# SUPPLEMENTAL MATERIAL

Packer et al., Effect of Empagliflozin on Worsening Heart Failure Events in Patients with Heart Failure and a Preserved Ejection Fraction: the EMPEROR-Preserved Trial

# Supplemental Figure I

Total (first and recurrent) hospitalizations for worsening heart failure, by subgroups

### Supplemental Figure II

Total cardiovascular hospitalizations, by subgroups

### Supplemental Figure III

Changes in hematocrit during double-blind treatment in the placebo and empagliflozin groups

### **Supplemental Figure IV**

Changes in uric acid during double-blind treatment in the placebo and empagliflozin groups

### Supplemental Figure V

Changes in body weight during double-blind treatment in the placebo and empagliflozin groups

#### **Supplemental Figure VI**

Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups

### Supplemental Figure VII

Changes in systolic blood pressure during double-blind treatment in the placebo and empagliflozin groups

# Supplemental Figure I Total (first and recurrent) hospitalizations for worsening heart failure, by subgroups

Subgroup	Empagliflozin no. of events / no	Placebo of patients	Hazard	ratio (95% CI)	Interaction p-value
Overall	407/2997	541/2991	0.73 (0.61-0.88)	· · · · · · · · · · · · · · · · · · ·	
Baseline diabetes status					0.9697
Diabetes	250/1466	335/1472	0.73 (0.57-0.94)		
No diabetes	157/1531	206/1519	0.74 (0.56-0.97)		
Age					0.0832
<70 yr	141/1066	159/1084	0.92 (0.67-1.26)		
≥70 yr	266/1931	382/1907	0.65 (0.52-0.82)	, <b>⊢∎</b> ⊣	
Sex					0.7800
Male	253/1659	308/1653	0.75 (0.59-0.95)	) +=-	
Female	154/1338	233/1338	0.71 (0.53-0.94)		
Race					0.4276
White	282/2286	368/2256	0.74 (0.59-0.92)		
Black	27/133	21/125	1.30 (0.55-3.11)		1
Asian	76/413	119/411	0.58 (0.37-0.91)		
Other	22/164	33/198	0.79 (0.37-1.69)		
Baseline body-mass index					0.0749
<30	211/1654	312/1642	0.63 (0.49-0.81)		
≥30	196/1343	229/1349	0.88 (0.67-1.15)	<b>⊢</b> ∎-4	
Baseline eGFR (CKD-EPI)					0.1369
260 mL/min/1 73 m <sup>2</sup>	150/1493	178/1505	0.88 (0.66-1.18)		
<60 mL/min/1 73 m²	257/1504	363/1484	0.66 (0.52-0.85)		
Baseline systolic blood pres	sure	999511994	0.00 (0.00 0.00)		0.9094
<median< td=""><td>215/1496</td><td>290/1474</td><td>0.74 (0.57-0.95)</td><td></td><td></td></median<>	215/1496	290/1474	0.74 (0.57-0.95)		
aMedian	192/1501	251/1517	0.72 (0.55-0.94)		
History of atrial fibrillation or	atrial futter	20101011	0.72 (0.00-0.04)		0.9424
No.	164/1417	223/1427	0.72 (0.54-0.95)		0.0424
Ves	243/1576	318/1559	0.73 (0.57-0.94)		
Baseline LVEE (%)	2401010	310/1000	0.10 (0.01-0.04)		0.0077
<50	122/005	200/688	0.57 (0.42-0.79)		0.0077
250 to 280	120/1028	182/1030	0.66 (0.48-0.01)		
20010-000	150/074	160/673	1.06 (0.76-1.46)		
Meant failure hospitalization	in £12 mo	100/01/0	1.00 (0.70-1.40)		0.6868
No.	200/2298	271/2321	0.70 (0.56-0.88)		0.0000
Ver	20072290	220420	0.76 (0.56-0.66)		
Baseline NVbiA class	2017000	210/010	0.76 (0.56-1.04)		0.2800
Dasenne remos class	235/2435	347/3463	0.67 (0.54 .0.93)		0.5000
11	172/682	104/530	0.07 (0.04-0.03)		
Basaline NT conBMD (calcul	In a course of the second seco	tion illustrationale	0.04 (0.09-1.19)		0.7560
chedian	104/1477	162/1608	*) 0.60/0.61_0.04)		0.7000
Median	202/1516	102/1000	0.09 (0.51-0.94)		
Reseline usic acid (testilas)	303/1010	300/14/0	0.73 (0.00-0.03)		0.6104
Dasenne unc ació (serores)	02/062	101/076	0.67 (0.47.0.06)		0.0194
11	92/903	131/9/5	0.67 (0.47-0.95)		
a11 and <12	99/1032	124/900	0.82 (0.58-1.10)		
812 Residence of 100 (	213/9/0	281/1018	0.75 (0.56-0.99)	,	0.0010
basenne use of ACE-inhibit	or, AHB of ARNI				0.8612
NO	117/509	101/08/	0.71 (0.46-1.04)		
165	290/2428	390/2404	0.74 (0.60-0.91)		0.0070
baseline use of MRA	0.0417.070	00014000			0.0379
NO	201/1878	308/1866	0.00 (0.47-0.77)		
Yes	206/1119	233/1125	0.90 (0.68-1.19)		
				0.25 0.5 1.0 2.0	4.0
				•	•
				Empagilfozin Placebo better better	

