

## SUPPLEMENTARY INFORMATION

**Supplementary Table 1: Baseline characteristics according to inpatient or outpatient randomization strata and randomized treatment**

	Inpatients (n=2084)		Outpatients (n=6148)	
	Omecamtiv mecarbil (n=1044)	Placebo (n=1040)	Omecamtiv mecarbil (n=3076)	Placebo (n=3072)
<i><u>Demographics</u></i>				
Age - yr	65.1 ± 11.2	65.0 ± 11.4	64.3 ± 11.4	64.4 ± 11.4
Sex, Female	213 (20.4%)	198 (19.0%)	662 (21.5%)	676 (22.0%)
<i><u>Race</u></i>				
Asian	91 (8.7 %)	93 (8.9 %)	264 (8.6 %)	262 (8.5 %)
Black	54 (5.2 %)	51 (4.9 %)	231 (7.5 %)	226 (7.4 %)
Other	42 (4.0 %)	47 (4.5 %)	242 (7.9 %)	232 (7.6 %)
White	857 (82.1%)	849 (81.6%)	2339 (76.0%)	2352 (76.6%)
<i><u>Geographic Region</u></i>				
Asia	88 (8.4 %)	89 (8.6 %)	247 (8.0 %)	246 (8.0 %)
Eastern Europe/Russia	457 (43.8%)	458 (44.0%)	887 (28.8%)	879 (28.6%)
Latin America	165 (15.8%)	161 (15.5%)	622 (20.2%)	626 (20.4%)
US And Canada	92 (8.8 %)	88 (8.5 %)	601 (19.5%)	605 (19.7%)
Western Europe/South Africa/Australasia	242 (23.2%)	244 (23.5%)	719 (23.4%)	716 (23.3%)
<i><u>Clinical Characteristics</u></i>				
Atrial fibrillation or flutter at screening	357 (34.2%)	366 (35.2%)	789 (25.7%)	733 (23.9%)
Hypertension	769 (73.7%)	726 (69.8%)	2141 (69.6%)	2148 (69.9%)
Type 2 diabetes mellitus	436 (41.8%)	434 (41.7%)	1216 (39.5%)	1223 (39.8%)
History of stroke	94 (9.0 %)	104 (10.0%)	283 (9.2 %)	273 (8.9 %)
Ischemic heart failure etiology	568 (54.4%)	577 (55.5%)	1625 (52.8%)	1645 (53.5%)
History of myocardial infarction	426 (40.8%)	467 (44.9%)	1267 (41.2%)	1275 (41.5%)
History of coronary artery bypass surgery	149 (14.3%)	171 (16.4%)	490 (15.9%)	507 (16.5%)
History of percutaneous coronary revascularization	295 (28.3%)	304 (29.2%)	937 (30.5%)	902 (29.4%)
LVEF - %	26.7 ± 6.4	26.3 ± 6.3	26.6 ± 6.2	26.6 ± 6.2
<i><u>NYHA Classification</u></i>				
Class II	404 (38.7%)	364 (35.0%)	1791 (58.2%)	1809 (58.9%)
Class III	580 (55.6%)	610 (58.7%)	1221 (39.7%)	1205 (39.2%)
Class IV	60 (5.7 %)	66 (6.3 %)	64 (2.1 %)	58 (1.9 %)
Median KCCQ Total Symptom Score	54.2 [34.4, 72.9]	52.1 [31.2, 69.8]	74.0 [54.2, 90.6]	75.0 [56.2, 91.7]
SBP — mmHg	114.1 ± 14.5	113.6 ± 14.2	117.0 ± 15.6	117.7 ± 15.5
Heart rate — beats/min	73.2 ± 11.5	73.1 ± 11.8	72.2 ± 12.4	72.1 ± 12.2
Median NT-proBNP — pg/mL	2434 [1197, 4983]	2579 [1285, 5370]	1876 [925, 3807]	1888 [924, 3744]
Median cardiac troponin I — ng/L	37 [19, 66]	37 [19, 70]	24 [12, 46]	24 [13, 46]
Median eGFR — mL/min/1.73m <sup>2</sup>	53.9 [41.0, 70.5]	55.0 [41.7, 69.9]	60.2 [45.8, 75.4]	59.8 [44.8, 74.8]
Baseline BMI (kg/m <sup>2</sup> )	28.2 ± 6.2	27.8 ± 5.9	28.6 ± 6.3	28.6 ± 6.1
Baseline weight (kg)	82.1 ± 20.8	81.2 ± 19.8	82.9 ± 20.8	82.8 ± 20.6
<i><u>Heart Failure Therapies</u></i>				
ACEi, ARB or ARNi	872 (83.5%)	871 (83.8%)	2711 (88.1%)	2705 (88.1%)
ARNi	163 (15.6%)	168 (16.2%)	656 (21.3%)	614 (20.0%)
Beta-blocker	970 (92.9%)	970 (93.3%)	2910 (94.6%)	2913 (94.8%)
MRA	852 (81.6%)	857 (82.4%)	2347 (76.3%)	2341 (76.2%)
SGLT2 inhibitor	24 (2.3 %)	31 (3.0 %)	80 (2.6 %)	83 (2.7 %)
Ivabradine	76 (7.3 %)	80 (7.7 %)	179 (5.8 %)	198 (6.4 %)
Digitalis glycosides	182 (17.4%)	175 (16.8%)	505 (16.4%)	523 (17.0%)
Cardiac resynchronization therapy	135 (12.9%)	132 (12.7%)	457 (14.9%)	434 (14.1%)
Implantable cardioverter defibrillator	310 (29.7%)	288 (27.7%)	1016 (33.0%)	1000 (32.6%)

