SUPPLEMENTAL DATA

**Supplemental Table S1.** Treatment status with empagliflozin and other medications (safety analysis set).\*

|  |  |
| --- | --- |
|  | All patients  n (%) |
| Duration of treatment (days)  N  Mean (SD)  Median  Initial dose  10 mg  25 mg  Other  Last dose  10 mg  25 mg  Other  Any background medication  Glucose-lowering  Number  0  1  2  3  ≥4  Unknown  Type  DPP-4 inhibitor  Biguanide  Sulfonylurea  Insulin  Alpha-glucosidase inhibitor  Thiazolidinedione  GLP-1 receptor agonist  Glinide  Others  Antihypertensive  ARB/ACE inhibitor  CCB  Diuretics  Loop diuretic  Other medications  Statin | 7,618 (100)  688.4 (294.1)  748.0  7,227 (94.9)  338 (4.4)  53 (0.7)  6,951 (91.2)  613 (8.1)  54 (0.7)  6,833 (89.7)  1,811 (23.8)  2,083 (27.3)  1,843 (24.2)  1,130 (14.8)  481 (6.3)  270 (3.5)  3,379 (44.4)  2,759 (36.2)  1,540 (20.2)  904 (11.9)  580 (7.6)  480 (6.3)  354 (4.7)  241 (3.2)  833 (10.9)  3,786 (49.7)  1,997 (26.2)  1,533 (20.1)  387 (5.1)  165 (2.2)  2,660 (34.9) |

ARB/ACE: angiotensin II receptor blocker/angiotensin-converting enzyme. CCB: calcium channel blocker. DPP-4: dipeptidyl peptidase-4. GLP-1: glucagon-like peptide-1. SD: standard deviation.

\*Data are n (%) or mean (SD).

**Supplemental Table S2.** Adverse drug reactions by system organ class (safety analysis set).

|  |  |  |  |
| --- | --- | --- | --- |
| System organ class, n (%) | SAS  (N = 7,618) | Pre-approval pooled Japanese safety data;  treatment ≥52 weeks | |
| EMPA 10 mg (N = 700) | EMPA 25 mg (N = 703) |
| Total with related adverse events  Blood and lymphatic system disorders  Cardiac disorders  Ear and labyrinth disorders  Endocrine disorders  Eye disorders  Gastrointestinal disorders  General disorders and administration site conditions  Hepatobiliary disorders  Infections and infestations  Injury, poisoning, and procedural complications  Investigations  Metabolism and nutrition disorders  Musculoskeletal and connective tissue disorders  Neoplasms: benign, malignant, and unspecified (including cysts and polyps)  Nervous system disorders  Psychiatric disorders  Renal and urinary disorders  Reproductive system and breast disorders  Respiratory, thoracic, and mediastinal disorders  Skin and subcutaneous tissue disorders  Surgical and medical procedures  Vascular disorders | 644 (8.5)  6 (0.1)  25 (0.3)  3 (<0.1)  1 (<0.1)  5 (0.1)  49 (0.6)  39 (0.5)  18 (0.2)  97 (1.3)  13 (0.2)  117 (1.5)  99 (1.3)  14 (0.2)  13 (0.2)  45 (0.6)  8 (0.1)  108 (1.4)  46 (0.6)  12 (0.2)  58 (0.8)  1 (<0.1)  10 (0.1) | 103 (14.7)  0  1 (0.1)  2 (0.3)  0  1 (0.1)  11 (1.6)  14 (2.0)  1 (0.1)  19 (2.7)  1 (0.1)  9 (1.3)  16 (2.3)  3 (0.4)  1 (0.1)  6 (0.9)  0  38 (5.4)  6 (0.9)  0  1 (0.1)  NA  4 (0.6) | 113 (16.1)  2 (0.3)  1 (0.1)  0  0  1 (0.1)  15 (2.1)  13 (1.8)  1 (0.1)  13 (1.8)  0  11 (1.6)  28 (4.0)  1 (0.1)  0  6 (0.9)  0  42 (6.0)  3 (0.4)  0  2 (0.3)  NA  1 (0.1) |

EMPA: empagliflozin. NA: not available. SAS: safety analysis set.

