

## **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**

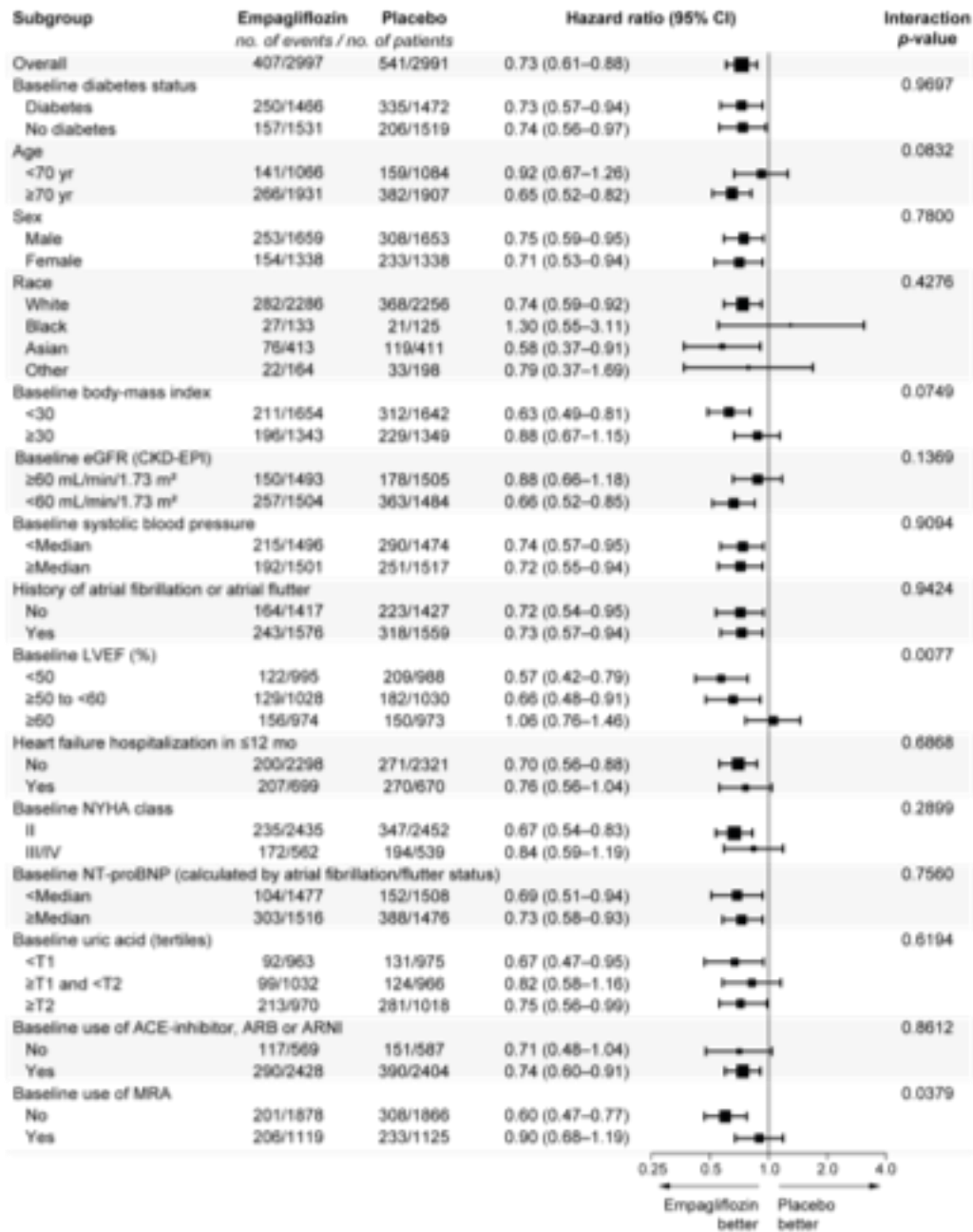
Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups

