Section A: Clarification on effectiveness data

Licensed population

A1: priority question
Please provide the information depicted in the following table for each of the subgroups listed below (i.e., 7 tables of information):

- subgroup of baseline resting heart rate ≥75 bpm (licensed population) achieving ***target*** β-blocker dose at baseline (n = 938; 22.6%);
- subgroup of baseline resting heart rate ≥75 bpm ***receiving β-blocker therapy at sub-target dose (i.e., optimal therapy)*** at baseline;
- subgroup of baseline resting heart rate ≥75 bpm ***not*** receiving a β-blocker at baseline;
- subgroup of baseline resting heart rate ≥75 bpm and aged ≥70 years;
- subgroup of baseline resting heart rate ≥75 bpm by subgroup of NYHA class, that is, separate tables for classes II, III, and IV.

Consistent with the approach taken in the published analysis of SHIfT, the following tables provide data on patients who are taking ESC recommended beta-blockers.

Licensed population – target dose beta-blocker N=938

Outcome	Ivabradine		Placebo	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from baseline), bpm (SD)	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

Licensed population – <100% target dose beta-blocker N=2647

Outcome	Ivabradine		Placebo	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from baseline), bpm (SD)	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

Licensed population – not receiving a beta-blocker at baseline N=511

Outcome	Ivabradine		Placebo	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from	[redacted]		[redacted]	

baseline), bpm (SD)				
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

Licensed population – aged ≥ 70 years **N=856**

Outcome	**Ivabradine**		**Placebo**	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from baseline), bpm (SD)	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

Licensed population – NYHA Class II **N=1952**

Outcome	**Ivabradine**		**Placebo**	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	

Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from baseline), bpm (SD)	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

Licensed population – NHYA Class III **N=2111**

Outcome	**Ivabradine**		**Placebo**	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from baseline), bpm (SD)	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

Licensed population – NYHA Class IV **N=87**

Outcome	Ivabradine		Placebo	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Hospitalisation for any cause	[redacted]		[redacted]	
Hospitalisation for cardiovascular reason	[redacted]		[redacted]	
Change in heart rate at last visit (change from baseline), bpm (SD)	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

A2: priority question
For the licensed population, please complete the table below to provide absolute numbers for the outcomes listed in the subgroup of patients on ≥50% target dose β-blockade.

Outcome	Ivabradine		Placebo	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

A3: priority question
For the licensed population, please complete the table below to provide data for the outcomes listed based on maximally tolerated β-blocker dose; a similar analysis based on β-blocker category and in the full population of SHIfT is presented in Table 19 (pg 78) of the submission.

Outcome	Ivabradine		Placebo	
	n	N	n	N
No β-blocker				
Mean resting heart rate (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Primary outcome (composite): CV death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	

Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	
<25%				
Mean resting heart rate (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	
25–<50%				
Mean resting heart rate (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

50–<100%				
Mean resting heart rate (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	
≥100%				
Mean resting heart rate (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes				
Cardiovascular death	[redacted]		[redacted]	
Hospitalisation for worsening heart failure	[redacted]		[redacted]	
Death from any cause	[redacted]		[redacted]	
Death from heart failure	[redacted]		[redacted]	
Additional outcome				
Cardiovascular death excluding death from heart failure	[redacted]		[redacted]	

n: number of people with the event
N: total number in the group

A4
Please provide the median baseline heart rate (and range) for the licensed population in the ivabradine and placebo groups; data on the full population of SHIfT are presented in Table 6 (pg 48) of the submission.

Ivabradine median (Q1;Q3) (min;max) = [redacted]
Placebo median (Q1;Q3) (min;max) = [redacted]

A5
Please provide the standard deviation for the baseline sitting SBP and DBP, as well as the median (and range) baseline values for the licensed population in the ivabradine and placebo groups; data on the full population of SHIfT are presented in Table 6 (pg 48) of the submission.

	Heart rate ≥ 75bpm at baseline	
	Ivabradine	**Placebo**
SBP (mmHg) **Mean (SD)** **Median (Q1;Q3) (range)**	121.6 [redacted]	121.2 [redacted]
DBP (mmHg) **Mean (SD)** **Median (Q1;Q3) (range)**	75.8 [redacted]	75.7 [redacted]

A6
For the licensed population, please complete the table below to provide details for the patients who experienced symptomatic bradycardia as an adverse event.

Please note, in the UK ICU implies that patients are ventilated. In the SHIfT study ICU definitions varied across countries according to local definitions. In general in non-UK sites this covers all non-general ward settings. Therefore it is important to note that none of the below patients in an 'ICU setting' were in fact ventilated, and the ICU definition correlates more closely with admission to Coronary Care Units (CCU) or High Dependency Units (HDU) in the UK. Nonetheless our subsequent economic modelling (question B5) takes the conservative approach of applying the ICU costs from the UK.

Safety Set, N = 4141 (ivabradine 2046; placebo 2095)

Outcome	Ivabradine		Placebo	
	N		N	
Symptomatic bradycardia				
Mean heart rate (SD) of patients recorded at the visit immediately prior to bradycardia		bpm [redacted]		bpm [redacted]
Number of patients experiencing symptomatic bradycardia who required treatment in an intensive care unit (ICU)	84	n [redacted]	14	N [redacted]
For patients requiring ICU care, mean duration of stay (SD) in ICU		days [redacted] (N/A)		days [redacted] (N/A)

n: number of people with the event
N: total number in the group
bpm: mean heart rate in beats per minute
days: mean duration of stay in days
N/A: not applicable

A7

For the licensed population, please complete the table below to provide details for the patients who experienced atrial fibrillation as an adverse event.

Safety Set, N = 4141 (ivabradine 2046; placebo 2095)

Outcome	Ivabradine		Placebo	
	N		N	
Atrial fibrillation				
Number of patients experiencing atrial fibrillation who required treatment in an ICU	161	N [redacted]	143	n [redacted]
For patients requiring ICU care, mean duration of stay (SD) in ICU		Days [redacted]		days [redacted]

n: number of people with the event
N: total number in the group
Days: mean duration of stay in days

A8

For the subgroup of patients aged ≥70 years in the licensed population (resting heart rate ≥75 bpm), please complete the table below to provide details for and the number of patients experiencing atrial fibrillation as an adverse event.

Safety Set aged ≥70 years, N = 854

Outcome	Ivabradine		Placebo	
	N		N	
Atrial fibrillation				
Number of patients experiencing atrial fibrillation	422	n 45	432	n 46
Number of patients experiencing atrial fibrillation who required treatment in an ICU	45	n [redacted]	46	n [redacted]
For patients requiring ICU care, mean duration of stay (SD) in ICU		days [redacted]		days [redacted]

n: number of people with the event
N: total number in the group

A9

Please provide follow-up data on the reduction in heart rate at various time points for the ivabradine and placebo on-treatment groups for the licensed population; follow-up data on the reduction in heart rate at various time points in the full SHIfT population are presented in the submission (Table 27, pg 99).

	Ivabradine		Placebo	
	N	HR lowering *vs* baseline (mean +/- SD) bpm	N	HR lowering *vs* baseline (mean +/- SD) bpm
Baseline	2052	84.3±9.1	2098	84.6±9.4
D28	[redacted]	[redacted]	[redacted]	[redacted]
M12	[redacted]	[redacted]	[redacted]	[redacted]
M24	[redacted]	[redacted]	[redacted]	[redacted]
M36	[redacted]	[redacted]	[redacted]	[redacted]

A10

Please complete the table below to provide data on the number of patients in the ivabradine and placebo groups for the full and licensed population of SHIfT who were available for follow-up at the various time points indicated.

	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**
Follow-up	n	n	n	n
After 6 months	[redacted]	[redacted]	[redacted]	[redacted]
After 12 months	[redacted]	[redacted]	[redacted]	[redacted]
After 18 months	[redacted]	[redacted]	[redacted]	[redacted]
After 24 months	[redacted]	[redacted]	[redacted]	[redacted]
After 36 months	[redacted]	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

B1: priority question
Please clarify which data from SHIfT (all patients or patients with baseline heart rate ≥75 bpm) were used to inform the regression model predicting NYHA progression within the model.

The cost-effectiveness model is informed by risk equations for all endpoints (including NYHA progression) which have been developed using data from the entire SHIfT cohort (patients with a baseline heart rate ≥70 bpm).

B2: priority question
Please provide the regression model for NYHA progression adjusted for patient baseline characteristics, in particular baseline heart rate.

The regression equation has been revised to predict NYHA distribution adjusting for treatment, time covariates and patient baseline characteristics. The covariates considered for the analysis were identical to those considered for mortality and hospitalisation risk equations (derived from the SHIfT clinical study protocol, a previous HF risk equation published by Levy et al. 2006 (1) and clinical advice). The risk equation developed for the base case analysis has been based using data from the entire SHIfT population (patients with a baseline heart rate ≥70bpm) and used to predict outcomes specific to the sub-population of interest (patients with a baseline heart rate ≥75bpm).

An initial set of covariates were identified using backwards stepwise elimination and cross validated using forwards stepwise selection (using a p-value of <0.1). The variables reviewed for treatment effect modification (treatment interaction terms) reflected those covariates with prior clinical evidence of potential modification of the treatment effect (age, heart rate (2)). The potential interaction of treatment with other baseline covariates and between baseline covariates was not considered to prevent the risk of spurious results. It is noted that covariates for ischaemia and beta-blocker use were not found to have a significant association with NYHA distribution and were not included as predictors in the final regression equation (and consequently interaction terms were also not considered). The regression model indicated that, unlike other clinical risk equations, there was no evidence that baseline heart rate (or age) modified the treatment effect of ivabradine. Whilst hospitalisation and mortality risk equations showed evidence of such an interaction (p=0.01, p=0.07 respectively) and the QoL risk equation indicated a possible trend (p=0.13), the generalised ordered logistic regression demonstrated no such effect (p>0.50 across all NYHA categories). In the QoL risk equation, in light of prior clinical evidence of potential interaction between baseline heart rate and ivabradine and given evidence of a possible trend, the interaction term was retained in this model. However, in the NYHA risk equation, in the absence of any evidence of interaction the term was excluded from the final NYHA regression model. The final revised NYHA regression model without interaction terms is documented in Table 1. The NYHA regression model with interaction terms has also been reported for reference purposes, see Table 2.

