

# Supplemental Material

## Blinded Withdrawal of Long-term Randomized Treatment with Empagliflozin or Placebo in Patients With Heart Failure

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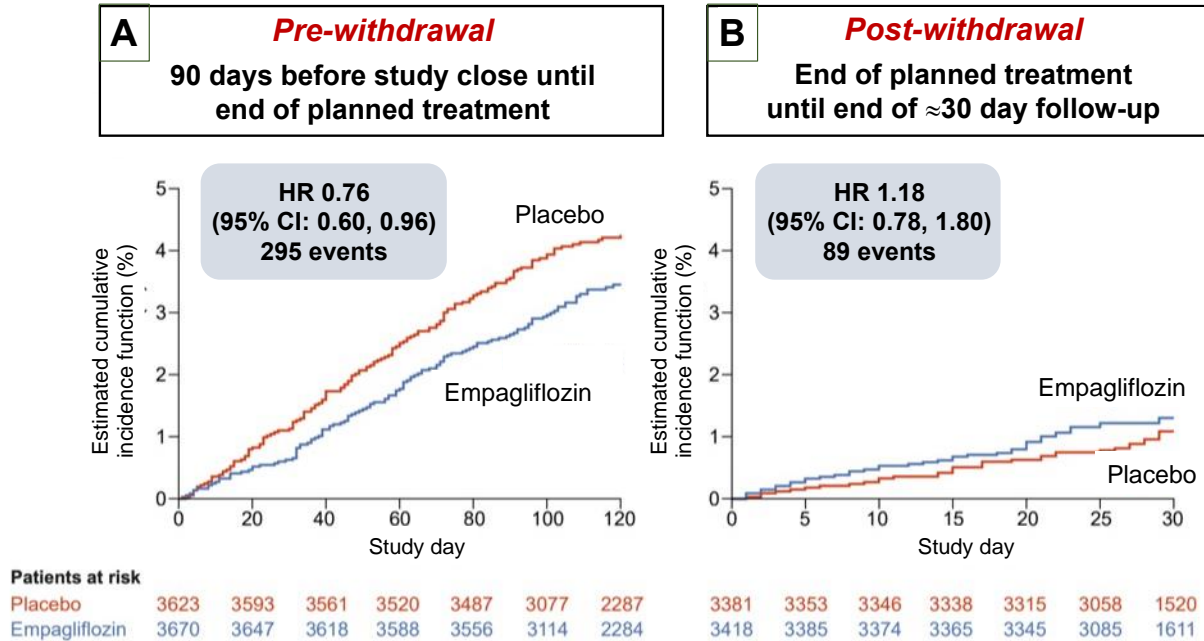
Cardiovascular Death or Heart Failure Hospitalization During the On-Treatment Period (90 Days From Start of Closeout to the End of Double-Blind Treatment) and During the Off-Treatment Withdrawal Period (From End of Double-Blind Treatment to End of Withdrawal Period  $\approx$ 30 Days Later), For EMPEROR-Reduced and EMPEROR-Preserved Separately

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**Figure S1.**

**Time to Cardiovascular Death or Hospitalization for Heart Failure During the Pre-Withdrawal and Post-Withdrawal Periods in the Placebo and Empagliflozin Groups**



Time-to-first-event plots for cardiovascular death or heart failure hospitalization. Panel A shows the patients who contributed data starting 90 days before the study closeout up to the planned end of treatment. Because of variations in the start of close-out between sites, the median duration of the end of double-blind phase was 110 days for EMPEROR-Reduced and 129 days for EMPEROR-Preserved with nearly all patients contributing data up to 90 days. Panel B shows the patients who were followed from the end of double-blind treatment until the end of the withdrawal period. The median duration of withdrawal phase was 29 days for EMPEROR-Reduced and 28 days for EMPEROR-Preserved. The treatment difference between empagliflozin and placebo in Panel A was no longer apparent in Panel B (time period-by-treatment interaction  $P = 0.068$ ).

**Table S1. Clinical Characteristics at Baseline in Patients Participating or Not Participating in the Off-Treatment Assessments for the Assessment of Heart Failure Events**