Data are presented as n (%) or mean ± standard deviation, unless otherwise specified.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2.

**Supplementary Table 2: Risk of the primary composite outcome according to time from most recent worsening heart failure event in those randomized as outpatients**

<b>Time since worsening HF event</b>	<b>HR (95% CI)</b>	<b>P-value</b>	<b>P for trend</b>
<i>0-3 months</i>	1.20 (1.01, 1.42)	0.039	0.008
<i>3-6 months</i>	1.09 (0.91, 1.31)	0.35	
<i>6-9 months</i>	1.06 (0.88, 1.29)	0.54	
<i>9-12 months</i>	REFERENT	-	

All patients, irrespective of treatment allocation, were included in this analysis. Hazard ratios (HR) with 95% confidence interval (CI) derived from Cox proportional Hazards models adjusted for randomized treatment (omecamtiv mecarbil or placebo), atrial fibrillation, etiology, ejection fraction, NYHA class, systolic blood pressure, heart rate, log-transformed NT-proBNP and eGFR.

**Supplementary Table 3: Adverse events by randomization setting and randomized treatment**

	Inpatient		Outpatient	
	Omecamtiv mecarbil n=1040	Placebo n=1034	Omecamtiv mecarbil n=3070	Placebo n=3067
<b>Any treatment-emergent serious adverse event</b>	640 (61.5%)	679 (65.7%)	1733 (56.4%)	1756 (57.3%)
<i>Odds ratio (95% confidence intervals)</i>	0.94 (0.88, 1.00)		0.99 (0.94, 1.03)	
<b>Ventricular tachyarrhythmia</b>	73 (8.1%)	67 (7.3%)	217 (7.9%)	237 (8.6%)
<i>Odds ratio (95% confidence intervals)</i>	1.11 (0.81, 1.53)		0.91 (0.77, 1.09)	
<b>Torsade de pointes / QT prolongation</b>	52 (5.8%)	37 (4.0%)	124 (4.5%)	158 (5.8%)
<i>Odds ratio (95% confidence intervals)</i>	1.44 (0.95, 2.17)		0.78 (0.62, 0.99)	
<b>Serious adverse ventr. arrhyth. leading to treatment discontinuation</b>	35 (3.4%)	20 (1.9%)	84 (2.7%)	107 (3.5%)
<i>Odds ratio (95% confidence intervals)</i>	1.74 (1.01, 2.99)		0.78 (0.59, 1.04)	
<b>First Major Cardiac Ischemic Event*</b>	47 (4.5%)	28 (2.7%)	153 (5.0%)	160 (5.2%)
<i>Odds ratio (95% confidence intervals)</i>	1.67 (1.05, 2.64)		0.96 (0.77, 1.19)	
<b>Positively Adjudicated myocardial infarction*</b>	32 (3.1%)	21 (2.0%)	90 (2.9%)	97 (3.2%)
<i>Odds ratio (95% confidence intervals)</i>	1.52 (0.88, 2.61)		0.93 (0.70, 1.23)	
<b>First Hospitalization for Unstable Angina*</b>	5 (0.5%)	0 (0.0%)	20 (0.7%)	12 (0.4%)
<i>Odds ratio (95% confidence intervals)</i>	-		1.67 (0.82, 3.40)	
<b>First Coronary Revascularization*</b>	25 (2.4%)	18 (1.7%)	90 (2.9%)	99 (3.2%)
<i>Odds ratio (95% confidence intervals)</i>	1.38 (0.76, 2.52)		0.91 (0.69, 1.20)	
<b>First Stroke*</b>	20 (1.9%)	32 (3.1%)	56 (1.8%)	80 (2.6%)
<i>Odds ratio (95% confidence intervals)</i>	0.62 (0.36, 1.08)		0.70 (0.50, 0.98)	

