**Supplemental Material**

Supplemental Table 1. Effect of empagliflozin on pre-specified measures of efficacy, by MRA use at baseline within subgroups of LVEF

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome events, n (%) | No MRA | | | MRA | | |  |
| LVEF 41-49% | | | | | | | |
|  | Placebo  N =520 | Empa.  N =539 | Treatment effect | Placebo  N =468 | Empa.  N =456 | Treatment effect | Interaction P-value |
| CV death or HF hosp. | 92 (17.7)  IR =8.9 | 68 (12.6)  IR =6.1 | 0.69 (0.50, 0.94) | 101 (21.6)  IR =11.3 | 77 (16.9)  IR =8.6 | 0.74 (0.55, 1.00) | 0.73 |
| Total (first and recurrent) HF hosp. | 93 | 49 | 0.50 (0.31, 0.82) | 116 | 73 | 0.60 (0.38, 0.96) | 0.60 |
| First HF hosp. | 62 (11.9)  IR =6.0 | 29 (5.4)  IR =2.6 | 0.44 (0.28, 0.69) | 64 (13.7)  IR =7.1 | 48 (10.5)  IR =5.3 | 0.72 (0.42, 1.05) | 0.10 |
| LVEF ≥50% | | | | | | | |
|  | Placebo  N =1346 | Empa.  N =1339 | Treatment effect | Placebo  N =657 | Empa.  N =663 | Treatment effect | InteractionP |
| CV death or HF hosp. | 214 (15.9)  IR =8.0 | 165 (12.3)  IR =6.1 | 0.75 (0.61, 0.92) | 104 (15.8)  IR =8.2 | 105 (15.8)  IR =8.1 | 0.99 (0.75, 1.29) | 0.12 |
| Total (first and recurrent) HF hosp. | 215 | 152 | 0.64 (0.48, 0.85) | 117 | 133 | 1.19 (0.83, 1.71) | 0.009 |
| First HF hosp. | 146 (10.8)  IR =5.5 | 102 (7.6)  IR =3.7 | 0.67 (0.52, 0.87) | 80 (12.2)  IR =6.3 | 80 (12.1)  IR =6.2 | 0.98 (0.72, 1.33) | 0.069 |

Values are n (%), hazard ratio (95% confidence interval). IR, incidence rate per 100 person-years (displayed whenever applicable).

Models included terms for age, baseline eGFR, baseline left ventricular ejection fraction, region, baseline diabetes status, sex, treatment arm, baseline use of MRA, and treatment by baseline use of MRA interaction, analyses were performed within each LVEF subgroup.

Supplemental Table 2. Effect of empagliflozin on pre-specified measures of efficacy, by MRA use at baseline within subgroups of Volume Overload

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome events, n (%) | No MRA | | | MRA | | |  |
| No Volume Overload | | | | | | | |
|  | Placebo  N =1105 | Empa.  N =1121 | Treatment effect | Placebo  N =645 | Empa.  N =627 | Treatment effect | Interaction P‑value |
| CV death or HF hosp. | 147 (13.3)  IR =6.7 | 118 (10.5)  IR =5.2 | 0.78 (0.61, 0.99) | 105 (16.3)  IR =8.5 | 99 (15.8)  IR =8.0 | 0.95 (0.72, 1.25) | 0.28 |
| Total (first and recurrent) HF hosp. | 134 | 88 | 0.62 (0.44, 0.88) | 130 | 87 | 0.75 (0.50, 1.11) | 0.51 |
| First HF hosp. | 94 (8.5)  IR =4.3 | 61 (5.4)  IR =2.7 | 0.62 (0.45, 0.86) | 76 (11.8)  IR =6.1 | 65 (10.4)  IR =5.3 | 0.86 (0.62, 1.20) | 0.17 |
| Volume Overload | | | | | | | |
|  | Placebo  N =759 | Empa.  N =757 | Treatment effect | Placebo  N =480 | Empa.  N =491 | Treatment effect | Interaction P‑value |
| CV death or HF hosp. | 157 (20.7)  IR =10.4 | 115 (15.2)  IR =7.3 | 0.68 (0.54, 0.87) | 100 (20.8)  IR =10.7 | 82 (16.7)  IR =8.6 | 0.77 (0.58, 1.03) | 0.53 |
| Total (first and recurrent) HF hosp. | 172 | 113 | 0.60 (0.43, 0.86) | 103 | 117 | 1.04 (0.69, 1.56) | 0.046 |
| First HF hosp. | 112 (14.8)  IR =7.4 | 70 (9.2)  IR =4.5 | 0.58 (0.43, 0.78) | 68 (14.2)  IR =7.3 | 62 (12.6)  IR =6.5 | 0.84 (0.59, 1.18) | 0.11 |