### **Supplemental Figure VII**

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

## Supplemental Figure 1

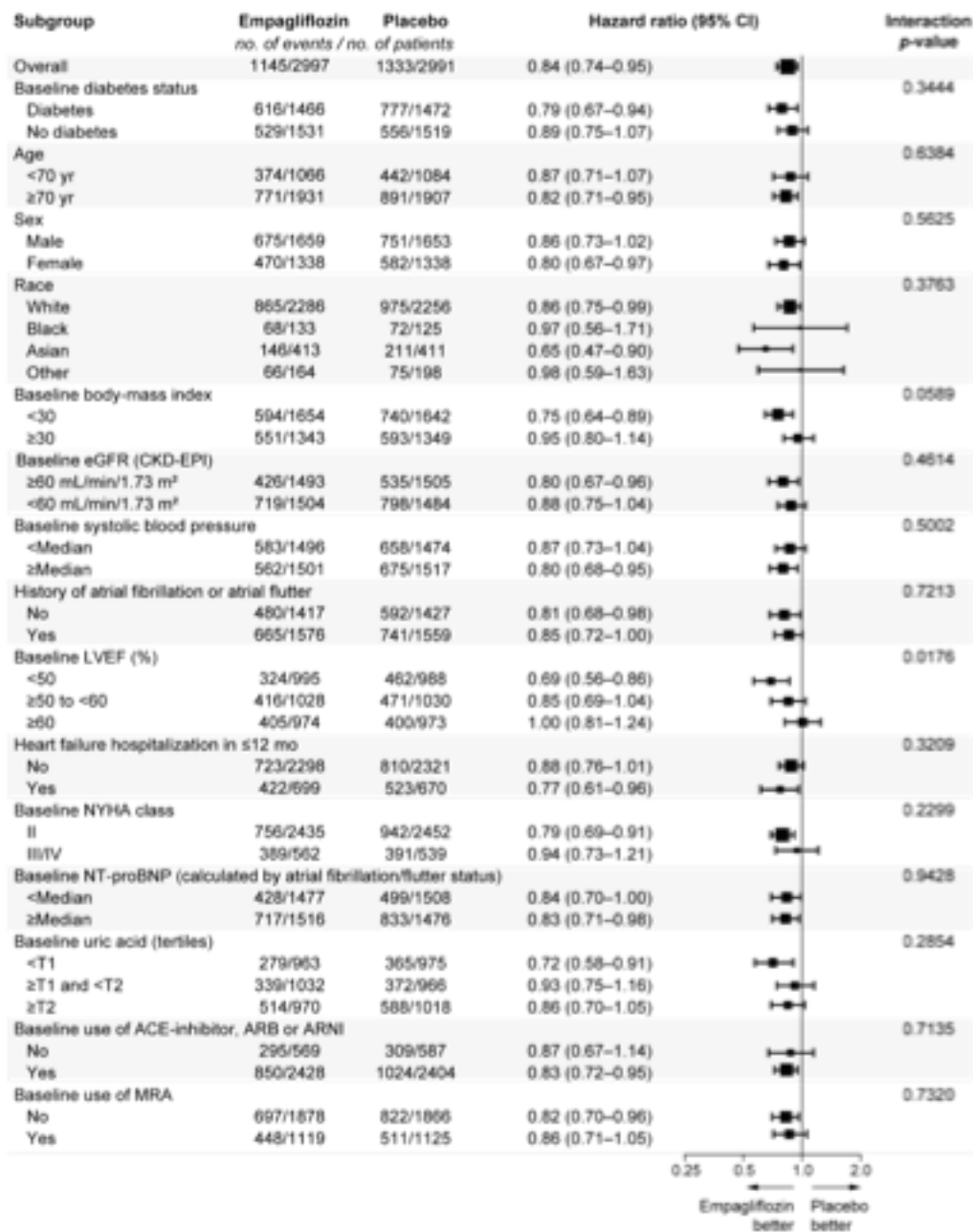
### Total (first and recurrent) hospitalizations for worsening heart failure, by subgroups