	Patients included in the analysis of planned treatment discontinuation		Patients not included in the Analysis (n=2919)	Between-group P value
	Placebo (n=3381)	Empagliflozin (n=3418)		
Age (years)	69.4 (10.4)	69.5 (10.1)	71.2 (10.5)	<0.001
Women (%)	1241 (36.7)	1255 (36.7)	1073 (36.8)	0.964
Race (%)				
Asian	530 (15.7)	569 (16.6)	397 (13.6)	< 0.001
Black or African American	163 (4.8)	166 (4.9)	186 (6.4)	
White	2482 (73.4)	2508 (73.4)	2181 (74.7)	
Other including mixed race	185 (5.5)	156 (4.6)	135 (4.6)	
Geographic region (%)				
Asia	430 (12.7)	453 (13.3)	296 (10.1)	<0.001
Europe	1451 (42.9)	1433 (41.9)	1158 (39.7)	
North America	312 (9.2)	345 (10.1)	487 (16.7)	
Latin America	1003 (29.7)	1009 (29.5)	789 (27.0)	
eGFR (ml/min/1.73 m <sup>2</sup> )	62.7 (20.2)	62.6 (20.3)	57.8 (20.8)	<0.001
Heart failure hospitalization within 1 year	807 (23.9)	856 (25.0)	857 (29.4)	<0.001
Body weight (kg)	80.6 (18.9)	80.6 (18.8)	80.8 (19.8)	0.737
Ischemic etiology (%)	1394 (41.2)	1444 (42.2)	1208 (41.4)	0.753
Ejection fraction (%)				
≤40%	1342 (39.7)	1372 (40.1)	1017 (34.8)	<0.001
41-<50%	654 (19.3)	665 (19.5)	662 (22.7)	
≥50%	1385 (41.0)	1381 (40.4)	1240 (42.5)	
NYHA class II (%)	2788 (82.5)	2807 (82.1)	2092 (71.7)	<0.001
KCCQ-CSS	72.4 (20.6)	72.5 (21.2)	66.1 (22.0)	<0.001
NT-proBNP (pg/ml)	1205 (610-2146)	1184 (643-2096)	1542 (789-2946)	<0.001
High-sensitivity cardiac troponin T (ng/L)	18.0 (11.9-26.8)	17.9 (12.0-27.5)	22.8 (14.9-36.1)	<0.001
Systolic blood pressure (mm Hg)	128 (16)	128 (16)	129 (17)	0.118
Hypertension (%)	2806 (83.0)	2842 (83.1)	2474 (84.8)	0.040
Diabetes mellitus (%)	1631 (48.2)	1647 (48.2)	1516 (51.9)	< 0.001
Atrial fibrillation (%)	1539 (45.5)	1508 (44.1)	1379 (47.2)	0.023
ACE-I or ARB (%)	2579 (76.3)	2600 (76.1)	2126 (72.8)	< 0.001
Angiotensin receptor neprilysin inhibitor (%)	313 (9.3)	305 (8.9)	243 (8.3)	0.224
Beta-blocker (%)	3058 (90.4)	3097 (90.6)	2545 (87.2)	<0.001
Mineralocorticoid receptor antagonist (%)	1762 (52.1)	1733 (50.7)	1410 (48.3)	0.005

P values in the far right column denote level of statistical significance of differences between patients included or not included in the analysis of the planned treatment discontinuation (both treatment groups combined). Patients not included in the analysis of planned treatment discontinuation included those who discontinued the study medications before the planned end of treatment and those who were not followed during the planned withdrawal period. For categorical variables, values are number of patients with % in parentheses. For continuous variables, values are means ± SD (in parentheses), except for NT-proBNP where medians and interquartile ranges are shown. P values for NT-proBNP and troponin are based on log transformed data. Data for NYHA class includes 4 patients with NYHA class I in the group with no withdrawal data. Abbreviations: eGFR= estimated glomerular filtration rate; NYHA= New York Heart Association; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire; NT=proBNP= N-terminal prohormone B-type natriuretic peptide; ACE= angiotensin converting-enzyme; ARB= angiotensin receptor blocker.

**Table S2. Clinical Characteristics at Baseline in Patients Participating or Not Participating in the Off-Treatment Assessments of KCCQ and Laboratory Tests**

