.0475	0.0464	0.1022	0.6500	–0.1539	0.2468
Beta-blocker use >=half td< td	0.7945	–0.2300	0.1156	0.0470	–0.4565	–0.0035
Beta-blocker use >=td	0.7406	–0.3003	0.1248	0.0160	–0.5450	–0.0557
NYHA III (vs II)	1.4013	0.3374	0.0694	0.0000	0.2013	0.4734
NYHA IV (vs II)	1.9916	0.6889	0.2072	0.0010	0.2829	1.0950
Digitalis use	1.5268	0.4232	0.0746	0.0000	0.2770	0.5694
Loop diuretics dose/kg/day	1.1375	0.1288	0.0262	0.0000	0.0775	0.1802
Allopurinol	1.3394	0.2923	0.1148	0.0110	0.0672	0.5173
Diabetes	1.2668	0.2365	0.0648	0.0000	0.1095	0.3635
Tobacco use	1.2239	0.2020	0.0662	0.0020	0.0723	0.3318
Sodium[a]	0.9789	–0.0213	0.0086	0.0130	–0.0382	–0.0044
HF duration >=0.6<2 yrs vs <0.6 yrs	1.2367	0.2124	0.1069	0.0470	0.0029	0.4220
HF duration >=2<4.8 yrs vs <0.6 yrs	1.5033	0.4077	0.1064	0.0000	0.1991	0.6162
HF duration >+4.8 yrs vs <0.6 yrs	1.9625	0.6742	0.0980	0.0000	0.4822	0.8663
Age (years)[a]	1.0144	0.0143	0.0033	0.0000	0.0079	0.0207
Systollic BP[a]	0.9913	–0.0087	0.0021	0.0000	–0.0129	–0.0046
Aldosterone	1.3054	0.2665	0.0705	0.0000	0.1284	0.4047
Treat*heart rate[a]	0.9926	–0.0074	0.0055	0.1790	–0.0183	0.0034
Cons	0.0085	–4.7674	0.1653	0.0000	–5.0914	–4.4433

*Variable centred on mean

Abbreviations used in table: BP, blood pressure; bpm, beats per minute; Cons, constant; HF, heart failure; LCI, lower confidence interval; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; RR, relative risk; SE, standard error; td, target dose; UCI, upper confidence interval.

Appendix 18. Details of quality of life studies identified by the manufacturer

Author & year	Population and interventions	HRQoL measures and sample size (N)	NYHA class	Mean score (SD) [CI]
Alehagen,[106] 2008	Sweden Elderly patients with symptoms of heart failure including dyspnoea, peripheral oedema and tiredness Intervention: NR	SF-36 and TTO N = 323	I–III and self-classified sI–sIV	***TTO:*** **I** 0.75 [0.72 to 0.78] **II** 0.71 [0.66 to 0.74] **III** 0.56 [0.49 to 0.63] **sI** 0.77 [0.74 to 0.80] **sII** 0.68 [0.65 to 0.72] **sIIIa** 0.61 [0.55 to 0.68] **sIIIb plus sIV** 0.50 [0.38 to 0.62]
Bennett,[107] 2002	USA All patients with heart failure, diagnosed by LVIDD ≥5.5 or FSS ≤18% or LVEF ≤40% or abnormal ventricular wall motion aged ≥18years Intervention: NR	SF-12, also CHQ and LHFQ N = 211	I–IV	***SF-12 Physical component*** **I** 45.86 **II** 33.45 **III** 27.96 **IV** 24.80 ***SF-12 Mental component*** **I** 52.99 **II** 48.12 **III** 40.95 **IV** 38.83

Eurich,[108] 2006	USA and Canada Patients with heart failure. All patients were aged ≥30 years with LVEF <0.40 Intervention: NR	EQ-5D: UK, USA and VAS scoring (also reports on KCCQ and RAND12) N = 298	I–IV	***NYHA class Improvement***: **UK** +2 = 0.79 (0.14) +1 = 0.70 (0.24) 0 = 0.71 (0.22) –1 = 0.65 (0.25) **USA** +2 = 0.82 0.06) +1 = 0.77 (0.16) 0 = 0.77 (0.16) –1 = 0.74 (0.17) **VAS** +2 = 77.50 (10.61) +1 = 62.10 (21.32) 0 = 65.74 (20.62) –1 = 60.38 (22.31)
Göhler,[100] 2009	Subset of patients with heart failure from multicentre RCT (EPHESUS trial) Intervention: Eplerenone (aldosterone antagonist)	EQ-5D N = 1359	I–IV	**I** 0.855 [0.845 to 0.864] **II** 0.771 [0.761 to 0.781] **III** 0.673 [0.665 to 0.690] **IV** 0.532 [0.480 to 0.584]
Havranek,[109] 2004 (reference details not reported in MS)	USA and Canada Patients with heart failure: a subset of patients from the OVERTURE trial. LVEF ≤30% Interventions: Omapatrilat vs enalapril	TTO (also VAS and DASI) N = 153	II–IV	**II** 0.82 (0.24) **III–IV** 0.70 (0.34)
Kirsch,[110] 2000	UK Heart failure patient sample drawn from SmithKline Beecham UK workforce and members of the SBRSAI Intervention: NR	TTO N = 64	I–IV	***2-year TTO*** **I** 0.934 (0.089) **II** 0.782 (0.244) **III** 0.553 (0.361)