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

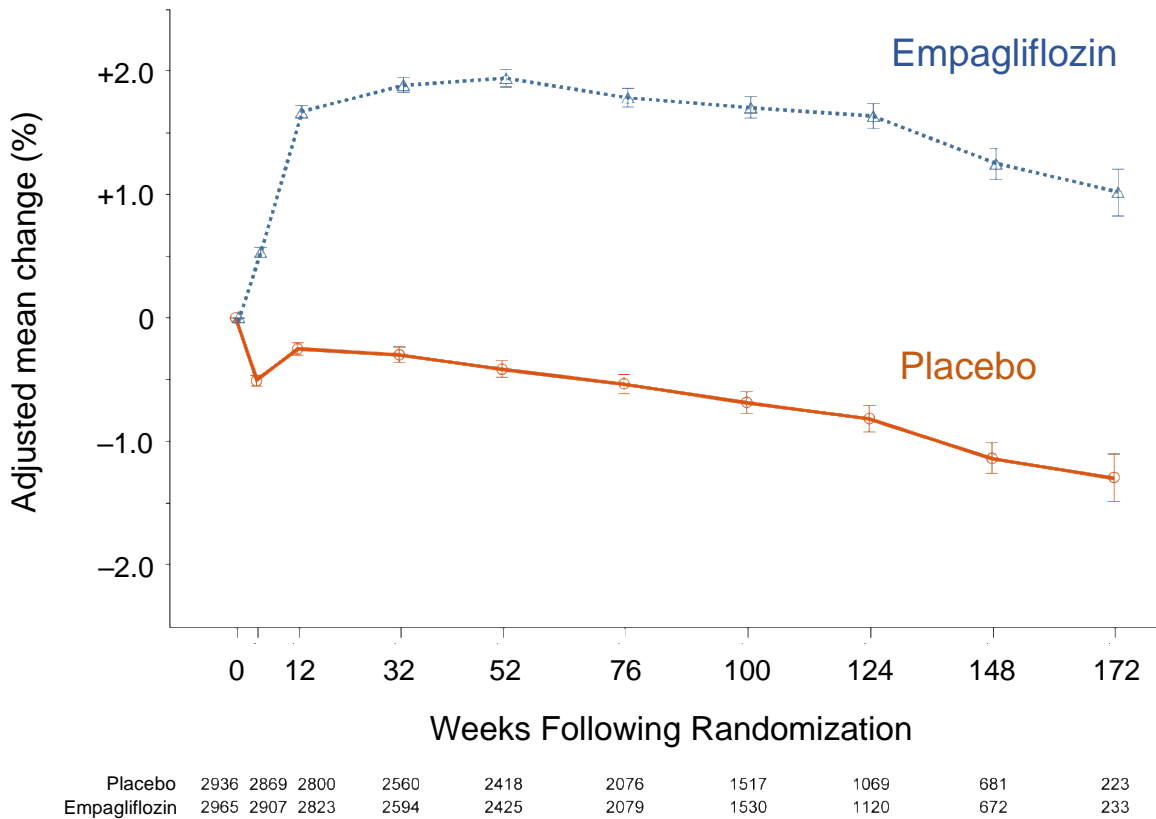
### Total cardiovascular hospitalizations, by subgroups