	Patients Included in Off-Treatment Assessments		Patients Not Included in Off-Treatment Assessments (n=5737)	Between-group P value
	Placebo (n=2020)	Empagliflozin (n=1961)		
Age (years)	70.3 (9.7)	70.3 (9.6)	69.7 (10.8)	0.009
Women (%)	789 (39.1)	770 (39.3)	2010 (35.0)	<0.001
Race (%)				
Asian	389 (19.3)	377 (19.2)	730 (12.7)	<0.001
Black or African American	83 (4.1)	76 (3.9)	356 (6.2)	
White	1424 (70.5)	1406 (71.7)	4341 (75.7)	
Other including mixed race	122 (6.0)	102 (5.2)	252 (4.4)	
Geographic region (%)				
Asia	367 (18.2)	354 (18.1)	458 (8.0)	<0.001
Europe	906 (44.9)	882 (45.0)	2254 (39.3)	
North America	177 (8.8)	197 (10.0)	770 (13.4)	
Latin America	472 (23.4)	449 (22.9)	1880 (32.8)	
eGFR, ml/min/1.73 m <sup>2</sup>	63.2 (19.8)	62.9 (19.7)	59.9 (21.0)	<0.001
Heart failure hospitalization within 1 year (%)	451 (22.3)	465 (23.7)	1604 (28.0)	<0.001
Body weight (kg)	80.6 (19.1)	80.9 (19.2)	80.6 (19.2)	0.767
Ischemic etiology (%)	796 (39.4)	786 (40.1)	2464 (42.9)	0.002
Ejection fraction (%)				
≤40%	471 (23.3)	464 (23.7)	2796 (48.7)	<0.001
41-<50%	500 (24.8)	470 (24.0)	1011 (17.6)	
≥50%	1049 (51.9)	1027 (52.4)	1930 (33.6)	
NYHA class II, n (%)	1700 (84.2)	1643 (83.8)	4344 (75.7)	<0.001
KCCQ-CSS,	74.1 (19.8)	73.7 (20.7)	68.2 (21.9)	<0.001
NT-proBNP (pg/ml)	1017 (523-1861)	1048 (534-1837)	1491 (786-2722)	<0.001
High-sensitivity cardiac troponin T (ng/L)	17.3 (11.4-25.9)	16.9 (11.4-26.1)	21.0 (13.9-32.3)	<0.001
Systolic blood pressure (mm Hg)	129.5 (15.8)	129.6 (15.6)	127.0 (16.7)	<0.001
Hypertension (%)	1742 (86.2)	1704 (86.9)	4676 (81.5)	<0.001
Diabetes mellitus (%)	960 (47.5)	927 (47.3)	2907 (50.7)	0.002
Atrial fibrillation (%)	956 (47.3)	936 (47.7)	2534 (44.2)	0.0014
ACE-I or ARB	1596 (79.0)	1547 (78.9)	4162 (72.5)	<0.001
Angiotensin receptor neprilysin inhibitor (%)	98 (4.9)	92 (4.7)	671 (11.7)	<0.001
Beta-blocker (%)	1801 (89.2)	1761 (89.8)	5138 (89.6)	0.894
Mineralocorticoid receptor antagonist (%)	917 (45.4)	870 (44.4)	3118 (54.3)	<0.001

P values in the far right column denote level of statistical significance of differences between patients included or not included in the post-treatment assessments, with both treatment groups combined. Patients not included in the analysis of planned treatment discontinuation included those who discontinued the study medications before the planned end of treatment and those who were not followed during the planned withdrawal period. For categorical variables, values are number of patients with percent in parentheses. For continuous variables, values are means ± SD (in parentheses), except for NT-proBNP where medians and interquartile ranges are shown. P-values for NT-proBNP and troponin are based on log transformed data. Data for NYHA class includes 4 patients with NYHA class I in the group of patients with no withdrawal data.

**Table S3.**  
**Cardiovascular Death or Heart Failure Hospitalization During the On-Treatment Period (90 Days From Start of Closeout to the End of Double-Blind Treatment) and During the Off-Treatment Withdrawal Period (From End of Double-Blind Treatment to End of Withdrawal Period ≈30 Days Later), For EMPEROR-Reduced and EMPEROR-Preserved Separately**

	Placebo	Empagliflozin
<b>Cardiovascular Death or Hospitalization for Heart Failure (EMPEROR-Preserved)</b>		
<i>On-Treatment (90 days from start of closeout to end of double-blind treatment)</i>		
Number of analyzed patients	2177	2191
Number of patients with event	74	59
Time at risk for event (years)	763.9	773.5
Incidence rate (events per 100 patient-years at risk)	9.69 (7.61-12.02)	7.63 (5.81-9.69)
Hazard ratio	0.74 (0.52-1.04)	
<i>Off-Treatment (≈30 days from end of double-blind treatment to end of withdrawal period)</i>		
Number of analyzed patients	2040	2046
Number of patients with event	18	25
Time at risk for event (years)	172.2	173.6
Incidence rate (events per 100 patient-years at risk)	10.45 (6.19-15.81)	14.40 (9.32-20.57)
Hazard ratio	1.33 (0.73-2.45)	
<b>Cardiovascular Death or Hospitalization for Heart Failure (EMPEROR-Reduced)</b>		
<i>On-Treatment (90 days from start of closeout to end of double-blind treatment)</i>		
Number of analyzed patients	1446	1479
Number of patients with event	89	73
Time at risk for event (years)	445.8	456.0
Incidence rate (events per 100 patient-years at risk)	19.96 (16.03-24.32)	16.01 (12.55-19.88)
Hazard ratio	0.78 (0.57-1.07)	
<i>Off-Treatment (≈30 days from end of double-blind treatment to end of withdrawal period)</i>		
Number of analyzed patients	1341	1372
Number of patients with event	22	24
Time at risk for event (years)	111.2	113.9
Incidence rate (events per 100 patient-years at risk)	19.78 (12.39-28.85)	21.06 (13.50-30.29)
Hazard ratio	1.07 (0.60-1.90)	

Hazard ratios for EMPEROR Pooled estimated from Cox regression models, adjusting for baseline values age, estimated glomerular filtration rate, LV ejection fraction, log troponin T, log NTproBNP, diabetes status, sex and region as well as use of mineralocorticoid receptor antagonists and angiotensin receptor neprilysin inhibition at the start of the relevant time period.