Table 1: NYHA generalised ordered logistic regression model adjusting for treatment, time and patient characteristics: final model (no interaction terms)

Description	Coef.	Std. Err.	P>z	95% LCI	95% UCI
Months NYHA II	-0.054	0.003	0.000	-0.060	-0.047
Treatment NYHA II	-0.191	0.100	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	0.000	0.426	1.010
HF duration ≥4.8 yrs	0.540	0.142	0.000	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	1.990	0.141	0.000	1.713	2.267
NYHA IV	1.604	0.490	0.001	0.644	2.563
Aldosterone	-0.266	0.110	0.015	-0.481	-0.051
Age (years)*	0.017	0.004	0.000	0.008	0.025
Sodium mmol/L*	0.063	0.015	0.000	0.034	0.092
Heart rate bpm*	-0.001	0.006	0.861	-0.012	0.010
Constant NYHA II	2.783	0.152	0.000	2.485	3.082
Months NYHA III	-0.041	0.002	0.000	-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	0.000	0.210	0.539
HF duration ≥4.8 yrs	0.511	0.083	0.000	0.348	0.675
Atrial Fibrillation	0.269	0.107	0.012	0.060	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	0.000	3.789	4.083
NYHA IV	5.120	0.305	0.000	4.522	5.718
Aldosterone	0.011	0.061	0.851	-0.108	0.131
Age (years)*	0.016	0.003	0.000	0.011	0.021
Sodium mmol/L*	0.043	0.008	0.000	0.027	0.058
Heart rate bpm*	0.013	0.003	0.000	0.006	0.019
Constant NYHA III	-2.784	0.107	0.000	-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	0.400	1.624
HF duration ≥2<4.8 yrs	0.580	0.307	0.059	-0.023	1.182
HF duration ≥4.8 yrs	0.938	0.297	0.002	0.355	1.520
Atrial Fibrillation	-0.267	0.326	0.413	-0.906	0.372
LVEF ≥26%<30%	-0.475	0.237	0.045	-0.941	-0.010
LVEF ≥30%<33%	-0.349	0.243	0.151	-0.826	0.127
LVEF ≥33%	-0.444	0.220	0.044	-0.875	-0.013
NYHA III	1.693	0.250	0.000	1.203	2.183
NYHA IV	6.601	0.294	0.000	6.025	7.176
Aldosterone	0.688	0.191	0.000	0.314	1.063
Age (years)*	0.016	0.007	0.021	0.002	0.030
Sodium mmol/L*	0.031	0.023	0.176	-0.014	0.075
Heart rate bpm*	0.031	0.008	0.000	0.014	0.047
Constant NYHA IV	-7.234	0.427	0.000	-8.071	-6.397

Footnotes:
bpm – beats per minute, LVEF – Left Ventricular Ejection Fraction, NYHA – New York Heart Association
*Variable centred on mean
**The NYHA regression equation includes a time covariate. In the original equation (which adjusted for treatment and time), the time variable was transformed into log months since this transformation was found to generate the best model fit. In the revised risk equation log months did not offer the best fit of the data and time has not been transformed in this risk equation.

Table 2 NYHA generalised ordered logistic regression model adjusting for treatment, time and patient characteristics: (with interaction terms – not used in model)

Description	Coefficient	Standard. Err.	P>z	95% LCI	95% UCI
Months NYHA II	-0.054	0.003	0.000	-0.060	-0.047
Treatment NYHA II	-0.191	0.100	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	0.000	0.427	1.011
HF duration ≥4.8 years	0.540	0.142	0.000	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	0.040	0.567
LVEF ≥33%	0.423	0.135	0.002	0.158	0.687
NYHA III	1.990	0.141	0.000	1.713	2.267
NYHA IV	1.613	0.493	0.001	0.646	2.579
Aldosterone	-0.266	0.110	0.015	-0.482	-0.051
Age (years)*	0.017	0.004	0.000	0.008	0.025
Sodium mmol/L*	0.063	0.015	0.000	0.034	0.092
Heart rate bpm*	-0.002	0.008	0.817	-0.017	0.013
Treatment*heart rate	0.002	0.011	0.889	-0.020	0.023
Constant NYHA II	2.783	0.152	0.000	2.485	3.081
Months NYHA III	-0.041	0.002	0.000	-0.046	-0.036
Treatment NYHA III	-0.152	0.058	0.010	-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	0.000	0.209	0.538
HF duration ≥4.8 years	0.511	0.083	0.000	0.348	0.674
Atrial Fibrillation	0.269	0.107	0.012	0.059	0.478
LVEF ≥26%<30%	-0.005	0.096	0.960	-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	0.000	3.789	4.083
NYHA IV	5.121	0.306	0.000	4.521	5.722
Aldosterone	0.011	0.061	0.857	-0.109	0.131
Age (years)*	0.016	0.003	0.000	0.011	0.021
Sodium mmol/L*	0.043	0.008	0.000	0.027	0.058
Heart rate bpm*	0.015	0.005	0.001	0.006	0.023
Treatment*heart rate	-0.004	0.006	0.531	-0.016	0.008
Constant NYHA III	-2.783	0.107	0.000	-2.993	-2.574
Months NYHA IV	0.011	0.009	0.242	-0.007	0.028

Description	Coefficient	Standard. Err.	P>z	95% LCI	95% UCI
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%	-0.350	0.243	0.151	-0.827	0.127
LVEF ≥33%	-0.445	0.220	0.043	-0.877	-0.013
NYHA III	1.692	0.250	0.000	1.202	2.182
NYHA IV	6.602	0.295	0.000	6.025	7.180
Aldosterone	0.687	0.189	0.000	0.317	1.057
Age (years)*	0.016	0.007	0.022	0.002	0.030
Sodium mmol/L*	0.030	0.022	0.177	-0.014	0.074
Heart rate bpm*	0.033	0.011	0.004	0.010	0.055
Treatment*heart rate	-0.004	0.016	0.786	-0.035	0.027
Constant NYHA IV	-7.235	0.429	0.000	-8.076	-6.394

Footnotes:
bpm – beats per minute, LVEF – Left Ventricular Ejection Fraction, NYHA – New York Heart Association
*Variable centred on mean

Table 3 Predicted percentage of patients distributed in each NYHA class: Standard care

Year	Month	NYHA I	NYHA II	NYHA III	NYHA IV
0	0	1.1%	54.9%	43.4%	0.6%
1	12	1.3%	57.3%	40.9%	0.6%
2	24	1.3%	57.9%	40.2%	0.6%
3	36	1.3%	58.1%	40.0%	0.6%
4	48	1.3%	58.1%	40.0%	0.6%
5	60	1.3%	58.1%	40.0%	0.6%

Footnotes:
NYHA – New York Heart Association

Table 4 Predicted percentage of patients distributed in each NYHA class: Ivabradine plus standard care

Year	Month	NYHA I	NYHA II	NYHA III	NYHA IV
0	0	1.3%	58.4%	39.8%	0.4%
1	12	1.5%	60.6%	37.4%	0.4%
2	24	1.6%	61.3%	36.7%	0.4%
3	36	1.6%	61.4%	36.5%	0.4%
4	48	1.6%	61.4%	36.5%	0.4%
5	60	1.6%	61.4%	36.5%	0.4%

Footnotes:
NYHA – New York Heart Association

B3: priority question
For consistency across all outcomes, please provide analyses using the heart rate covariate in the regression equation for NYHA distribution, as has been done for mortality, hospitalisation and quality of life.

See previous response (B2).

B4: priority question
During extrapolation of NYHA classes, it has been assumed that 5% of patients will move from NYHA I to NYHA II and from NYHA II to NYHA III, and that there will be no change in the proportion of patients categorised as NYHA IV. Please describe the basis of this assumption.

The manufacturer wishes to clarify that in the base case model the extrapolation does not assume that 5% of patients will move from NYHA I to II and from NYHA II to III; the assumption has only been used as a sensitivity analysis.

The cost-effectiveness model assumes that the distribution of patients by NYHA class is equivalent to the last observation carried forward (LOCF) at 29 months. In the modelled NYHA extrapolation the proportion of patients in each NYHA class remains fixed post trial (although in absolute terms numbers in each category vary according to the number of patients alive) (See Figure 1 and Figure 2). It is noted that the NYHA risk equation, which includes a time covariate, predicted a (small) increase in the absolute number of patients in NYHA I and II over time, a pattern observed during SHIfT. Whilst it is likely that many of the observed deaths would be in the higher NYHA classes (III, IV), hence increasing the relative proportion of the cohort alive in NYHA I and II, and some improvement in symptoms could be anticipated by optimal heart failure management, it would be clinically unexpected to find an overall increase in the absolute numbers of patients in NYHA I and II in the long term given the progressive nature of the disease. The assumption applied in the base case (LOCF) was recommended by an expert panel convened to review the ivabradine cost-effectiveness model and was suggested in light of evidence from SHIfT and a lack of published external data on the distribution of patients by NYHA class over time.

In a sensitivity analysis it was assumed a greater proportion of patients were distributed into NYHA class II and III each year. This was a simple scenario analysis that used an arbitrary 5% change in distribution between NYHA classes and was undertaken to explore alternative assumptions on NYHA distribution in the post-trial period (i.e. a modelled scenario in which a greater proportion of patients were distributed into higher NYHA classes). This scenario analysis has been revised to accommodate an additional change whereby 5% of patients distributed into NYHA move to NYHA IV each year. The distribution of patients in each NYHA class in the revised analysis is detailed in

Table 5.

Figure 1 Standard care: predicted distribution of patients by NYHA class over time (using revised generalised ordered logistic regression model adjusting for treatment, time and patient baseline characteristics)

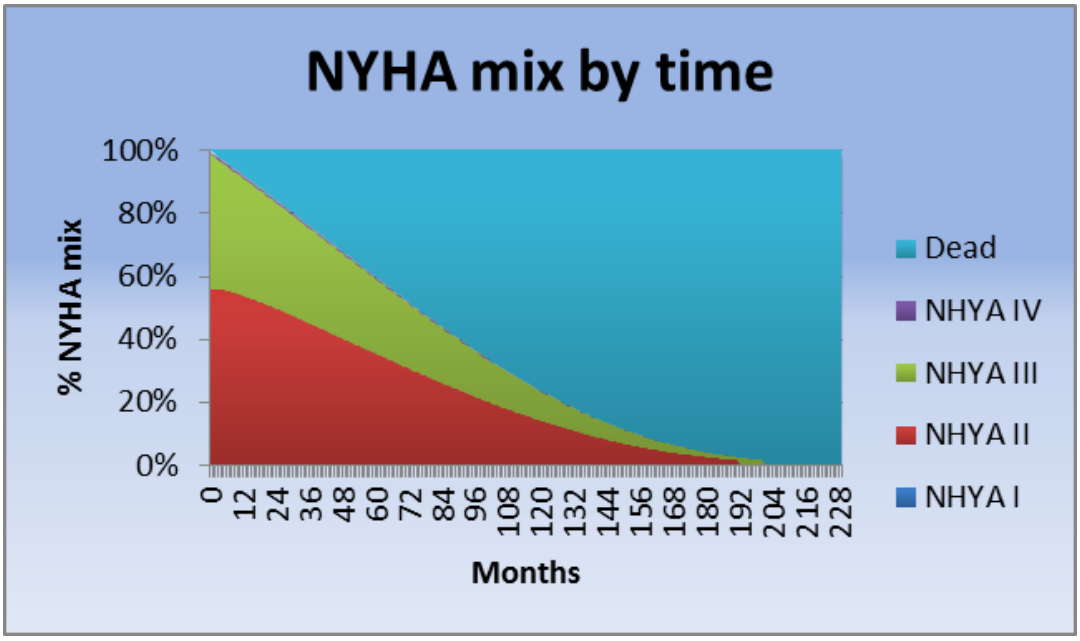


Figure 2 Ivabradine plus standard care: predicted distribution of patients by NYHA class over time (using revised generalised ordered logistic regression model adjusting for treatment, time and patient baseline characteristics)