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

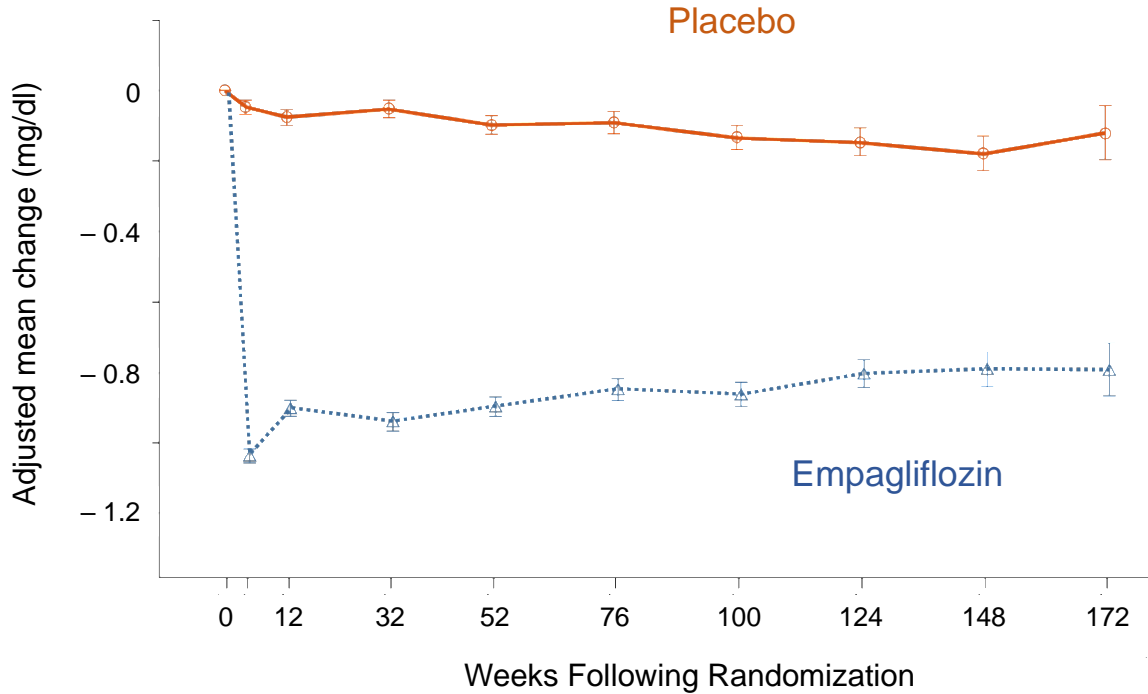
#### Changes in hematocrit during double-blind treatment in the placebo and empagliflozin groups



Shown are adjusted mean changes (and standard errors) 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.

