

SUPPLEMENTAL MATERIAL

Table S1. Annual Hospitalization Rates From US Claims

Parameter (Type/Number of Hospitalization[s])	Commercial Reference Rate (95% CI) (Base Case)	Medicare Advantage Reference Rate
First HF for patients with no non-HF CV	0.54 (0.50-0.59)	0.66
First HF for patients with 1+ non-HF CV	0.91 (0.75-1.09)	1.13
2 HF	2.01 (1.67-2.39)	2.01
3 HF	2.01 (1.67-2.39)	2.01
≥ 3 HF	2.01 (1.67-2.39)	2.01
Non-HF CV for patients with 0 CV	0.05 (0.04-0.05)	0.06
Non-HF CV for patients with 1 CV	0.14 (0.13-0.16)	0.19
Non-HF CV for patients with 2 CV	0.19 (0.16-0.22)	0.25
Non-HF CV for patients with ≥ 3 CV	0.28 (0.23-0.34)	0.38
Non-CV	0.52 (0.50-0.54)	0.65

Source: US claims hospitalization rates analysis scaled based on SHIFT hospitalization

rates. Analysis of SHIFT trial data showed that patients are subject to higher risk of HF hospitalization as they experience more HF hospitalizations, and are subject to higher risk of non-HF CV hospitalization as they experience more CV hospitalizations. The US claims data analysis only estimated the cumulative (1, 2, and ≥ 3) hospitalization rate for HF and non-HF CV hospitalizations. To derive the hospitalization rate specifically for 1, 2, and ≥ 3 hospitalizations based on the cumulative rate from US claims data, the corresponding cumulative rates were estimated in SHIFT and then used to estimate a scaling factor (US claims data rate/SHIFT rate) between the hospitalization rate from US claims data and SHIFT. This scaling factor was then applied to the event rates in Supplemental Table 2 to

derive the hospitalization rate for 1, 2, and ≥ 3 hospitalizations for US claims data. To minimize the risk of overestimating hospitalization rates using US claims data, the rate was capped at the highest rate reported in SHIFT (2.01).

CI indicates confidence interval; CV, cardiovascular; HF, heart failure; and SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

**Table S2. Annual Hospitalization Rates and Treatment Effect on Hospitalization
From SHIFT**

Parameter (Type/Number of Hospitalization[s])	Hospitalization Rate (Reference Case)	Hazard Ratio (95% CI) Ivabradine vs Placebo
First HF for patients with no non-HF CV	0.12	0.73 (0.64-0.82)
First HF for patients with 1+ non-HF CV	0.20	0.84 (0.63-1.11)
2 HF	0.66	0.84 (0.70-1.01)
3 HF	0.99	1.09 (0.83-1.42)
≥ 3 HF	2.01	0.94 (0.73-1.21)
Non-HF CV for patients with 0 CV	0.12	0.97 (0.86-1.09)
Non-HF CV for patients with 1 CV	0.37	0.99 (0.83-1.18)
Non-HF CV for patients with 2 CV	0.48	1.08 (0.83-1.39)
Non-HF CV for patients with ≥ 3 CV	0.72	0.96 (0.74-1.24)
Non-CV	0.14	0.89 (0.80-0.98)

Source: SHIFT data analysis.

CI indicates confidence interval; CV, cardiovascular; HF, heart failure; and SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

Table S3. Annual Mortality Rates and Hazard Ratios Derived From SHIFT Data

Parameter	Annual Incidence Rate for Background Therapy (95% CI)	Hazard Ratio (95% CI) Ivabradine vs Placebo
HF mortality	0.026 (0.022-0.030)	0.74 (0.58-0.94)
Non-HF CV mortality	0.057 (0.052-0.064)	0.98 (0.84-1.14)
Non-CV mortality	Informed by US life table adjusted to exclude CV-related deaths	

Source: SHIFT data analysis.

CI indicates confidence interval; CV, cardiovascular; HF, heart failure; and SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

Table S4. AE Rates per Year

Type of AE	Annual Event Rate, Placebo, %	Annual Event Rate, Ivabradine, %
Asymptomatic bradycardia	0.8	3.6
Symptomatic bradycardia	0.6	2.9
Atrial fibrillation	4.6	5.8
Blurred vision	0.1	0.4
Phosphenes	0.3	1.8

Source: SHIFT data analysis.

AE indicates adverse event; and SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

Table S5. Hospitalization and AE Costs

	Cost per Event Commercial, \$	Cost per Event Medicare Advantage, \$	Reference/Resource Used
Type of hospitalization (survive or die)			
First HF	39,779	24,746	US claims data
Second HF	31,171	19,899	US claims data
≥ Third HF	32,422	18,684	US claims data
First non-HF CV	29,082	18,596	US claims data
Second non-HF CV	27,684	16,082	US claims data
Third+ non-HF CV	30,915	15,610	US claims data
Non-CV related	17,904	11,489	US claims data
Type of AE			
Asymptomatic bradycardia	142	73	Physician visit for cardiac issue of “moderate severity” ^{1,2}
Symptomatic bradycardia	686	367	Physician visit for cardiac issue of “moderate severity” or ED visit for cardiac issue of “high severity” ^{1,2}
Atrial fibrillation	686	367	Physician visit for cardiac issue of “moderate severity” or ED visit for cardiac issue of “high severity” ^{1,2}

Blurred vision	187	126	Physician visit for comprehensive ophthalmological services ^{1,2}
Phosphenes	187	126	Physician visit for comprehensive ophthalmological services ^{1,2}

AE indicates adverse event; CV, cardiovascular; ED, emergency department; and HF, heart failure.

Table S6. Utility Regression Equations

Independent Variable	Parameter Estimates	
	Explicit No. of Hospitalizations (SE) (Base Case)	Minimum No. of Hospitalizations (SE)
Intercept	0.425 (0.008)	0.425 (0.008)
Treatment	0.009 (0.005)	0.009 (0.005)
Beta-blocker use (no vs yes) at baseline	-0.011 (0.008)	-0.011 (0.008)
Baseline EQ-5D index score	-0.540 (0.010)	-0.540 (0.010)
≥ 1 HF hospitalization		-0.084 (0.006)
≥ 1 non-HF CV hospitalization		-0.032 (0.005)
1 HF hospitalization	-0.076 (0.007)	
2 HF hospitalizations	-0.074 (0.013)	
≥ 3 HF hospitalizations	-0.133 (0.016)	
1 non-HF CV hospitalization	-0.020 (0.006)	
2 non-HF CV hospitalizations	-0.053 (0.011)	
3 non-HF CV hospitalizations	-0.072 (0.015)	

Source: PRO-SHIFT study data analysis (Amgen Data on File, 2014)

CV indicates cardiovascular; EQ-5D, EuroQol-5D; HF, heart failure; SE, standard error; and SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.