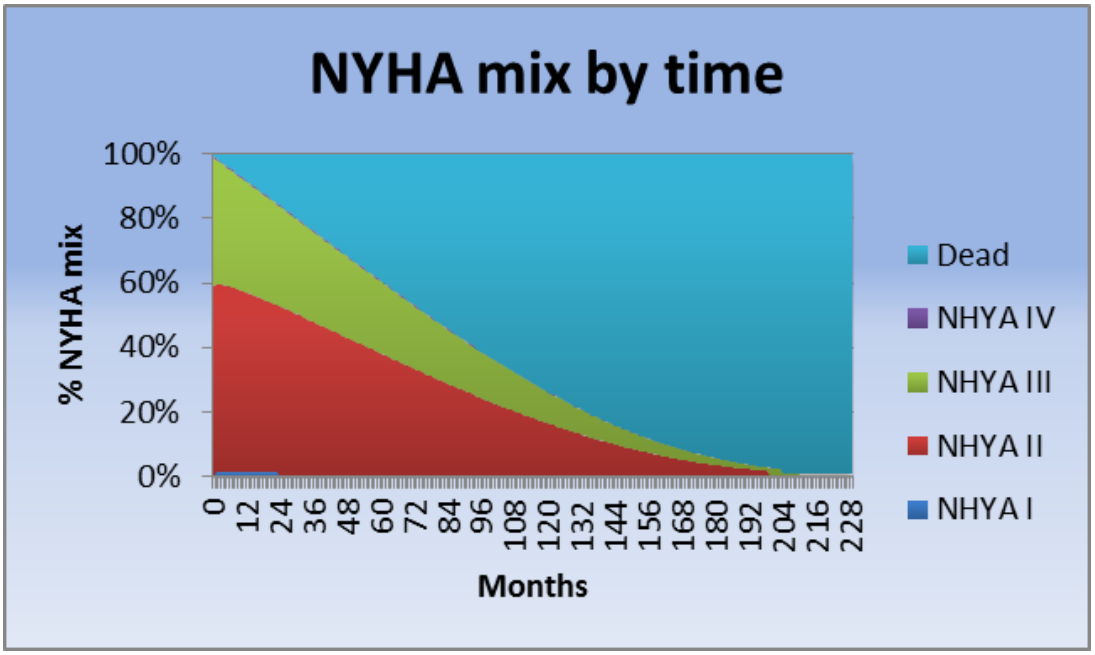


Table 5 Proportion of patients distributed in each NYHA class over time: revised sensitivity analysis (greater percentage of distributed in higher NYHA classes over time in post-trial period)

Months	NYHA I	NYHA II	NYHA III	NYHA IV
24	7.3%	55.6%	36.3%	0.8%
36	6.9%	53.2%	37.3%	2.6%
48	6.6%	50.9%	38.1%	4.5%
60	6.3%	48.6%	38.7%	6.4%
72	6.0%	46.5%	39.2%	8.3%
84	5.7%	44.5%	39.6%	10.3%
96	5.4%	42.6%	39.8%	12.2%
108	5.1%	40.7%	40.0%	14.2%
120	4.8%	38.9%	40.0%	16.2%
132	4.6%	37.2%	40.0%	18.2%
144	4.4%	35.6%	39.8%	20.2%
156	4.2%	34.0%	39.6%	22.2%
168	3.9%	32.5%	39.3%	24.2%
180	3.8%	31.1%	39.0%	26.2%

Footnotes:
NYHA – New York Heart Association

B5

The Evidence Review Group's clinical advisor has emphasised that patients experiencing symptomatic bradycardia or atrial fibrillation may require treatment in an ICU. Please provide a scenario analysis in which additional costs for adverse events associated with bradycardia and atrial fibrillation are incorporated in the base case analysis.

An additional sensitivity analysis has been considered in the model in which a proportion of patients experiencing symptomatic bradycardia and atrial fibrillation are treated in an ICU. The proportion of patients experiencing bradycardia or atrial fibrillation has been modelled according to SHIfT data using estimates from patients with a baseline heart rate ≥75bpm (by treatment arm), consistent with the population considered in the base case model. The proportion of the 402 patients with bradycardia or atrial fibrillation subsequently admitted to ICU has also been modelled according to SHIfT (both arms combined, [redacted]), consistent with the data provided in response to questions A7 and A7. The cost per day for ICU treatment has been based on a weighted estimate of ICU admissions reported in 2010-2011 NHS reference cost data (£1213 per day), multiplied by the reported length of stay for patients admitted to ICU following bradycardia or atrial fibrillation in SHIfT (ivabradine plus standard care 10.53 days, standard care alone 7.47 days). The total cost per admission was estimated to be £9,063 and £12,775 for ivabradine plus standard care *versus* standard care alone, respectively.

The effect of this analysis on the cost-effectiveness estimate is to increase the ICER from a base case £7,553 per QALY to £8,036 per QALY (see Table 25).

Table 6 Proportion of patients experiencing symptomatic bradycardia or atrial fibrillation (heart rate ≥ 75bpm)

Description	Ivabradine plus Standard care	Standard care	Total
Symptomatic bradycardia or AF	245	157	402
No bradycardia or AF	1801	1938	3739
Total*	**2046**	**2095**	**4141**

Footnotes:
AF: atrial fibrillation
*Total number of patients excludes patients that did not take study medication (patients with a baseline heart rate ≥75bpm)

Table 7 Patients admitted to ICU for bradycardia or atrial fibrillation (heart rate ≥75bpm)

Description	Ivabradine* n=161	Placebo* n=143	Total
Hospitalisation in an ICU following AF	[redacted]	[redacted]	[redacted]
Hospitalisation in an ICU following bradycardia	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*AF: atrial fibrillation

Table 8 Duration (in days) in ICU following atrial fibrillation admission (patients with heart rate ≥75bpm)

Intervention	Mean	Standard Deviation
Standard care (n=15)*	[redacted]	[redacted]
Ivabradine (n=19)	[redacted]	[redacted]

*1 patient with missing data

Please note, as specified in question A6, in the UK ICU implies that patients are ventilated. In the SHIfT study ICU definitions varied across countries according to local definitions. In general in non-UK sites this covers all non-general ward settings. Therefore it is important to note that none of the below patients in an 'ICU setting' were in fact ventilated, and the ICU definition correlates more closely with admission to Coronary Care Units (CCU) or High Dependency Units (HDU) in the UK. Nonetheless our subsequent economic modelling (Question B5) takes the conservative approach of applying the ICU costs from the UK.

It is also worth noting that there is a possibility of double counting here. The resource use and quality of life effects of ivabradine relating to adverse events is already captured by the treatment covariates in the hospitalisation and quality of life regression models.

B6

Please provide separate sensitivity analyses that use:

i. Overall mortality data (i.e., non-CV overall mortality) from SHIfT rather than UK population mortality data;
ii. Non-HF CV death calculated from a regression model (adjusted for patient baseline characteristics) based on non-HF CV mortality data from SHIfT.

Question B6 (i) and (ii) reflect substantial reanalysis of the dataset and substantial remodelling that we have been unable to perform in the time available to us. This is partly a function of Servier being a small company with limited internal resource and therefore reliant on external providers for modelling assignments such as this. We have nevertheless identified the concerns that may be underpinning question B6 and sought to address these as fully as possible within the existing model framework.

B6 (i) UK interim life-table data were used to estimate the underlying risk of non-CV death since this was believed to provide the most reliable estimate for non-CV death for a UK population. This approach is considered to be standard practice and has been used in a number of other cost-effectiveness models in CHF (3; 4). Furthermore it is noted that no treatment benefit is modelled on this endpoint. Consequently the risk of non-CV death is modelled to be the same across treatment groups.

Nonetheless, a regression model which considers a non-CV mortality endpoint adjusted for patient baseline characteristics has been used in a sensitivity analysis to predict non-CV mortality. The results of this sensitivity analysis demonstrate that a change in the modelling of the underlying risk of non-CV death to reflect SHIfT data does not have a substantial impact on the ICER estimate (ICER with SHIfT predicted non-CV death: £9142), see Figure 4.[1]

B6 (ii) Non-HF CV death has been captured in the model using two regression models. We have used regression models for CV death and HF death, with non-HF CV death effectively back-calculated as the difference between these endpoints. The rationale for taking this approach was to provide the most reliable estimate of the underlying risk of HF and CV death, to maintain statistical power in the regression models used to estimate the underlying risk of a clinical event (and consequently generate the best predictions across patients subgroups) and to keep the regression models consistent with trial clinical endpoints.

It should be noted that the model already addresses a scenario in which ivabradine is modelled to have an effect purely on HF death and HF hospitalisation, with no treatment effect modelled on other non-HF endpoints. This analysis was undertaken as a structural sensitivity analysis in the original model and was reported in the cost-

[1] It is noted that in addition to including a sensitivity analysis which predicts non-CV mortality from SHIfT, UK non-CV mortality rates have been updated to the most recently published UK mortality data for the base case model.

effectiveness section of the ivabradine submission (see submission p.129, Section 6.3.1; and Figure 19, Section 6.7.9).

Therefore the model has been fully re-analysed to provide a comprehensive set of results with the treatment effect of ivabradine modelled only on HF mortality and HF hospitalisation. The full results, including one way sensitivity analyses, probabilistic sensitivity analyses and subgroup results have been reported below. Please note that these results are based on the revised model, which includes the revised NYHA regression equation and updated BNF cost data. The results of this scenario analysis indicate the ICER remains increases slightly from our current base case and remains well below the £20,000 threshold (ICER: £8,991 per QALY), see Table 9, Table 10 and Figure 3 to Figure 6.

Table 9 Heart failure endpoint: base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Baseline	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Std Care	*9749.31*	*5.82*	*4.08*		-	*-*	*-*	*-*	*-*
Ivabradine plus Std Care	*12865.30*	*6.19*	*4.42*	*Std Care*	*3116*	*0.36*	*0.35*	*8616*	*8991*

Footnotes:

QALY – Quality Adjusted Life Year

ICER calculated by applying individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time and averaging costs and effects over all patient profiles with subgroup characteristic of interest see full report for details