### Supplemental Figure IV

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

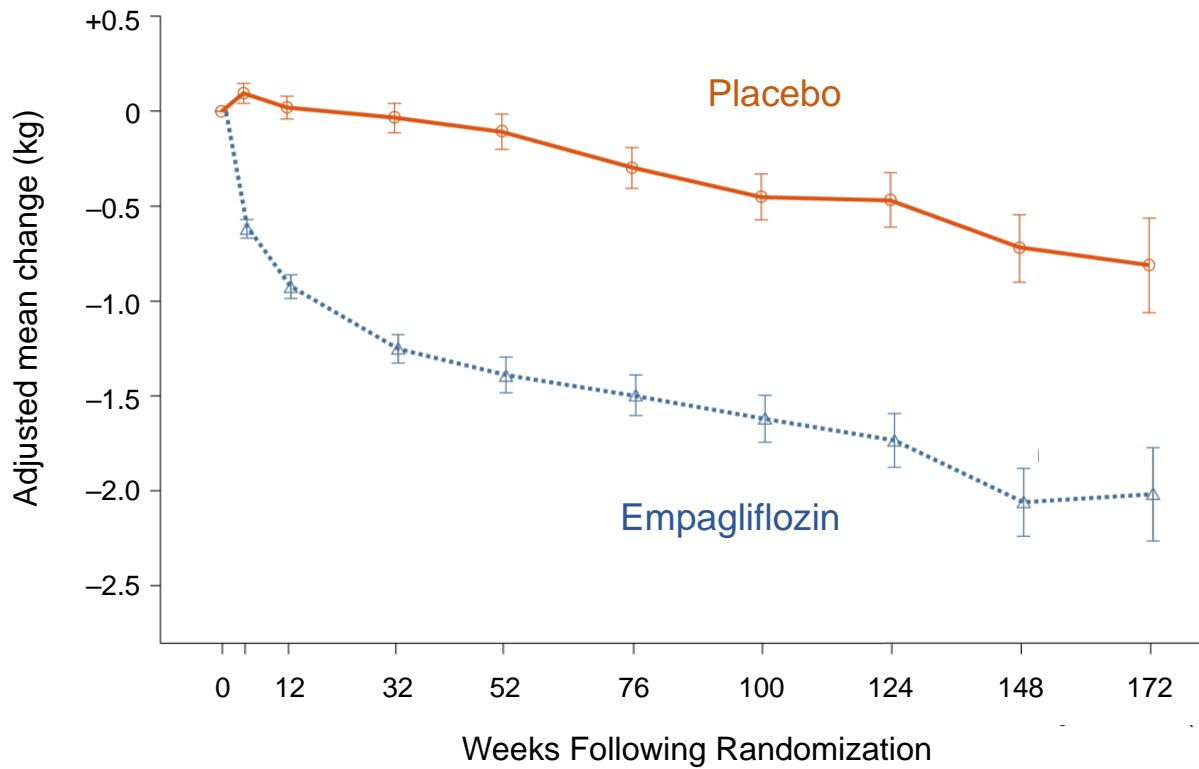


|               |      |      |      |      |      |      |      |      |     |     |
|---------------|------|------|------|------|------|------|------|------|-----|-----|
| Placebo       | 2913 | 2881 | 2792 | 2567 | 2429 | 2099 | 1532 | 1086 | 691 | 230 |
| Empagliflozin | 2937 | 2901 | 2824 | 2604 | 2447 | 2092 | 1534 | 1116 | 680 | 241 |

Shown are adjusted mean changes (and standard errors) 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.

