## Supplementary Appendix

Figure S1: Effect of Empagliflozin on KCCQ Changes in Total Symptom Score at 52 Weeks by subgroup.

Figure S2: Effect of Empagliflozin on KCCQ Changes in Overall Summary Score at 52 weeks by sub-group.

## Figure S1: Effect of Empagliflozin on KCCQ Changes in Total Symptom Score at 52 Weeks by sub-group.

Subgroups	Empagliflozin	Placebo	Difference	(*)	<i>p</i> -trend p-interaction)
LVEF, %					
<50	6.10 (4.95, 7.24)	4.19 (3.04, 5.34)	1.91 (0.29, 3.53)	<b>⊞</b> 1	
50-<60	5.74 (4.63, 6.85)	2.97 (1.85, 4.09)	2.77 (1.19, 4.34)	<b>⊢-≣</b> 1	0.710
≥60	5.70 (4.56, 6.83)	4.20 (3.07, 5.34)	1.49 (-0.11, 3.09)	ı <b>⊢_</b> ∰1	
Age, years					
<65	7.21 (5.74, 8.68)	5.56 (4.10, 7.03)	1.65 (-0.42, 3.71)	₽┼─₩───	
65-<75	5.58 (4.53, 6.64)	3.86 (2.78, 4.94)	1.72 (0.22, 3.23)	<b>⊢_≣_</b> -1	0.409
≥75	5.43 (4.43, 6.44)	2.87 (1.87, 3.87)	2.56 (1.15, 3.97)	┝╍╋╍┥	
Gender					
Male	4.79 (3.92, 5.67)	2.82 (1.94, 3.69)	1.98 (0.74, 3.21)	⊢-≣1	0.000*
Female	7.14 (6.16, 8.11)	4.95 (3.97, 5.93)	2.19 (0.81, 3.57)		0.822*
Region					
North America	3.85 (1.92, 5.78)	4.00 (2.05, 5.95)	-0.15 (-2.89, 2.59)	<b>⊢</b>	
Latin America	10.24 (8.92, 11.56)	8.07 (6.75, 9.38)	2.17 (0.31, 4.03)	<b>⊢</b> ■1	
Europe	4.63 (3.68, 5.59)	2.01 (1.04, 2.97)	2.63 (1.27, 3.98)	│ ⊢∎→	0.310*
Asia Pacific	1.63 (-0.25, 3.52)	0.67 (-1.22, 2.56)	0.96 (-1.70, 3.62)	►_ <b>+</b> ₩1	
Other	8.58 (5.88, 11.28)	4.63 (1.95, 7.32)	3.94 (0.14, 7.75)	• <b>-</b>	•
Diabetes mellitus	;				
Yes	6.79 (5.85, 7.73)	4.07 (3.14, 5.01)	2.72 (1.39, 4.04)	⊢≣-1	0.400*
No	4.95 (4.05, 5.85)	3.49 (2.58, 4.40)	1.46 (0.18, 2.74)	<b>⊢-⊞-</b> 4	0.182*
History of atrial f	ibrillation or atrial flut	ter			
Yes	5.80 (4.90, 6.71)	3.18 (2.27, 4.08)	2.63 (1.35, 3.90)	┝╌╋╌┥	0.209*
No	5.88 (4.93, 6.83)	4.44 (3.48, 5.40)	1.44 (0.10, 2.78)	<b>▶8</b> 1	0.200
Atrial fibrillation	or atrial flutter at enro	Iment			
Yes	6.69 (5.60, 7.79)	3.00 (1.89, 4.11)	3.69 (2.13, 5.25)	<b>⊢</b> ∎1	0.012*
No	5.39 (4.58, 6.21)	4.18 (3.38, 4.99)	1.21 (0.06, 2.35)	┝╌╋╌┥	0.012
Chronic kidney d					
Yes	6.17 (5.27, 7.06)	3.61 (2.70, 4.51)	2.56 (1.29, 3.83)	┝╌╋╌┥	0.057*
No	5.46 (4.51, 6.41)	3.97 (3.02, 4.91)	1.49 (0.15, 2.83)	<b>₩</b> 1	0.257*
Anaemia					
Yes	5.92 (4.67, 7.18)	3.88 (2.63, 5.13)	2.05 (0.28, 3.81)	<b>⊢≣</b> _I	0.981*
No	5.80 (5.04, 6.57)	3.73 (2.96, 4.50)	2.07 (0.99, 3.15)	⊢∎→	0.901
Body mass index	, kg/m²				
<25	3.30 (1.91, 4.68)	2.10 (0.64, 3.57)	1.19 (-0.79, 3.18)	₽ <del>\</del> +₩1	
25-<30	4.30 (3.16, 5.44)	3.40 (2.27, 4.52)	0.90 (-0.70, 2.51)	₽ <b>┼╋</b> ─┩	0.000
30-<35	7.69 (6.43, 8.94)	4.12 (2.83, 5.41)	3.57 (1.77, 5.36)	<b>⊢_≣_</b> →	0.080
≥35	8.70 (7.15, 10.24)	6.05 (4.58, 7.53)	2.64 (0.52, 4.76)	⊢₩4	
				-4-20246	8