Table 10 Heart failure endpoint: subgroup results

	Standard Care			Ivabradine							
Subgroup	**Total Costs (£)**	**Total LYs**	**Total QALYs**	**Total Costs (£)**	**Total LYs**	**Total QALYs**	**Incremental Costs (£)**	**Incremental LYs**	**Incremental QALYs**	**Incremental Cost/LY (£)**	**Incremental Cost/QALY (£)**
All patients (HR>=75 b.p.m.)	*9749*	*5.82*	*4.08*	*12865*	*6.19*	*4.42*	*3116*	*0.36*	*0.35*	*8616*	*8991*
Age<75 years	*9830*	*5.99*	*4.21*	*13045*	*6.37*	*4.57*	*3215*	*0.38*	*0.36*	*8556*	*8918*
Age>=75 years	*8979*	*4.22*	*2.78*	*11154*	*4.45*	*2.99*	*2176*	*0.23*	*0.21*	*9559*	*10169*
NYHA II	*10035*	*6.56*	*4.89*	*13618*	*6.93*	*5.26*	*3584*	*0.37*	*0.37*	*9674*	*9621*
NYHA III	*9608*	*5.28*	*3.44*	*12369*	*5.64*	*3.77*	*2760*	*0.36*	*0.33*	*7686*	*8409*
NYHA IV	*6775*	*2.68*	*1.36*	*8041*	*2.91*	*1.57*	*1267*	*0.23*	*0.21*	*5603*	*6027*
HF duration <0.6 years	*10375*	*7.01*	*5.16*	*14258*	*7.42*	*5.58*	*3883*	*0.41*	*0.42*	*9401*	*9315*
HF duration >=0.6<2 years	*9686*	*5.94*	*4.22*	*12875*	*6.28*	*4.55*	*3189*	*0.34*	*0.33*	*9490*	*9547*
HF duration >=2<4.8 years	*8773*	*5.48*	*3.70*	*11711*	*5.85*	*4.04*	*2937*	*0.37*	*0.34*	*7960*	*8698*
HF duration >=4.8 years	*10174*	*4.91*	*3.26*	*12656*	*5.24*	*3.56*	*2482*	*0.33*	*0.30*	*7477*	*8245*
No beta blocker	*9942*	*4.56*	*3.11*	*12707*	*5.03*	*3.52*	*2765*	*0.47*	*0.41*	*5890*	*6792*
Beta blocker < half target dose	*9500*	*5.23*	*3.69*	*12232*	*5.57*	*4.02*	*2732*	*0.34*	*0.33*	*7932*	*8307*
Beta blocker =>half target dose < target dose	*10036*	*6.49*	*4.54*	*13525*	*6.86*	*4.90*	*3489*	*0.37*	*0.36*	*9386*	*9685*
Beta blocker =>target dose	*9762*	*6.83*	*4.77*	*13329*	*7.15*	*5.10*	*3566*	*0.32*	*0.33*	*11072*	*10824*
LVEF < 26%	*10046*	*4.69*	*3.31*	*12674*	*5.11*	*3.69*	*2628*	*0.43*	*0.38*	*6144*	*6830*
LVEF >=26%<30%	*9175*	*5.33*	*3.72*	*11939*	*5.67*	*4.05*	*2764*	*0.35*	*0.33*	*7929*	*8362*
LVEF >=30<33%	*9488*	*6.18*	*4.31*	*12689*	*6.50*	*4.63*	*3200*	*0.32*	*0.32*	*9986*	*9975*
LVEF >= 33%	*10056*	*6.88*	*4.80*	*13772*	*7.23*	*5.15*	*3716*	*0.34*	*0.34*	*10784*	*10814*
Non-diabetic	*9048*	*5.84*	*4.13*	*12221*	*6.21*	*4.48*	*3173*	*0.36*	*0.35*	*8702*	*9056*
Diabetic	*11280*	*5.79*	*3.96*	*14271*	*6.14*	*4.30*	*2992*	*0.36*	*0.34*	*8421*	*8843*
No prior CAD	*9221*	*5.78*	*4.26*	*12371*	*6.21*	*4.66*	*3150*	*0.42*	*0.40*	*7468*	*7785*
Prior CAD	*9966*	*5.84*	*4.00*	*13068*	*6.18*	*4.32*	*3102*	*0.34*	*0.32*	*9205*	*9612*

Footnotes:

QALY – Quality Adjusted Life Year

ICER calculated by applying individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time and averaging costs and effects over all patient profiles with subgroup characteristic of interest see full report for details

Figure 3 Heart failure endpoint: One way sensitivity analyses: parameter values

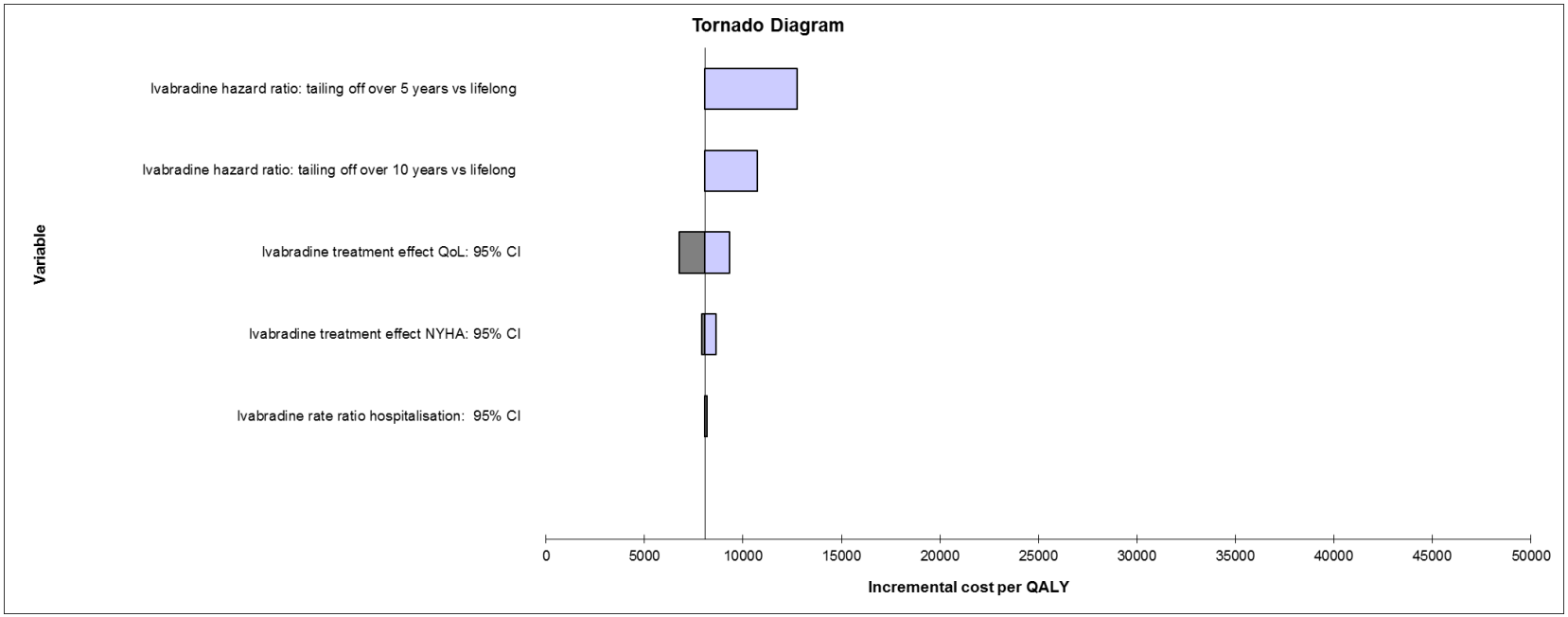
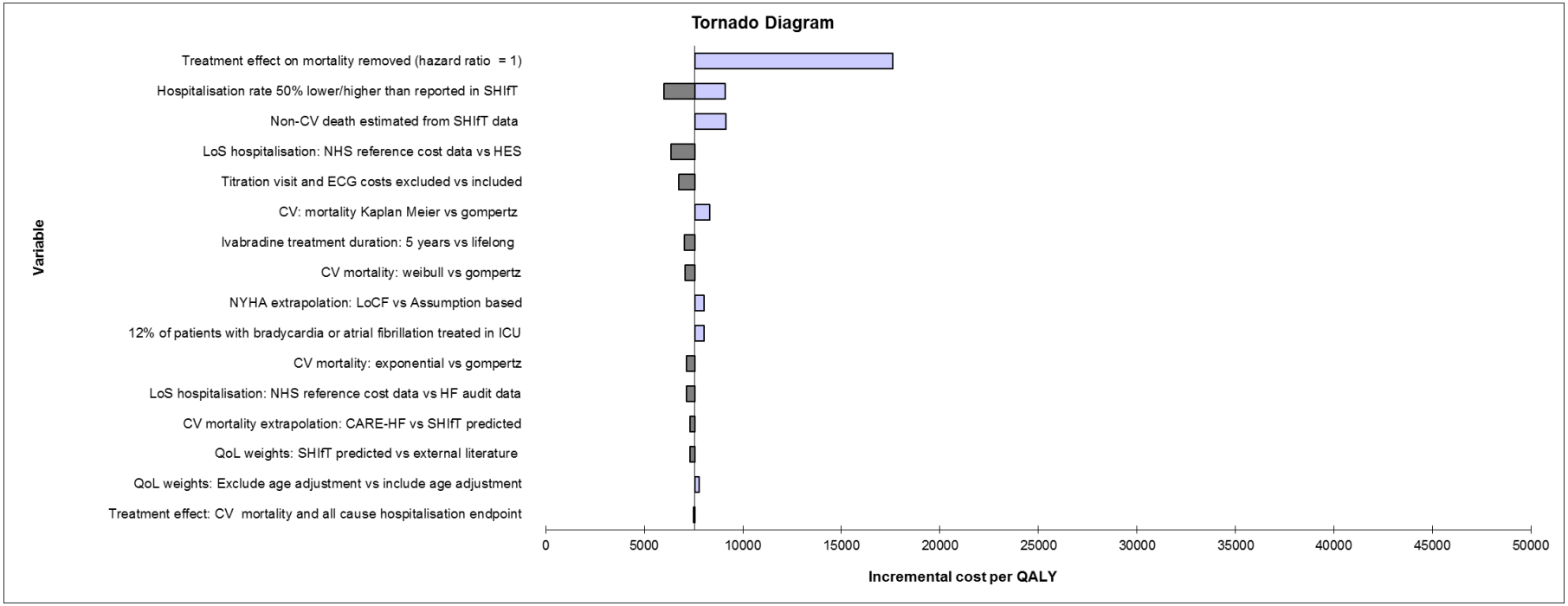


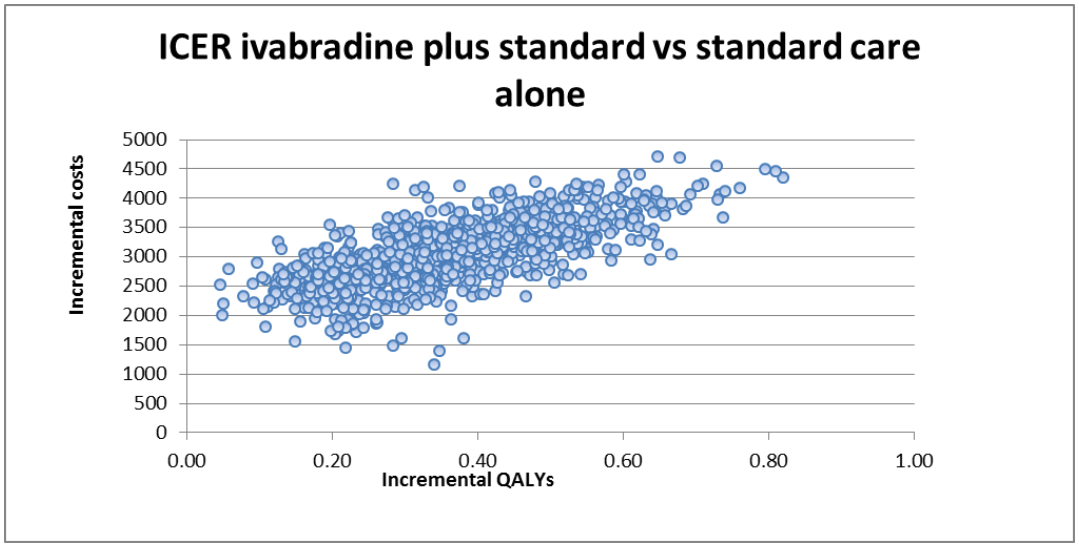
Figure 4 Heart failure endpoint: One way sensitivity analyses: structural sensitivity analyses



Footnotes:

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £8063 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