				IV 0.372 (0.407) ***10-year TTO*** **I** 0.930 (0.093) **II** 0.765 (0.183) **III** 0.509 (0.351) **IV** 0.284 (0.404)
Kurtalic,[111] 2011	Bosnia Hertzegovina Previously diagnosed heart failure patients who were hospitalised and ambulatory treated at the Clinic for International Medicine of University Clinical Centre in Tuzla, Bosnia Hertzegovina during 2010 Intervention: NR	SF-36 N = 120 with heart failure 10 healthy patients were also included	I–IV	**Control group** 98.6 (0.0) **I** 90.76 (4.51) **II** 70.14 (10.64) **III** 36.45 (9.52) **IV** 25.41 (5.91)
Pressler,[112] 2011	USA Heart failure patients recruited from primary care and heart clinics affiliated with a Midwestern University Medical Centre between 9/1998 and 8/2000 Intervention: NR	HUI-3 and SF-12 (also LHFQ and CHQ) N = 211	I–IV	Baseline (mean) **I** 0.76 **II** 0.56 **III** 0.35 **IV** 0.24
Soriano,[113] 2010	Spain Heart failure patients admitted to hospital in all regions of Spain; clinicians from each Centre were invited to participate such that no regions were missed Intervention: NR	SF-36 (also MLHFQ) N = 670	I–IV	***Evolution Physical Component Score*** **NYHA I–II** Baseline = 38 M1 = 39.3 M3 = 40.3 M6 = 38.9 M9 = 40.6 M12 = 40

				NYHA III–IV Baseline = 33.7 M1 = 36.5 M3 = 37.9 M6 = 38 M9 = 38.3 M12 = 38.7
Abbreviations used in the table: CHQ, Chronic Heart Failure Questionnaire; CI, confidence interval; DASI, Duke Activity Status Index; EQ-5D, EuroQol 5 dimensions questionnaire; HUI, health utility index; KCCQ, Kansas City Cardiomyopathy Questionnaire; LHFQ, Living with Heart Failure Questionnaire; LVEF, left-ventricular ejection fraction; LVIDD, left ventricular internal diameter at end diastole; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MS, manufacturer's submission; NR, not reported; NYHA, New York Heart Association; RAND-SF36, Research and Development Short Form Health Survey 36 Item; SD, standard deviation; SF-36; General Health Survey Short-form 36; TTO, time trade off; VAS, visual analogue scale.				

Appendix 19. Base case and subgroup results: ivabradine model developed using risk equations from the entire SHIfT (≥70 bpm) population

Subgroup	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
All patients (heart rate ≥75 bpm)	Standard care	9,446	3.987			
	Ivabradine plus standard care	11,822	4.267	2,376	0.28	8,498
Age <75 years	Standard care	9,585	4.139			
	Ivabradine plus standard care	12,061	4.432	2,476	0.293	8,464
Age >=75 years	Standard care	8,117	2.537			
	Ivabradine plus standard care	9,538	2.693	1,421	0.156	9,101
NYHA II	Standard care	9,752	4.554			
	Ivabradine plus standard care	12,496	4.836	2,744	0.283	9,712
NYHA III	Standard care	9,280	3.554			
	Ivabradine plus standard care	11,369	3.834	2,090	0.28	7,467
NYHA IV	Standard care	6,610	1.792			
	Ivabradine plus standard care	7,693	2	1,083	0.208	5,197
Heart failure duration <0.6 years	Standard care	10,078	5.024			
	Ivabradine plus standard care	12,997	5.353	2,919	0.329	8,886
Heart failure duration >=0.6<2 years	Standard care	9,373	4.104			
	Ivabradine plus standard care	11,839	4.394	2,466	0.29	8,489
Heart failure duration >=2<4.8 years	Standard care	8,540	3.657			
	Ivabradine plus standard care	10,858	3.918	2,318	0.26	8,901
Heart failure duration >=4.8 years	Standard care	9,805	3.197			
	Ivabradine plus standard care	11,625	3.437	1,820	0.24	7,573
No beta-blocker	Standard care	9,689	3.081			
	Ivabradine plus standard care	11,342	3.389	1,652	0.308	5,361
Beta-blocker < half target dose	Standard care	9,198	3.603			
	Ivabradine plus standard care	11,296	3.874	2,098	0.271	7,726
Beta-blocker =>half target dose < target dose	Standard care	9,746	4.449			
	Ivabradine plus standard care	12,449	4.728	2,703	0.279	9,689