Trend test p-value is shown for baseline uric acid (using sex-specific tertiles, T1 and T2) and ejection fraction subgroups. The size of the squares for the hazard ratios is proportional to the size of the subgroup. The body-mass index is the weight in kilograms divided by the square of the height in meters. Race was reported by the patients. NYHA class II includes 4 patients with NYHA class I. Baseline uric acid tertiles calculated separately for males and females. ARNi= angiotensin receptor–neprilysin inhibitor, CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration, HF= heart failure, eGFR= estimated glomerular filtration rate, LVEF= left ventricular ejection fraction, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal prohormone of brain natriuretic peptide, NYHA= New York Heart Association.

# Supplemental Figure II Total cardiovascular hospitalizations, by subgroups

Subgroup	Empagliflozin no. of events / no.	Placebo of patients	Hazard ra	atio (95% CI)	Interaction p-value			
Overall	1145/2997	1333/2991	0.84 (0.74-0.95)	•				
Baseline diabetes status					0.3444			
Diabetes	616/1466	777/1472	0.79 (0.67-0.94)	HEH				
No diabetes	529/1531	556/1519	0.89 (0.75-1.07)					
Age					0.6384			
<70 yr	374/1066	442/1084	0.87 (0.71-1.07)					
≥70 yr	771/1931	891/1907	0.82 (0.71-0.95)					
Sex					0.5625			
Male	675/1659	751/1653	0.86 (0.73-1.02)					
Female	470/1338	582/1338	0.80 (0.67-0.97)					
Race					0.3763			
White	865/2286	975/2256	0.86 (0.75-0.99)					
Black	68/133	72/125	0.97 (0.56-1.71)					
Asian	146/413	211/411	0.65 (0.47-0.90)	<b>—</b>				
Other	66/164	75/198	0.98 (0.59-1.63)					
Baseline body-mass index					0.0589			
<30	594/1654	740/1642	0.75 (0.64-0.89)	H <b>B</b> -1				
≥30	551/1343	593/1349	0.95 (0.80-1.14)	H <b>H</b> -1				
Baseline eGFR (CKD-EPI)					0.4614			
260 mL/min/1.73 m <sup>2</sup>	426/1493	535/1505	0.80 (0.67-0.96)	H <b>H</b> +				
<60 mL/min/1.73 m²	719/1504	798/1484	0.88 (0.75-1.04)					
Baseline systolic blood press	lure				0.5002			
<median< td=""><td>583/1496</td><td>658/1474</td><td>0.87 (0.73-1.04)</td><td></td><td></td></median<>	583/1496	658/1474	0.87 (0.73-1.04)					
≥Median	562/1501	675/1517	0.80 (0.68-0.95)	H <b>B</b> -1				
History of atrial fibrillation or	atrial flutter				0.7213			
No	480/1417	592/1427	0.81 (0.68-0.98)	+=-				
Yes	665/1576	741/1559	0.85 (0.72-1.00)					
Baseline LVEF (%)					0.0176			
<50	324/995	462/988	0.69 (0.56-0.86)	H=				
≥50 to <60	416/1028	471/1030	0.85 (0.69-1.04)	+ <b>•</b> +				
≥60	405/974	400/973	1.00 (0.81-1.24)	H#H				
Heart failure hospitalization i	n ≤12 mo				0.3209			
No	723/2298	810/2321	0.88 (0.76-1.01)					
Yes	422/699	523/670	0.77 (0.61-0.96)					
Baseline NYHA class					0.2299			
	756/2435	942/2452	0.79 (0.69-0.91)					
IIVIV	389/562	391/539	0.94 (0.73-1.21)					
Baseline NT-proBNP (calculated by atrial fibrillation/flutter status) 0.9428								