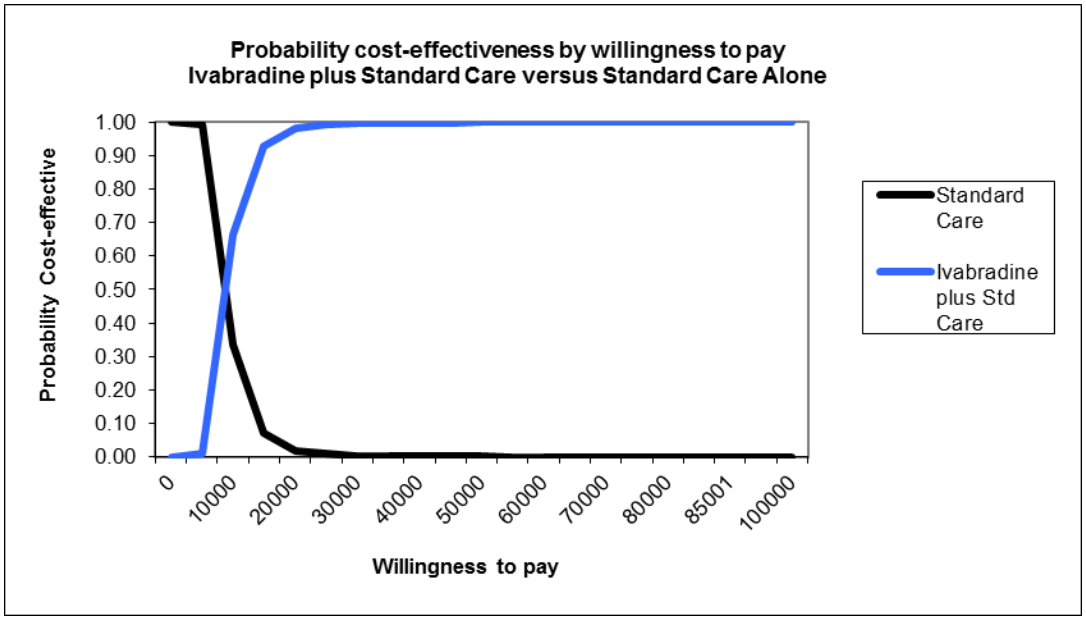
Figure 5 Heart failure endpoint: Probabilistic sensitivity analysis: scatter plot



Footnotes:

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £8063 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

Figure 6 Heart failure endpoint: Probabilistic sensitivity analysis: cost-effectiveness acceptability curve (CEAC)



Footnotes:

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £8063 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

B7
In the submission (pg 152), the manufacturer states that "...due to the inclusion of a weakly significant interaction term, the treatment covariate appears non-significant in the final regression equation". However, the treatment covariate in the full risk equation presented in Table 53 (pg 157) is associated with a p-value of 0.0270. Please clarify this potential discrepancy.

The sentence should be revised to,

> "...due to a weaker interaction between ivabradine and heart rate for patient quality of life, the treatment interaction term appears non-significant in the final regression equation."

Ivabradine demonstrated greater efficacy with increasing baseline heart rate for mortality and hospitalisation endpoints. It was consequently considered clinically plausible that there would also be an interaction effect of ivabradine and baseline heart rate for patient quality of life (i.e. that patients experiencing the greatest clinical benefits would also experience the greatest improvement in quality of life). However, in the quality of life regression model the interaction term was non-significant (p=0.13) although there appeared to be possible evidence of a trend towards this effect and, given strong prior clinical rationale for an interaction between treatment and heart rate, the interaction term was retained.

B8
The trial analysis is limited to 29 months, at which point 20% of the cohort is ***at risk***. Please clarify what is meant by "at risk".

In SHIfT 20% of the cohort had survival data reported until 29 months and were consequently still at risk of death (i.e. they had at least 29 months follow up data post-randomisation and had neither died nor been censored by the analysis cut-off date - 31st March 2010).

B9
Please provide an updated base case analysis using the latest drug acquisition costs as reported in BNF 63 for all drugs used in the standard care arm.

British National Formulary (BNF) drug prices have been revised to reflect 2012 estimates, see

Table 11. The Tables which reported therapy costs in the STA submission document have also been revised accordingly, see Table 12 to Table 14.

The results and clinical outcomes have also been re-reported for the revised cost-effectiveness model, which includes the new NYHA risk equation, updated BNF prices and new sensitivity analyses.

Table 11 Standard care therapy costs

Drug class	Most common drug	SHIfT % of cohort	UK dose (mg)	Price per pack	Tablets per pack	mg per tablet	Price per tablet (£)	Price per mg (£)	Total cost per month (£)
Ace inhibitors	Ramipril ǂ	78.9%	5.00	1.24	28.00	5.00	0.04	0.0089	1.0634
ARBs	Candesartan ǂ	14.3%	16.00	12.72	28.00	16.00	0.45	0.0284	1.9790
Aldosterone	Sprionolactone	62.4%	34.79	2.15	28.00	50.00	0.08	0.0015	1.0143
Digitalis	Digoxin ǂ	21.9%	0.13	1.00	28.00	0.06	0.04	0.5714	0.4753
Loop diuretics	Furosemide	74.2%	59.36	0.73	28.00	40.00	0.03	0.0007	0.8735
Beta blockers	Bisoprolol ǂ	89.7%	5.00	1.00	28.00	5.00	0.04	0.0071	0.9751
Statins	Simvastatin	60.8%	23.39	0.81	28.00	10.00	0.03	0.0029	1.2525
Antiarrhythmics	Bendroflumethiazide ǂ	14.1%	5.00	0.80	28.00	5.00	0.03	0.0057	0.1227
Anticoagulants	Clopidogrel	12.2%	74.71	2.33	28.00	75.00	0.08	0.0011	0.3076
Anticoagulants	Warfarin ǂ	16.3%	3.00	0.86	28.00	3.00	0.03	0.0102	0.1523
Nitrates	Isosorbide mononitrate	35.4%	53.24	1.48	56.00	40.00	0.03	0.0007	0.3795
Total									**8.60**

Footnotes:

Cost used reflects most commonly prescribed therapy in drug class. Unit prices based on British National Formulary list prices 2012

ǂ UK standard doses used to estimate treatment dose (dose based on expert clinical advise)

Table 12 Unit costs associated with the technology in the economic model

Items	Ivabradine plus Standard Care (£)	Ref. in submission	Standard care alone (£)	Ref. in submission
Technology cost per pack	40.17	Section 6.5.5	-	Section 6.5.5
Mean cost of technology treatment (per month)	42.10	Section 6.5.5	8.60	Section 6.5.5
Mean cost Standard Care treatment	8.60	Section 6.5.5	-	Section 6.5.5
Administration cost	-	Section 6.5.5	-	Section 6.5.5
Specialist visit (one off)	118.81	Section 6.5.5	-	Section 6.5.5
ECG (one off)	31.28	Section 6.5.5	-	Section 6.5.5
Total cost per month i (month 1)	**200.78**		**8.60**	
Total cost per month subsequent months	**50.69**		**8.60**	

Table 13 List of health states and associated costs in the economic model

Health states	Items	Value (£)	Reference in submission
Alive	Therapy costs Ivabradine plus standard care per month	42.10	Section 6.5.5
	Therapy costs standard care per month	8.60	Section 6.5.5
	Hospitalisation HF diagnosis	2801.55	Section 6.5.7
	Hospitalisation CV diagnosis	1836.02	Section 6.5.7
	Hospitalisation All cause diagnosis	2643.56	Section 6.5.7
	Heart failure management per month	26.77	Section 6.5.8

Table 14 Summary of variables applied in the economic model

Parameter description	Base case value	95% LCI	95% UCI	PSA Distribution	Reference for section in NICE submission
Model structure	Two State Markov cohort model	-	-	-	Section 2.3.1-2.3.3
Modelled cycle length	1 month	-	-	-	Section 6.2.6; **Error! Reference source not found.**
Time horizon	Lifetime	-	-	-	Section 6.2.6; **Error! Reference source not found.**
Population	SHIFT population HR >75b.p.m.	-	-	-	Section 2.3.1
Costs discount rate	3.50%	-	-	-	Section 6.2.6; **Error! Reference source not found.**
Effects discount rate	3.50%	-	-	-	Section 6.2.6; **Error! Reference source not found.**
Treatment duration months ivabradine	360.00	-	-	Section 6.3.1	Section 6.3.1
Parametric survival model CV mortality	Gompertz	See Footnotes		Lognormal	Section 6.3.1
Extrapolation CV mortality post trial	Gompertz	See Footnotes		Lognormal	Section 6.3.1
Hazard ratio CV mortality ivabradine vs Standard care	0.90	0.80	1.03	Section 6.3.1	Section 6.3.1
Regression model hospitalisation	Poisson	See Footnotes		Lognormal	Section 6.3.1
Rate ratio hospitalisation ivabradine vs Standard care	0.83	0.78	0.93	Section 6.3.1	Section 6.3.1
Regression model NYHA class	Generalised ordered logistic regression	See Footnotes		Lognormal	Section 6.3.1
Regression model QoL	Mixed model	See Footnotes		Lognormal	Section 6.4.9; **Error! Reference source not found.**
NYHA I	0.82	See Footnotes		Normal	Section 6.4.9; **Error! Reference source not found.**
NYHA II	0.74	See Footnotes		Normal	Section 6.4.9; **Error! Reference source not found.**
NYHA III	0.64	See Footnotes		Normal	Section 6.4.9; **Error! Reference source not found.**
NYHA IV	0.46	See Footnotes		Normal	Section 6.4.9; **Error! Reference source not found.**

Parameter description	Base case value	95% LCI	95% UCI	PSA Distribution	Reference for section in NICE submission
Utility decrement hospitalisation	-0.21	See Footnotes		Normal	Section 6.4.9; Table B15
Utility increment ivabradine	0.01	See Footnotes		Normal	Section 6.4.9; Table B15
Drug costs per month					
Standard care	8.60	-	-	Deterministic	Section 6.4.9; **Error! Reference source not found.**
Ivabradine	42.10	-	-	Deterministic	Section 6.4.9; **Error! Reference source not found.**
Other therapy related costs		**Lower quartile**	**Upper quartile**		
ECG ivabradine	31.28	12.01	44.30	Lognormal	Section 6.2.8; 6.5.5; **Error! Reference source not found.**
Cardiovascular specialist visit	118.81	89.48	138.97	Lognormal	Section 6.2.8; 6.5.5; **Error! Reference source not found.**
Hospitalisations cost per event					
HF diagnosis (general ward)	2307.98	-	-	Lognormal	Section 6.5.7 **Error! Reference source not found.**
HF diagnosis (cardiac ward)	3295.12	-	-	Lognormal	Section 6.5.7 **Error! Reference source not found.**
Other CV diagnosis (general ward)	1942.44	-	-	Lognormal	Section 6.5.7 **Error! Reference source not found.**
Other CV diagnosis (cardiac ward)	1729.60	-	-	Lognormal	Section 6.5.7 **Error! Reference source not found.**
Non-CV diagnosis (general ward)	2643.56	-	-	Lognormal	Section 6.5.7 **Error! Reference source not found.**
Probability of general ward admission HF or CV diagnosis	0.50	0.40	0.60	Lognormal	Section 6.5.7 **Error! Reference source not found.**
Probability of cardiac ward admission HF or CV diagnosis	0.50	-	-		Section 6.5.7 **Error! Reference source not found.**
Other resource use					
HF management costs	26.77	20.08	33.47	Lognormal	Section 6.5.8 **Error!**

Parameter description	Base case value	95% LCI	95% UCI	PSA Distribution	Reference for section in NICE submission
					Reference source not found.