Values are n (%), hazard ratio (95% confidence interval). IR, incidence rate per 100 person-years (displayed whenever applicable).

Models included terms for age, baseline eGFR, baseline left ventricular ejection fraction, region, baseline diabetes status, sex, treatment arm, baseline use of MRA, and treatment by baseline use of MRA interaction, analyses were performed within subgroup of volume overload status.

Supplemental Table 3. Effect of empagliflozin on hyperkalemia and use of potassium binders

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All patients | | | No MRA | | | MRA | | |  |
|  | Placebo | Empa. |  | Placebo | Empa |  | Placebo | Empa. |  |  |
|  | n/N (%) | n/N (%) | HR (95%CI) | n/N (%) | n/N (%) | HR (95%CI) | n/N (%) | n/N (%) | HR (95%CI) | Interaction P‑value |
| New potassium-binder use † | 51/2980 (1.7)  IR=0.9 | 45/2986 (1.5)  IR=0.8 | 0.82 (0.55, 1.23)  P =0.35 | 34/1857 (1.8)  IR=1.0 | 27/1870 (1.4)  IR=0.8 | 0.70 (0.42, 1.16) | 17/1123 (1.5)  IR=0.8 | 18/1116 (1.6)  IR=0.9 | 1.11 (0.57, 2.16) | 0.27 |
| Investigator-reported hyperkalemia | 220/2989 (7.4)  IR=4.1 | 186/2996 (6.2)  IR=3.4 | 0.83 (0.68, 1.00)  P =0.056 | 97/1865 (5.2)  IR=2.9 | 94/1878 (5.0)  IR=2.7 | 0.93 (0.70, 1.24) | 123/1124 (10.9)  IR=6.2 | 92/1118 (8.2)  IR=4.7 | 0.75 (0.57, 0.98) | 0.27 |
| Serum potassium >5.5 mmol/L \* | 277/2872 (9.6)  IR=5.9 | 235/2869 (8.2)  IR=4.9 | 0.82 (0.69, 0.98)  P =0.026 | 130/1807 (7.2)  IR=4.3 | 130/1807 (7.2)  IR=4.2 | 0.98 (0.77, 1.25)  P =0.85 | 147/1065 (13.8)  IR=8.6 | 105/1062 (9.9)  IR=6.1 | 0.68 (0.53, 0.88) | 0.044 |
| Serum potassium >6.0 mmol/L \*\* | 82/2937 (2.8)  IR=1.6 | 47/2929 (1.6)  IR=0.9 | 0.56 (0.39, 0.80)  P =0.002 | 37/1837 (2.0)  IR=1.2 | 24/1842 (1.3)  IR=0.7 | 0.62 (0.37, 1.04) | 45/1100 (4.1)  IR=2.4 | 23/1087 (2.1)  IR=1.2 | 0.51 (0.31, 0.84) | 0.59 |

The Cox model includes terms for age, sex, baseline eGFR, baseline LVEF, region, diabetes status, randomized treatment (empagliflozin or placebo), and for the subgroup analyses additionally baseline use of MRA, and treatment by MRA interaction.

Considered potassium binding drugs were sodium polystyrene sulfonate, calcium polystyrene sulfonate, patiromer, patiromer (sorbitex) calcium, zirconium silicate and sodium zirconium cyclosilicate.

†Only patients without use of potassium binder at baseline are considered.   
\*Analysis performed in patients with potassium level of <5.5 mmol/L. \*\*Analysis performed in patients with potassium level of <6.0 mmol/L.

Shown are adverse events up to 7 days and serum potassium levels up to 3 days following discontinuation of the study medication.