Beta-blocker =>target dose	Standard care	9,413	4.64			
	Ivabradine plus standard care	12,309	4.92	2,896	0.279	10,374
LVEF <26%	Standard care	9,930	3.312			
	Ivabradine plus standard care	11,715	3.597	1,785	0.285	6,258
LVEF >=26%<30%	Standard care	8,890	3.664			
	Ivabradine plus standard care	11,075	3.936	2,185	0.272	8,030
LVEF >=30<33%	Standard care	9,114	4.188			
	Ivabradine plus standard care	11,696	4.472	2,582	0.284	9,090
LVEF >=33%	Standard care	9,629	4.64			
	Ivabradine plus standard care	12,494	4.915	2,865	0.275	10,427
Diabetic	Standard care	8,802	4.044			
	Ivabradine plus standard care	11,289	4.324	2,487	0.28	8,883
Non-diabetic	Standard care	10,850	3.862			
	Ivabradine plus standard care	12,986	4.141	2,135	0.279	7,654
No prior CAD	Standard care	9,111	4.203			
	Ivabradine plus standard care	11,588	4.521	2,477	0.318	7,785
Prior CAD	Standard care	9,583	3.898			
	Ivabradine plus standard care	11,918	4.162	2,335	0.264	8,851
Abbreviations used in table: bpm, beats per minute; CAD, coronary artery disease; ICER, incremental cost-effectiveness ratio; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; QALY, quality adjusted life year.						

Appendix 20. Base case and subgroup results: ivabradine model developed using risk equations from the SHIfT ≥75 bpm population

Subgroup	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)/(QALYs)
All patients (heart rate ≥75 bpm)	Standard care	9,588	3.92			
	Ivabradine plus standard care	12,121	4.32	2,532	0.4	6,307
Age <75 years	Standard care	9,721	4.06			
	Ivabradine plus standard care	12,357	4.48	2,637	0.42	6,286
Age >=75 years	Standard care	8,325	2.54			
	Ivabradine plus standard care	9,860	2.77	1,535	0.23	6,666
NYHA II	Standard care	9,670	4.44			
	Ivabradine plus standard care	12,566	4.86	2,896	0.42	6,945
NYHA III	Standard care	9,635	3.52			
	Ivabradine plus standard care	11,881	3.91	2,246	0.39	5,731
NYHA IV	Standard care	6,627	1.83			
	Ivabradine plus standard care	7,953	2.12	1,326	0.29	4,625
Heart failure duration <0.6 years	Standard care	10,163	4.89			
	Ivabradine plus standard care	13,177	5.35	3,014	0.46	6,585
Heart failure duration >=0.6<2 years	Standard care	9,491	4			
	Ivabradine plus standard care	12,099	4.41	2,608	0.41	6,291
Heart failure duration >=2<4.8 years	Standard care	8,929	3.61			
	Ivabradine plus standard care	11,400	3.99	2,471	0.38	6,492
Heart failure duration >=4.8 years	Standard care	9,785	3.21			
	Ivabradine plus standard care	11,838	3.57	2,052	0.35	5,786
No beta-blocker	Standard care	9,861	3.12			
	Ivabradine plus standard care	11,718	3.52	1,857	0.4	4,700
Beta-blocker < half target dose	Standard care	9,205	3.56			
	Ivabradine plus standard care	11,513	3.95	2,308	0.39	5,919
Beta-blocker =>half target dose < target dose	Standard care	9,454	4.21			
	Ivabradine plus standard care	12,239	4.62	2,785	0.41	6,855
Beta-blocker =>target dose	Standard care	10,266	4.65			
	Ivabradine plus standard care	13,278	5.07	3,012	0.42	7,169

LVEF < 26%	Standard care	10,038	3.26			
	Ivabradine plus standard care	12,032	3.66	1,994	0.4	5,025
LVEF >=26%<30%	Standard care	9,334	3.76			
	Ivabradine plus standard care	11,765	4.16	2,431	0.4	6,093
LVEF >=30<33%	Standard care	9,489	4.12			
	Ivabradine plus standard care	12,184	4.53	2,696	0.41	6,595
LVEF >= 33%	Standard care	9,408	4.45			
	Ivabradine plus standard care	12,363	4.85	2,955	0.4	7,369
Diabetic	Standard care	9,028	3.96			
	Ivabradine plus standard care	11,650	4.37	2,622	0.4	6,485
Non-diabetic	Standard care	10,812	3.82			
	Ivabradine plus standard care	13,148	4.22	2,335	0.4	5,909
No prior CAD	Standard care	9,501	4.09			
	Ivabradine plus standard care	12,094	4.54	2,592	0.45	5,814
Prior CAD	Standard care	9,624	3.85			
	Ivabradine plus standard care	12,132	4.23	2,508	0.38	6,542
Abbreviations used in table: bpm, beats per minute; CAD, coronary artery disease; ICER, incremental cost-effectiveness ratio; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; QALY, quality adjusted life year.						