Footnotes:

LCI – lower confidence interval, UCI upper confidence interval, PSA – probabilistic sensitivity analysis, NYHA New York Heart Association

SHIFT population - only patients with a heart rate (HR) >= 75 beats per minute (b.p.m.) were considered in the current model

Confidence intervals for regression model estimates not reported (see full regression equations on "BL", "Hosp", "NYHA" and "QoL" worksheets for full reporting of equations (including 95% confidence intervals).

Confidence intervals for cardiovascular general ward admission not reported (see full calculation on "Resource" worksheet (including 95% confidence intervals).

Revised results

Table 15 Standard care: proportion of cohort in each health state over time

Time (years)	Time (months)	Proportion of patients Alive Standard Care	Proportion of patients Alive Ivabradine plus Standard Care
0	0	100%	100%
1	12	92%	93%
2	24	85%	86%
3	36	77%	78%
4	48	68%	71%
5	60	60%	63%
6	72	52%	56%
7	84	45%	48%
8	96	37%	41%
9	108	30%	34%
10	120	24%	28%
11	132	19%	22%
12	144	14%	17%
13	156	10%	12%
14	168	7%	9%
15	180	5%	6%

Table 16: Standard care: QALYs accrued in each health state over time

Time (years)	QALMs NYHA I	QALMs NYHA II	QALMs NYHA III	QALMs NYHA IV	Decrement (total QALMs) hospitalisation within 30 days end of cycle	Total QALMs
1	20.06	820.22	509.95	5.66	-4.54	1351.35
2	19.03	758.60	458.52	5.21	-4.12	1237.24
3	17.40	688.63	413.03	4.73	-3.73	1120.07
4	15.56	615.88	369.40	4.23	-3.33	1001.73
5	13.73	543.46	325.96	3.73	-2.94	883.94
6	11.91	471.23	282.64	3.24	-2.55	766.46
7	10.14	401.18	240.62	2.76	-2.17	652.53
8	8.46	335.00	200.93	2.30	-1.81	544.88
9	6.91	273.69	164.16	1.88	-1.48	445.16
10	5.51	218.15	130.84	1.50	-1.18	354.82
11	4.24	168.01	100.77	1.15	-0.91	273.26
12	3.16	124.97	74.95	0.86	-0.68	203.26
13	2.27	89.71	53.80	0.62	-0.49	145.91
14	1.56	61.86	37.10	0.42	-0.33	100.61
15	1.03	40.76	24.45	0.28	-0.22	66.30

Table 17: Ivabradine plus standard care: QALYs accrued in each health state over time

Time (years)	QALMs NYHA I	QALMs NYHA II	QALMs NYHA III	QALMs NYHA IV	Decrement (total QALMs) hospitalisation within 30 days end of cycle	Total QALMs
1	24.80	891.67	480.33	4.09	-3.66	1397.22
2	23.73	830.67	435.10	3.80	-3.36	1289.94
3	21.90	761.00	395.56	3.48	-3.06	1178.87
4	19.79	687.91	357.57	3.14	-2.77	1065.64
5	17.68	614.39	319.36	2.81	-2.47	951.75
6	15.54	540.04	280.71	2.47	-2.17	836.58
7	13.43	466.90	242.69	2.13	-1.88	723.27
8	11.41	396.71	206.21	1.81	-1.60	614.55
9	9.51	330.53	171.81	1.51	-1.33	512.03
10	7.75	269.36	140.01	1.23	-1.08	417.27
11	6.12	212.71	110.57	0.97	-0.86	329.51
12	4.68	162.76	84.60	0.74	-0.65	252.13
13	3.47	120.63	62.70	0.55	-0.49	186.87
14	2.48	86.24	44.83	0.39	-0.35	133.59
15	1.70	59.19	30.77	0.27	-0.24	91.70

Table 18: Summary of model results compared with clinical data

Outcome	Clinical trial result Standard Care	Model result Standard Care	% error in predictions	Clinical trial result Ivabradine	Model result Ivabradine	% error prediction
HF mortality	*126.00*	*108.98*	*-15.62%*	*78.00*	*75.51*	*-3.30%*
Cardiovascular mortality	*364.00*	*329.21*	*-10.57%*	*304.00*	*294.36*	*-3.28%*
All-cause mortality	*407.00*	*366.59*	*-11.02%*	*340.00*	*332.12*	*-2.37%*
All Cause hospitalisations	*2213.00*	*1821.75*	*-21.48%*	*1754.00*	*1649.13*	*-6.36%*

Table 19: Model outputs by clinical outcomes

	Outcome	LY	QALY	Cost (£)
Standard care	*NYHA I*	*0.14*	*0.12*	*58.64*
	NYHA II	*3.29*	*2.47*	*1398.41*
	NYHA III	*2.41*	*1.54*	*1024.68*
	NYHA IV	*0.08*	*0.04*	*34.60*
	Hospitalisation	*-*	*-0.01*	*7398.48*
	Total	***5.93***	***4.15***	***9914.81***
Ivabradine plus standard care	**Outcome**	**LY**	**QALY**	**Cost (£)**
	NYHA I	*0.17*	*0.15*	*167.07*
	NYHA II	*3.53*	*2.69*	*3420.29*
	NYHA III	*2.43*	*1.58*	*2374.34*
	NYHA IV	*0.08*	*0.04*	*76.94*
	Hospitalisation	*-*	*-0.01*	*6397.44*
	Total	***6.21***	***4.44***	***12436.09***

Table 20: Summary of QALY gain by health state

Health state	QALY Standard Care	QALY Ivabradine plus Standard Care	Absolute increment	% Absolute increment
NYHA I	*0.12*	*0.15*	*0.03*	*11%*
NYHA II	*2.47*	*2.69*	*0.22*	*75%*
*NYHA III**	*1.54*	*1.58*	*0.04*	*13%*
*NYHA IV**	*0.04*	*0.04*	*0.00*	*0%*
Hospitalisation	*-0.01*	*-0.01*	*0.00*	*1%*
Total	***4.15***	***4.44***	***0.29***	***100%***

Footnotes
*Fewer patients in NYHA III and IV in Ivabradine plus Standard care
QALY, quality-adjusted life year

Table 21: Summary of costs by health state

Health state	Costs Standard Care	Costs Ivabradine plus Standard Care	Absolute increment	% Absolute increment
NYHA I	*58.64*	*167.07*	*108.43*	*4%*
NYHA II	*1398.41*	*3420.29*	*2021.88*	*80%*
*NYHA III**	*1024.68*	*2374.34*	*1349.66*	*54%*
*NYHA IV**	*34.60*	*76.94*	*42.34*	*2%*
Hospitalisation	*7398.48*	*6397.44*	*-1001.04*	*-40%*
Total	***9914.81***	***12436.09***	***2521.28***	***100%***

Table 22: Summary of predicted resource use by category of cost

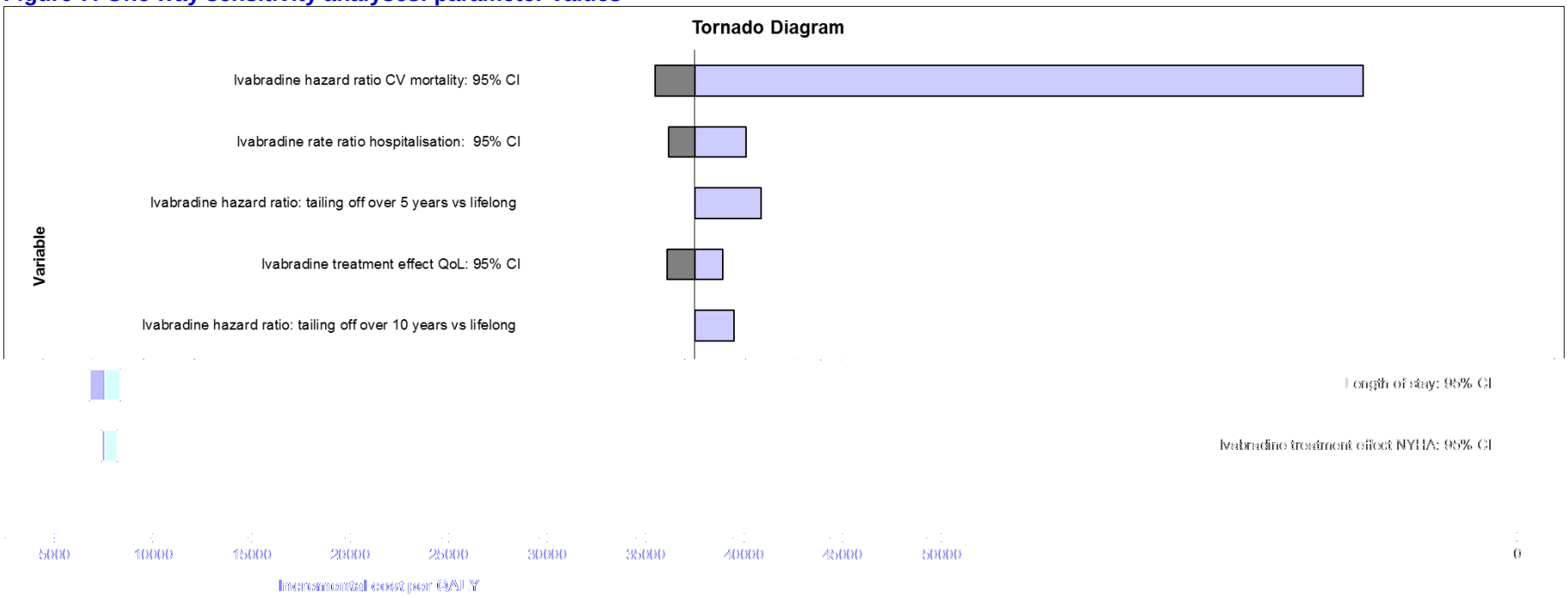
Item	Cost Standard Care	Cost Ivabradine plus Standard Care	Absolute increment	% absolute increment
Technology cost (therapy initiation and drug costs)	*611.50*	*4044.12*	*3432.62*	*136%*
Follow up costs	*1904.82*	*1994.53*	*89.71*	*4%*
Hospitalisations	*7398.48*	*6397.44*	*-1001.04*	*-40%*
Total costs	***9914.81***	***12436.09***	***2521.28***	***100%***

Table 23: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Baseline	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (LYs)	ICER (£) incremental (QALYs)
Standard Care	*9914.81*	*5.93*	*4.15*		*-*	*-*	*-*	*-*	*-*
Ivabradine plus Standard Care	*12436.09*	*6.21*	*4.44*	*Standard Care*	*2521*	*0.28*	*0.29*	*9030*	*8698*