\*Adjudicated events

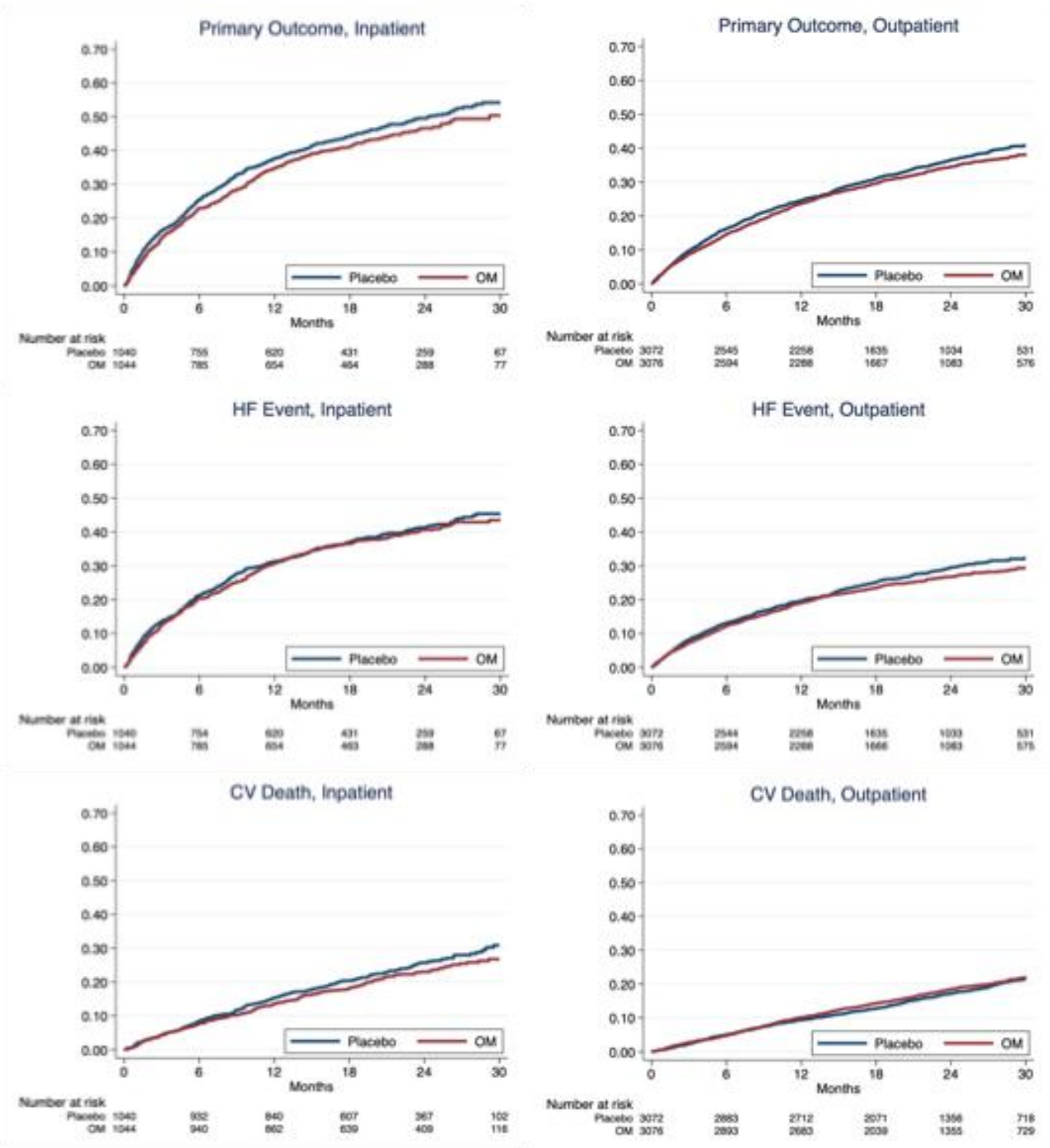
**Supplementary Table 4: Effect of omecamtiv mecarbil compared with placebo on vital signs and laboratory measurements by randomization setting**