**Table S4. Effect of Empagliflozin on Clinical and Laboratory Variables ≈30 Days Following Withdrawal Study Medications at End of Trial (Changes from Last Value on Double-Blind Treatment)**

	EMPEROR-Reduced			EMPEROR-Preserved			P value for study interaction
	Placebo (n= 470)	Empagliflozin (n= 464)	Treatment effect	Placebo (n=1550)	Empagliflozin (n= 1497)	Treatment effect	
Systolic blood pressure (mm Hg)	+ 0.3 ± 0.7	+ 2.2 ± 0.7	+ 1.8 ± 1.0	- 1.5 ± 0.4	+ 1.0 ± 0.4	+ 2.5 ± 0.5	0.53
Body weight (kg)	+ 0.1 ± 0.2	+ 0.4 ± 0.2	+ 0.3 ± 0.2	+ 0.0 ± 0.1	+ 0.6 ± 0.1	+ 0.6 ± 0.1	0.36
eGFR (ml/min/1.73m <sup>2</sup> )	+ 0.1 ± 0.4	+ 2.7 ± 0.4	+ 2.6 ± 0.6	+ 0.3 ± 0.2	+ 3.0 ± 0.2	+ 2.7 ± 0.3	0.83
NT-proBNP (pg/ml)	1.01 (0.96-1.06)	1.03 (0.98-1.09)	1.02 (0.95-1.10)	1.01 (0.98-1.03)	1.09 (1.06-1.12)	1.08 (1.04-1.13)	0.18
Serum albumin (g/L)	- 0.01 ± 0.01	- 0.07 ± 0.01	- 0.06 ± 0.02	- 0.01 ± 0.01	- 0.05 ± 0.01	- 0.04 ± 0.01	0.36
Hemoglobin (g/L)	+ 0.0 ± 0.0	- 0.4 ± 0.0	- 0.5 ± 0.1	- 0.0 ± 0.0	- 0.4 ± 0.0	- 0.4 ± 0.0	0.49
Hematocrit (%)	- 0.2 ± 0.1	- 1.8 ± 0.1	- 1.6 ± 0.2	- 0.1 ± 0.1	- 1.5 ± 0.1	- 1.4 ± 0.1	0.49
Serum sodium (mmol/L)	- 0.2 ± 0.1	- 0.1 ± 0.1	+ 0.2 ± 0.2	+ 0.0 ± 0.1	- 0.2 ± 0.1	- 0.1 ± 0.1	0.17
Serum potassium (mmol/L)	+ 0.01 ± 0.02	- 0.05 ± 0.02	- 0.06 ± 0.03	+ 0.01 ± 0.01	+ 0.00 ± 0.01	- 0.02 ± 0.02	0.17
Serum bicarbonate (mmol/L)	- 0.1 ± 0.1	+ 0.1 ± 0.1	+ 0.2 ± 0.2	+ 0.2 ± 0.1	+ 0.5 ± 0.1	+ 0.3 ± 0.1	0.52
Fasting glucose (mg/dL)	+ 2.3 ± 1.9	+ 4.8 ± 2.0	+ 2.5 ± 2.7	+ 0.1 ± 1.0	+ 4.5 ± 1.0	+ 4.4 ± 1.4	0.53
Serum uric acid (mg/dL)	- 0.1 ± 0.1	+ 0.6 ± 0.1	+ 0.6 ± 0.1	- 0.0 ± 0.0	+ 0.5 ± 0.0	+ 0.5 ± 0.0	0.20
KCCQ-CSS	+ 0.0 ± 0.6	- 2.9 ± 0.6	- 2.9 ± 0.8	- 0.6 ± 0.3	- 1.7 ± 0.3	- 1.2 ± 0.5	0.06

Changes in KCCQ-CSS following randomization and initiation of the study medications were assessed at 12 weeks, whereas the laboratory tests were assessed at 4 weeks. Shown are adjusted means ± SE or adjusted geometric mean ratio (95% CI for NT-proBNP. (Models for NT-proBNP are based on log transformed data.) The precise number of patients with available data for each physiological or laboratory assessment varied slightly but was generally ≈1430 in each treatment group for EMPEROR-Preserved and ≈420 in each treatment group for EMPEROR-Reduced. Abbreviations: eGFR=estimated glomerular filtration rate; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire; NT=proBNP= N-terminal prohormone B-type natriuretic peptide.