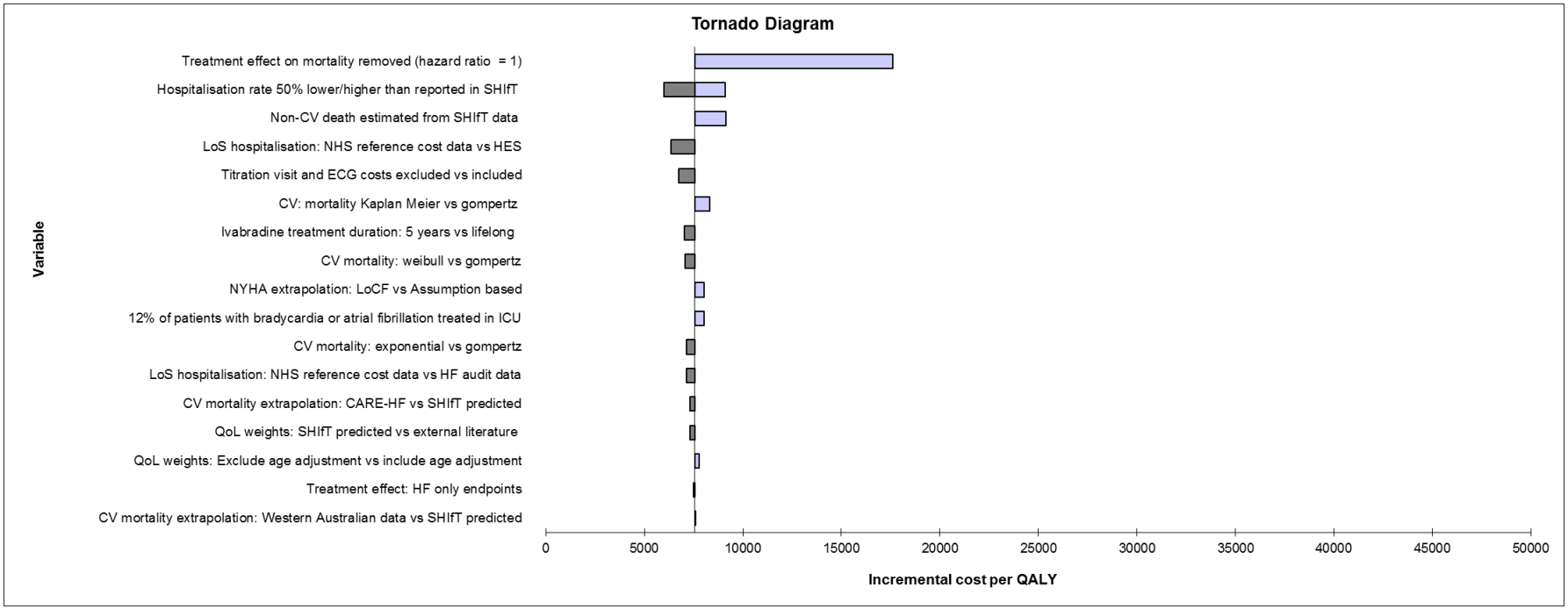
Footnotes:
ICER calculated by applying individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time and averaging costs and effects over all patient profiles see full report for details

Figure 7: One way sensitivity analyses: parameter values



Footnotes:
The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £7553 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

Figure 8: One way sensitivity analyses: structural sensitivity analyses



Footnotes:

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £7553 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

Table 24: Results of one way sensitivity analyses: parameter values

Description	Base case	Sensitivity value 1	Sensitivity value 2	Sensitivity value 1 (£)	Sensitivity value 2 (£)
Ivabradine rate ratio hospitalisation: 95% CI	SHIFT predicted	95% LCI	95% UCI	6235	10150
Ivabradine hazard ratio CV mortality: 95% CI	SHIFT predicted	95% LCI	95% UCI	5531	41464
Ivabradine treatment effect NYHA: 95% CI	SHIFT predicted	95% LCI	95% UCI	7389	8168
Ivabradine treatment effect QoL: 95% CI	SHIFT predicted	95% LCI	95% UCI	8972	6164
Length of stay: 95% CI	SHIFT predicted	95% LCI	95% UCI	8318	6788
Ivabradine hazard ratio: tailing off over 5 years vs lifelong	Lifelong	5 years post trial	Lifelong	10929	7553
Ivabradine hazard ratio: tailing off over 10 years vs lifelong	Lifelong	10 years post trial	Lifelong	9554	7553

Footnotes:

LCI – lower confidence interval, UCI upper confidence interval, NYHA New York Heart Association, QoL – Quality of Life

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £7553 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

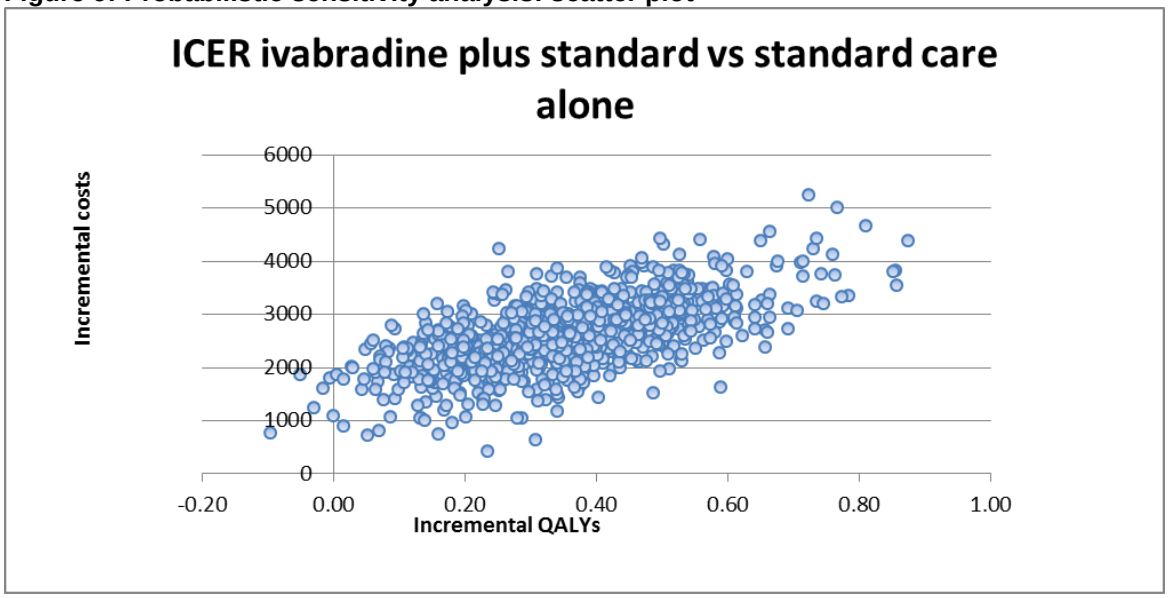
Table 25: Results of one way sensitivity analyses: structural sensitivity analyses

Description	Base case	Sensitivity value 1	Sensitivity value 2	Sensitivity value 1 (£)	Sensitivity value 2 (£)
CV: mortality Kaplan Meier vs Gompertz	Gompertz	Kaplan Meier	Gompertz	8318	7553
CV mortality: Weibull vs Gompertz	Gompertz	Weibull	Gompertz	7059	7553
CV mortality: exponential vs Gompertz	Gompertz	Exponential	Gompertz	7122	7553
CV mortality extrapolation: CARE-HF vs SHIfT predicted	Gompertz	CARE-HF	Gompertz	7311	7553
CV mortality extrapolation: Western Australian data vs SHIfT predicted	Gompertz	Australian data	Gompertz	7562	7553
Treatment effect: HF only endpoints	CV endpoint	HF endpoint	CV endpoint	7482	7553
Ivabradine treatment duration: 5 years vs lifelong	Lifelong	5 years	Lifelong	7023	7553
LoS hospitalisation: NHS reference cost data vs HES	NHS reference cost	HES data	NHS reference cost	6364	7553
LoS hospitalisation: NHS reference cost data vs HF audit data	NHS reference cost	NHF audit	NHS reference cost	7134	7553
NYHA extrapolation: LoCF vs SHIfT predicted	LoCF	SHIFT predicted	LoCF	7547	7553
NYHA extrapolation: LoCF vs Assumption based	LoCF	Assumption based	LoCF	8043	7553
QoL weights: SHIfT predicted vs external literature	SHIfT predicted	External Lit	SHIFT predicted	7326	7553
QoL weights: Exclude age adjustment vs include age adjustment	Included	Excluded	Included	7778	7553
Titration visit and ECG costs excluded vs included	Included	Excluded	Included	6749	7553
12% of patients with bradycardia or atrial fibrillation treated in ICU	ICU costs excluded	ICU costs included	ICU excluded	8036	7553
Non-CV death estimated from SHIfT data	UK mortality rates	SHIfT predicted	UK mortality rates	9143	7553
Hospitalisation rate 50% lower/higher than reported in SHIfT	SHIfT predicted	50% reduction	50% increase	9112	6004
Treatment effect on mortality removed (hazard ratio = 1)	SHIfT predicted	Hazard ratio = 1	SHIFT predicted	17625	7553

Footnotes

NYHA - New York Heart Association, HES – Hospital Episode Statistics, LoCF – Last observation Carried Forward,

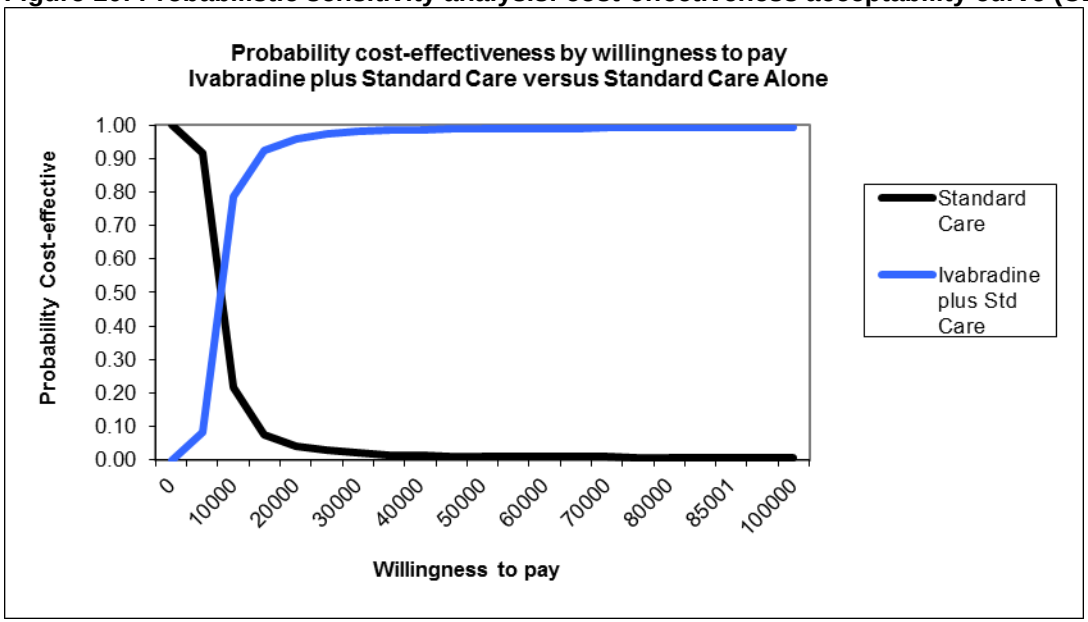
Figure 9: Probabilistic sensitivity analysis: scatter plot



Footnotes:

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £7553 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

Figure 10: Probabilistic sensitivity analysis: cost-effectiveness acceptability curve (CEAC)



Footnotes:

The one way sensitivity analyses have been estimated by employing average values in the risk equations (e.g. 0.24 for gender). The ICER for the base case analysis is £7553 using this method (lower than the ICER reported using the full heterogeneity analysis which calculates the ICER by individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time – see full report for details).