Variable	Inpatients				
	Baseline		Follow-up		Ratio or Difference
	Omecamtiv mecarbil	Placebo	Omecamtiv mecarbil	Placebo	
Systolic BP (mm Hg) week 0 to 2 (n = 1965)	114.1±14.5	113.6±14.2	115.9±16.5	115.4±16.1	0.1 (-1.1, 1.3)
Heart rate (BPM) week 0 to 2 (n = 1965)	73.2±11.5	73.1±11.8	72.9±12.3	74.3±13.3	-1.5 (-2.5, -0.5)
Potassium (mmol/L) week 0 to 12 (n = 1496)	4.48±0.55	4.53±0.52	4.58±0.60	4.60±0.53	-0.00 (-0.06, 0.05)
Creatinine (mg/dl) week 0 to 12 (n = 1535)	1.37±0.47	1.36±0.47	1.35±0.51	1.35±0.57	0.01 (-0.03, 0.05)
NT-proBNP (pg/ml) week 0 to 2 [Ratio] (n = 1933)	2434 [1197, 4983]	2579 [1285, 5370]	2672 [1222, 5030]	2767 [1320, 6035]	0.96 (0.90, 1.02)
NT-proBNP (pg/ml) week 0 to 24 [Ratio] (n = 1653)	2434 [1197, 4983]	2579 [1285, 5370]	1602 [644, 3571]	2032 [862, 4414]	0.85 (0.77, 0.94)
Troponin I (ng/L) week 0 to 2 [Median Difference] (n = 1900)	37 [19, 66]	37 [19, 70]	43 [21, 76]	34 [18, 62]	4 (3, 5)
Troponin I (ng/L) week 0 to 24 [Median Difference] (n = 1631)	37 [19, 66]	37 [19, 70]	39 [18, 74]	30 [13, 56]	5 (3, 7)

Variable	Outpatients				
	Baseline		Follow-up		Ratio or Difference
	Omecamtiv mecarbil	Placebo	Omecamtiv mecarbil	Placebo	
Systolic BP (mm Hg) week 0 to 2 (n = 5874)	117.0±15.6	117.7±15.5	116.9±16.8	118.0±16.7	-0.7 (-1.3, -0.1)
Heart rate (BPM) week 0 to 2 (n = 5873)	72.2±12.4	72.1±12.2	71.0±12.1	72.0±12.0	-0.9 (-1.4, -0.5)
Potassium (mmol/L) week 0 to 12 (n = 3941)	4.59±0.52	4.58±0.52	4.57±0.54	4.58±0.53	-0.02 (-0.05, 0.01)
Creatinine (mg/dl) week 0 to 12 (n = 3966)	1.28±0.46	1.28±0.45	1.30±0.49	1.28±0.48	0.01 (-0.01, 0.03)
NT-proBNP (pg/ml) week 0 to 2 [Ratio] (n = 5923)	1876 [925, 3807]	1888 [924, 3744]	1702 [843, 3404]	1727 [836, 3600]	0.98 (0.95, 1.01)
NT-proBNP (pg/ml) week 0 to 24 [Ratio] (n = 5381)	1876 [925, 3807]	1888 [924, 3744]	1345 [558, 2881]	1423 [637, 3079]	0.91 (0.87, 0.95)
Troponin I (ng/L) week 0 to 2 [Median Difference] (n = 5867)	24 [12, 46]	24 [13, 46]	31 [15, 58]	24 [12, 45]	3 (3, 3)
Troponin I (ng/L) week 0 to 24 [Median Difference] (n = 5333)	24 [12, 46]	24 [13, 46]	31 [14, 64]	23 [10, 46]	4 (3, 5)

Supplementary Figure 1: Kaplan Meier estimates of the primary outcome and its individual components according to randomization setting and randomized treatment



Abbreviations: CV, cardiovascular; HF, heart failure; OM, omeamtiv mecarbil

Supplementary Figure 2: Effect of omecamtiv compared with placebo on the primary composite outcome in outpatients according to time since most recent worsening HF event prior to randomization