**Supplemental Figure V**

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

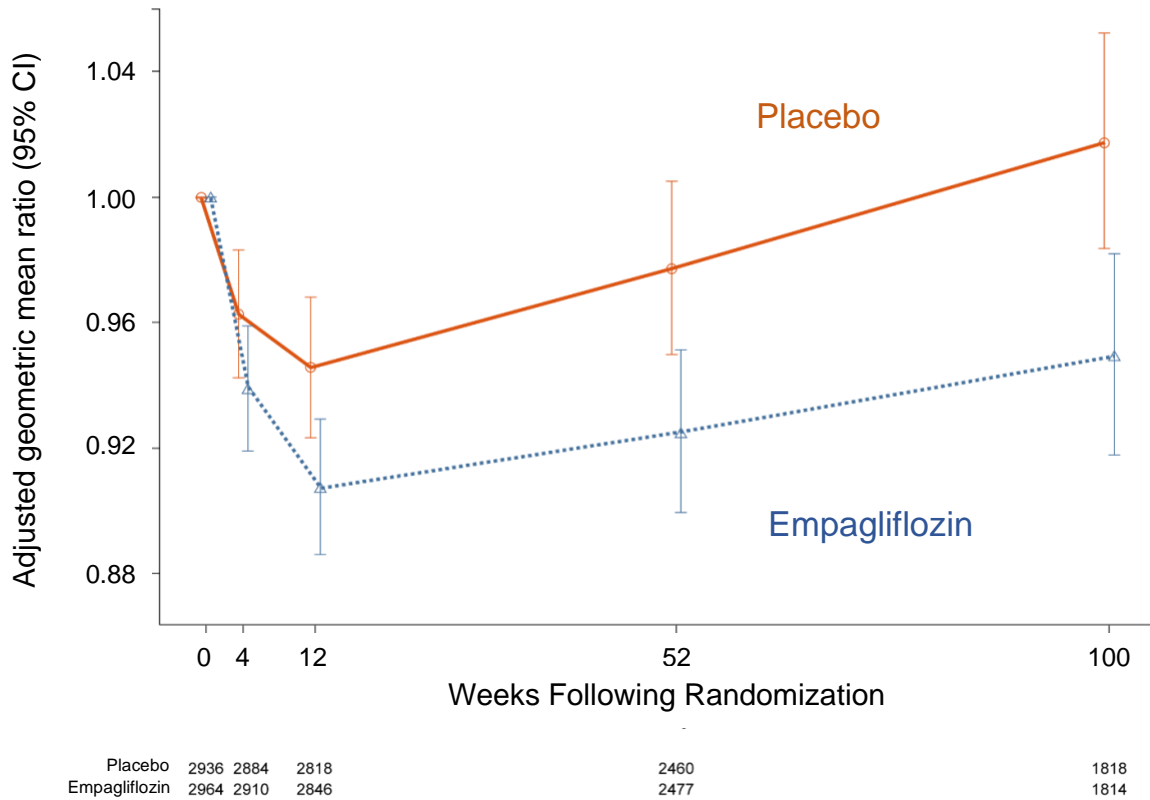


|               |      |      |      |      |      |      |      |      |     |     |
|---------------|------|------|------|------|------|------|------|------|-----|-----|
| Placebo       | 2948 | 2925 | 2852 | 2636 | 2497 | 2169 | 1602 | 1127 | 704 | 239 |
| Empagliflozin | 2967 | 2951 | 2873 | 2662 | 2516 | 2172 | 1603 | 1154 | 704 | 247 |

Shown are adjusted mean changes (and standard errors) 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.

### Supplemental Figure VI

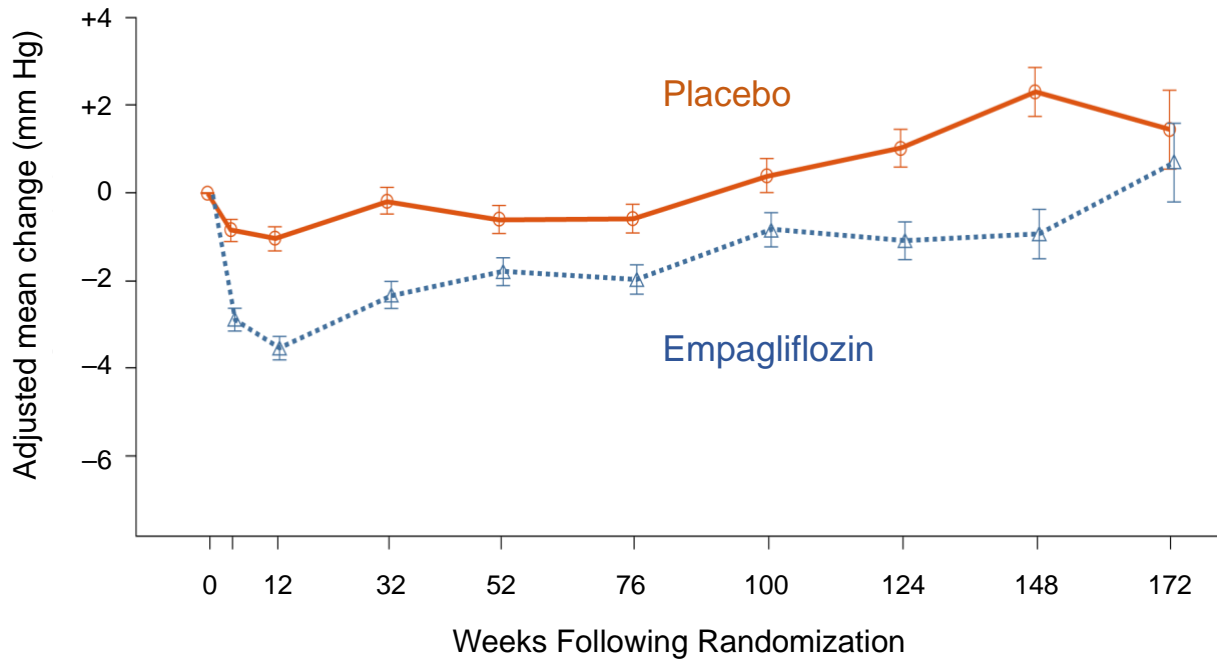
### Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups



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



|               |      |      |      |      |      |      |      |      |     |     |
|---------------|------|------|------|------|------|------|------|------|-----|-----|
| Placebo       | 2946 | 2925 | 2844 | 2619 | 2476 | 2147 | 1588 | 1112 | 702 | 241 |
| Empagliflozin | 2970 | 2955 | 2864 | 2645 | 2501 | 2145 | 1598 | 1145 | 702 | 247 |

Shown are adjusted mean changes (and standard errors) 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.