Favours placebo Favours empagliflozin

## Figure S2: Effect of Empagliflozin on KCCQ Changes in Overall Summary Score at 52 weeks by sub-group.

Subgroups	Empagliflozin	Placebo	Difference		<i>p</i> -trend (* <i>p</i> -interaction)
LVEF, %					
<50	5.32 (4.28, 6.36)	3.77 (2.72, 4.82)	1.55 (0.07, 3.02)		
50-<60	5.04 (4.03, 6.05)	2.73 (1.71, 3.75)	2.30 (0.87, 3.74)	<b>⊢</b> ∎	0.551
≥60	4.53 (3.49, 5.57)	3.61 (2.57, 4.64)	0.92 (-0.54, 2.39)	▶ ■ ■	
Age, years	(,,		,		
<65	6.43 (5.09, 7.77)	5.09 (3.75, 6.43)	1.34 (-0.54, 3.22)	₽	
65-<75	5.47 (4.51, 6.44)	4.02 (3.04, 5.00)	1.45 (0.08, 2.83)	▶ <b></b>	0.644
≥75	3.82 (2.90, 4.73)	1.99 (1.08, 2.89)	1.83 (0.54, 3.12)	┝╌╋╌┥	
Gender			()		
Male	4.04 (3.24, 4.84)	2.26 (1.46, 3.06)	1.78 (0.65, 2.91)		
Female	6.10 (5.21, 6.99)	4.72 (3.82, 5.61)	1.39 (0.13, 2.65)	<b>₽</b> 1	0.650*
Region					
North America	3.24 (1.49, 5.00)	3.32 (1.55, 5.09)	-0.08 (-2.57, 2.42)	<b>⊢</b>	
Latin America	9.29 (8.08, 10.49)	7.67 (6.47, 8.87)	1.62 (-0.08, 3.32)	, <b>⊢</b> ,	
Europe	3.60 (2.73, 4.47)	1.57 (0.70, 2.45)	2.03 (0.79, 3.26)	⊢₩	0.459*
Asia Pacific	1.47 (-0.25, 3.20)	0.72 (-1.01, 2.45)	0.75 (-1.68, 3.18)	┍─┼╋──┥	
Other	7.37 (4.91, 9.83)	4.03 (1.58, 6.48)	3.34 (-0.13, 6.82)		
Diabetes mellitus	S				
Yes	5.63 (4.77, 6.49)	3.37 (2.52, 4.22)	2.26 (1.05, 3.47)	<b>⊢⊞</b> -1	0.4000
No	4.33 (3.51, 5.15)	3.34 (2.51, 4.18)	0.99 (-0.18, 2.16)	ı <b>⊢_⊞</b> _−1	0.138*
History of atrial f	fibrillation or atrial flut	ter			
Yes	4.86 (4.03, 5.68)	2.87 (2.05, 3.70)	1.98 (0.82, 3.14)	■1	0.345*
No	5.07 (4.20, 5.94)	3.90 (3.03, 4.77)	1.17 (-0.05, 2.40)	┝╌═╌┥	0.545
Atrial fibrillation	or atrial flutter at enro	Iment			
Yes	5.56 (4.56, 6.56)	2.83 (1.81, 3.85)	2.73 (1.31, 4.16)	<b>⊢-⊞</b> 1	0.053*
No	4.63 (3.89, 5.37)	3.64 (2.90, 4.38)	0.99 (-0.06, 2.03)	- <b>-</b> -	0.053*
Chronic kidney of					
Yes	4.52 (3.70, 5.34)	2.95 (2.12, 3.78)	1.57 (0.41, 2.73)	∊∊∎⊷	
No	5.46 (4.59, 6.33)	3.82 (2.96, 4.69)	1.63 (0.41, 2.86)	<b>⊢_⊞_</b> -1	0.941*
Anaemia					
Yes	4.91 (3.77, 6.05)	2.79 (1.65, 3.93)	2.12 (0.51, 3.73)	⊢₩4	0.4500
No	4.97 (4.28, 5.67)	3.58 (2.88, 4.28)	1.40 (0.41, 2.38)		0.452*
Body mass index					
<25	3.27 (2.00, 4.53)	2.57 (1.24, 3.91)	0.69 (-1.12, 2.51)	▶	
25-<30	3.69 (2.65, 4.74)	3.04 (2.02, 4.07)	0.65 (-0.81, 2.12)	₽ <b>⊣</b> ∎-4	0.070
30-<35	6.14 (5.00, 7.29)	3.14 (1.96, 4.32)	3.00 (1.37, 4.64)	╵╺╌┲╌┙	0.078
≥35	7.35 (5.94, 8.76)	5.23 (3.88, 6.57)	2.12 (0.19, 4.06)		
-		, ,,	, ,,		
				-4 -2 0 2 4	6 8
				<	•

Favours placebo Favours empagliflozin