Table 26: Results: subgroup analyses

Subgroup	Total Costs	Total LYs	Total QALYs	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental Cost/LY	Incremental Cost/QALY
All patients (HR>=75 b.p.m.)	*9915*	*5.93*	*4.15*	*12436*	*6.21*	*4.44*	*2521*	*0.28*	*0.29*	*9030*	*8698*
Age<75 years	*10003*	*6.10*	*4.29*	*12619*	*6.39*	*4.59*	*2616*	*0.29*	*0.30*	*8991*	*8666*
Age>=75 years	*9072*	*4.26*	*2.80*	*10693*	*4.43*	*2.98*	*1622*	*0.17*	*0.18*	*9671*	*9221*
NYHA II	*10241*	*6.69*	*4.99*	*13151*	*6.96*	*5.29*	*2909*	*0.27*	*0.30*	*10844*	*9751*
NYHA III	*9742*	*5.35*	*3.49*	*11962*	*5.65*	*3.78*	*2220*	*0.29*	*0.29*	*7629*	*7765*
NYHA IV	*6790*	*2.69*	*1.36*	*7918*	*2.92*	*1.56*	*1127*	*0.24*	*0.19*	*4774*	*5817*
HF duration <0.6 years	*10634*	*7.18*	*5.29*	*13747*	*7.49*	*5.64*	*3113*	*0.31*	*0.34*	*9997*	*9055*
HF duration >=0.6<2 years	*9801*	*6.02*	*4.27*	*12403*	*6.31*	*4.57*	*2601*	*0.29*	*0.30*	*9073*	*8689*
HF duration >=2<4.8 years	*8939*	*5.58*	*3.77*	*11390*	*5.85*	*4.04*	*2451*	*0.27*	*0.27*	*9246*	*9129*
HF duration >=4.8 years	*10302*	*4.97*	*3.30*	*12242*	*5.23*	*3.55*	*1941*	*0.25*	*0.25*	*7626*	*7785*
No beta blocker	*10223*	*4.69*	*3.20*	*12006*	*5.03*	*3.52*	*1782*	*0.34*	*0.32*	*5227*	*5560*
Beta blocker < half target dose	*9626*	*5.31*	*3.74*	*11843*	*5.58*	*4.02*	*2217*	*0.27*	*0.28*	*8067*	*7919*
Beta blocker =>half target dose < target dose	*10242*	*6.63*	*4.64*	*13110*	*6.89*	*4.93*	*2868*	*0.27*	*0.29*	*10684*	*9903*
Beta blocker =>target dose	*9888*	*6.92*	*4.84*	*12960*	*7.19*	*5.13*	*3072*	*0.27*	*0.29*	*11576*	*10561*
LVEF < 26%	*10289*	*4.80*	*3.39*	*12155*	*5.10*	*3.68*	*1866*	*0.29*	*0.29*	*6338*	*6398*
LVEF >=26%<30%	*9285*	*5.40*	*3.77*	*11589*	*5.68*	*4.05*	*2304*	*0.28*	*0.28*	*8339*	*8227*
LVEF >=30<33%	*9597*	*6.26*	*4.37*	*12338*	*6.54*	*4.66*	*2741*	*0.28*	*0.30*	*9679*	*9281*
LVEF >= 33%	*10234*	*7.02*	*4.90*	*13309*	*7.28*	*5.19*	*3074*	*0.26*	*0.29*	*11690*	*10633*
Non-diabetic	*9212*	*5.95*	*4.21*	*11842*	*6.23*	*4.50*	*2629*	*0.28*	*0.29*	*9511*	*9094*
Diabetic	*11448*	*5.88*	*4.02*	*13734*	*6.16*	*4.32*	*2285*	*0.29*	*0.29*	*8012*	*7842*
No prior CAD	*9433*	*5.92*	*4.36*	*12019*	*6.23*	*4.68*	*2586*	*0.31*	*0.33*	*8298*	*7937*
Prior CAD	*10113*	*5.93*	*4.06*	*12607*	*6.20*	*4.34*	*2495*	*0.27*	*0.28*	*9382*	*9069*

Footnotes:

QALY – Quality Adjusted Life Year

ICER calculated by applying individual patient profiles from SHIfT patients (with a heart rate ≥ 75bpm) into the risk equations sequentially one at time and averaging costs and effects over all patient profiles with subgroup characteristic of interest see full report for details

Section C: Textual clarifications and additional points

C1

The manufacturer indicates that they "anticipate that ivabradine would be initiated by either a consultant cardiologist, a primary care GPwSI (GP with special interest) or other suitably qualified member of a multidisciplinary heart failure team" (pg 29), and goes on to highlight that an additional consultation may be needed to titrate the ivabradine dose. Please clarify whether post-titration of ivabradine dose patients can be safely discharged to continuous maintenance treatment by a non-specialist GP. Please provide an indication of how long after titration of ivabradine dose it will no longer be necessary for monitoring to be carried out by a specialist in the management of chronic heart failure.

We wish to clarify that after titration of the ivabradine dose, these patients can be safely discharged to continuous maintenance treatment by a non-specialist GP. This is for two main reasons:

- GPs in the UK are accustomed to the continuous maintenance of ivabradine for its indication in angina for which it has been available in the UK over the last 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.

Regarding the question as to how long after titration of ivabradine dose it will no longer be necessary for monitoring to be carried out by a specialist, we would like to clarify the following;

It is only if the patients' heart failure worsens that we would expect that a patient is referred back to the specialist team. This is the case for the majority of heart failure treatments.

In fact we would suggest that our assumptions are very conservative in terms of the need for specialist involvement, especially regarding the up-titration of ivabradine. This is because titrating ivabradine to maximum dose or reducing to the minimum dose can be achieved in one titration step and is based on the resting heart rate as measured by the treating clinician. As stated above, GPs already have this clinical knowledge from use of ivabradine in angina. The base case model is therefore likely to under-estimate the true cost effectiveness of ivabradine in the 'real world' scenario.

C2

The number of patients in the full population of SHIfT who achieved target dose of β-blocker is reported to be 23% in Table 30 (pg 104), but 26.0% in Table 94 (pg 304). Please confirm the percentage of patients achieving target dose of β-blocker.

The manufacturer wishes to apologise for the confusion regarding the quoted usage of optimal beta-blocker dose. In the right context both figures are actually correct. For clarification please note the following:

1) 23% of all patients included in SHIfT (main trial population) received target dose beta-blockade.

2) 26% of all patients receiving a beta-blocker in SHIfT (main trial population) received target dose beta-blockade.

The difference may be explained by the observation that 11% of patients in SHIfT were not taking a beta-blocker (owing to contra-indication or intolerance).

C3

In Table 6 (pg 48) in the submission, the lower value for the range of resting heart rates (presented with median resting heart) in both the ivabradine and placebo groups indicates that patients with resting heart rate <70 bpm were included in the trial. Please state how many patients in each group with a heart rate <70 bpm were enrolled in the trial and included in any analysis.

8 patients with baseline heart rate <70 bpm were enrolled in the trial and included in all analyses, 5 in the ivabradine group and 3 in the placebo group.

These patients were included in the ITT analysis (as opposed to per-protocol, in which patients who violated the clinical trial protocol are excluded) in order to avoid an imbalance between the randomised groups and a potential source of selection bias.

C4

Please confirm that the baseline characteristics presented below for smoking habits are correct (reproduced from Table 6, pg 48). In the ivabradine arm for the licensed population, the number of patients assessed represents 89.1% of the population.

We wish to acknowledge a typographical error in the construction of this table, which has now been corrected below.

	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
Smoking habits, n (%)				
Yes	541 (16.7)	577 (17.7)	381 (18.6)	402 (19.2)
Previous	1355 (41.8)	1364 (41.8)	847 (40.9)	857 (40.9)
Never	1345 (41.5)	1323 (40.5)	824 (40.2)	839 (40.0)

C5

Throughout the clinical effectiveness section, analyses for the licensed population are based on 4,150 patients. However, in the cost effectiveness section, the text indicates that the licensed population includes 4,154 patients (e.g., section 6.2.1; pg 116 of the MS). Please clarify this potential discrepancy.

4154 patients had heart rate ≥75 bpm at baseline, however 4 of these patients were not in sinus rhythm (had atrial fibrillation) and have therefore been excluded from clinical analyses based on heart rate subgroups.

Measuring heart rate in patients with atrial fibrillation can provide inflated and/or variable estimates of resting heart rate. The statistical analysis plan for the SHIFT trial therefore pre-defined any subgroups based on heart rate to exclude such

patients. However our economic agency were not made aware of this definition and therefore the four patients in atrial fibrillation remained in the economic analyses pertaining to the licensed subgroup.
Importantly, including these patients makes no material difference to the clinical results observed for the licensed population.

C6
Please provide the definitions for the terms “low dose”, “moderate dose” and “target dose” used in Table 30 of the submission (pg 104).

Definition of beta-blocker dose (expressed as % of target dose):

SHIfT; National HF Audit: Low dose <50%, Moderate dose ≥50%, Target 100%
Hull Audit - for bisoprolol, carvedilol, nebivolol, atenolol and timolol: Low <50%, moderate 50-99%, target 100%
Hull Audit - for metoprolol, propranolol, sotolol: Low <25%, moderate 25%-99%, target 100%
Hull Audit - for celiprolol: Low 25%, moderate 50%, target 100%

C7
In section 5.3.4 (pg 50 of the MS), there seems to be an incomplete sentence “Further details on therapy post-randomisation are provided in.” Please indicate where the additional details on post-randomisation therapy are provided.

… are provided in Table 95, Appendix 15.

C8
The tables presenting data for the regression models (Tables 37 [pg 131], 38 [pg 133], and 42 [pg 137]) contain duplicate descriptions for evaluated LVEF parameters (example provided below). Please clarify which, if any, of the descriptions is incorrect and provide corrected description(s).

We wish to acknowledge a typographical error in the labelling of this table, which has now been corrected below.

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
LVEF ≥26% <30% *vs* <26%	0.8625	-0.1479	0.0929	0.111	-0.33	0.0342
LVEF ≥30% <33% *vs* <26%	0.7122	-0.3394	0.0893	0	-0.5145	-0.1644
LVEF ≥33% *vs* <26%	0.5905	-0.5268	0.0921	0	-0.7073	-0.3462

Reference List

(1) Levy W, Mozaffarian D, Linker D, et al. The Seattle Heart Failure Model: Prediction of Survival in Heart Failure. Circulation 2006;113:1424-33.

(2) Swedberg K, Komadja M, Bohm M, et al. Ivrabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet 2010;376(9744):875-85.

(3) McKenna C, Burch J, Suekarran S, Walker S, Bakhai A, Witte K, et al. A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure. Health Technology Assessment 2010;14(24):1-162.

(4) McMurray JJ, Andersson FL, Stewart S, Svensson K, Cohen SA, Dietz R, et al. Resource utilization and costs in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. European Heart Journal 2006;27(12):1447-58.