<median< td=""><td>428/1477</td><td>499/1508</td><td>0.84 (0.70-1.00)</td><td></td><td></td></median<>	428/1477	499/1508	0.84 (0.70-1.00)					
≥Median	717/1518	833/1476	0.83 (0.71-0.98)	HEH				
Baseline uric acid (tertiles)					0.2854			
<t1< td=""><td>279/963</td><td>365/975</td><td>0.72 (0.58-0.91)</td><td>H<b>B</b>-1</td><td></td></t1<>	279/963	365/975	0.72 (0.58-0.91)	H <b>B</b> -1				
≥T1 and <t2< td=""><td>339/1032</td><td>372/966</td><td>0.93 (0.75-1.16)</td><td>H</td><td></td></t2<>	339/1032	372/966	0.93 (0.75-1.16)	H				
2T2	514/970	588/1018	0.86 (0.70-1.05)	+ <b>•</b> +				
Baseline use of ACE-inhibito	r, ARB or ARNI				0.7135			
No	295/569	309/587	0.87 (0.67-1.14)	H				
Yes	850/2428	1024/2404	0.83 (0.72-0.95)					
Baseline use of MRA					0.7320			
No	697/1878	822/1866	0.82 (0.70-0.96)	+=+				
Yes	448/1119	511/1125	0.88 (0.71-1.05)	+ <b>•</b> +				
				0.25 0.5 1.0 2.0				
				Empaglificzin Placebo				

Trend test p-value is shown for baseline uric acid (using sex-specific tertiles, T1 and T2) and ejection fraction subgroups. The size of the squares for the hazard ratios is proportional to the size of the subgroup. The body-mass index is the weight in kilograms divided by the square of the height in meters. Race was reported by the patients. NYHA class II includes 4 patients with NYHA class I. Baseline uric acid tertiles calculated separately for males and females. ARNi= angiotensin receptor–neprilysin inhibitor, CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration, HF= heart failure, eGFR= estimated glomerular filtration rate, LVEF= left ventricular ejection fraction, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal prohormone of brain natriuretic peptide, NYHA= New York Heart Association.

### **Supplemental Figure III**

Changes in hematocrit during double-blind treatment in the placebo and empagliflozin groups



# **Supplemental Figure IV**

Changes in uric acid during double-blind treatment in the placebo and empagliflozin groups



### **Supplemental Figure V**

Changes in body weight during double-blind treatment in the placebo and empagliflozin groups



### **Supplemental Figure VI**

Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups



Shown are adjusted geometric mean ratio and 95% confidence intervals at prespecified study visits based on mixed model for repeated measures, which included age and baseline estimated glomerular filtration rate and ejection fraction as linear covariates and baseline score by visit, visit by treatment, sex, region, individual last projected visit based on dates of randomization and trial closure, and baseline diabetes status as fixed effects. N-terminal proBNP was log-transformed prior the analysis.

# Supplemental Figure VII

Changes in systolic blood pressure during double-blind treatment in the placebo and empagliflozin groups