**Supplemental Table S3.** Serious ADRs of special interest (safety analysis set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Serious ADRs, n (%) | Total  N = 7,618 | <65 years old  N = 4,828 | ≥65 to <75 years old  N = 1,988 | ≥75 years old  N = 802 |
| Total serious ADRs  Serious ADRs of special interest  Hypoglycemia  Urinary tract infection  Genital infection  Volume depletion  Cardiovascular event  Renal impairment  Liver injury  Bone fracture  Malignancy  Excessive/frequent urination  AEs relating to ketone increase  Diabetic ketoacidosis  Lower limb amputation | 74 (0.97)  0  3 (0.04)  0  2 (0.03)  26 (0.34)  0  1 (0.01)  2 (0.03)  12 (0.16)  0  1 (0.01)  0  2 (0.03) | 34 (0.70)  0  0  0  0  13 (0.27)  0  1 (0.02)  1 (0.02)  2 (0.04)  0  1 (0.02)  0  1 (0.02) | 27 (1.36)  0  2 (0.10)  0  2 (0.10)  8 (0.40)  0  0  0  9 (0.45)  0  0  0  1 (0.05) | 13 (1.62)  0  1 (0.12)  0  0  5 (0.62)  0  0  1 (0.12)  1 (0.12)  0  0  0  0 |

ADR: adverse drug reaction. AE: adverse event.

**Supplemental Table S4.** Adverse drug reactions of special interest in patients with an empagliflozin dose increase from 10 mg to 25 mg (safety analysis set; N = 293).

|  |  |  |
| --- | --- | --- |
| ADRs, n (%) | All | Serious |
| Total ADRs | 48 (16.38) | 4 (1.37) |
| ADRs of special interest |  |  |
| Hypoglycemia | 0 | 0 |
| Urinary tract infection | 1 (0.34) | 0 |
| Genital infection | 2 (0.68) | 0 |
| Volume depletion | 2 (0.68) | 0 |
| Cardiovascular event | 0 | 0 |
| Renal impairment | 2 (0.68) | 0 |
| Liver injury | 3 (1.02) | 0 |
| Bone fracture | 1 (0.34) | 0 |
| Malignancy | 3 (1.02) | 2 (0.68) |
| Excessive/frequent urination | 1 (0.34) | 0 |
| AEs relating to ketone increase | 10 (3.41) | 0 |
| Diabetic ketoacidosis | 0 | 0 |
| Lower limb amputation | 1 (0.34) | 1 (0.34) |

ADR: adverse drug reaction. AE: adverse event.

**Supplemental Table S5.** Change from baseline in HbA1c and FPG at last observation by baseline eGFR subgroup (effectiveness analysis set).\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | Baseline eGFR (ml/min/1.73 m2) | N | Baseline | At last observation | Change from baseline | 95% CI |
| HbA1c (%) | ≥90  60 to <90  45 to <60  30 to <45 | 2,035  3,268  755  106 | 8.34 (1.58)  7.86 (1.32)  7.82 (1.36)  7.99 (1.51) | 7.30 (1.21)  7.15 (0.99)  7.27 (1.13)  7.30 (1.09) | –1.04 (1.43)  –0.72 (1.13)  –0.55 (1.21)  –0.69 (1.28) | –1.10, –0.97  –0.76, –0.68  –0.64, –0.47  –0.93, –0.44 |
| FPG (mg/dl) | ≥90  60 to <90  45 to <60  30 to <45 | 686  1,053  235  28 | 168.2 (57.9)  157.7 (53.7)  161.0 (62.1)  159.1 (54.7) | 130.0 (39.2)  130.4 (36.7)  136.6 (41.7)  135.1 (31.5) | –38.2 (58.0)  –27.3 (49.8)  –24.4 (52.7)  –24.0 (50.8) | –42.5, –33.8  –30.4, –24.3  –31.1, –17.6  –43.7, –4.3 |

CI: confidence interval. eGFR: estimated glomerular filtration rate. FPG: fasting plasma glucose. HbA1c: glycosylated hemoglobin A1c. SD: standard deviation.

\*Data are mean (SD) unless otherwise stated.

**Supplemental Table S6.** Change in HbA1c and FPG from baseline and from before dose increase at last observation in patients with an empagliflozin dose increase from 10 mg to 25 mg.\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | N | Baseline | Before dose increase | At last observation | Change from baseline at last observation | 95% CI | Change from before dose increase at last observation | 95% CI |
| HbA1c (%) | 259 | 8.03 (1.52) | 7.56 (1.13) | 7.28 (0.99) | –0.75 (1.37) | –0.92, –0.59 | –0.28 (0.99) | –0.40, –0.16 |
| FPG (mg/dl) | 83 | 155.7 (49.8) | 141.2 (40.6) | 130.3 (30.4) | –25.4 (43.7) | –35.0, –15.9 | –11.0 (36.1) | –18.8, –3.1 |

CI: confidence interval. FPG: fasting plasma glucose. HbA1c: glycosylated hemoglobin A1c. SD: standard deviation.

\*Data are mean (SD) unless otherwise stated.

**Supplemental Table S7.** Change from baseline in body weight and eGFR at last observation by baseline eGFR subgroup (safety analysis set).\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | Baseline eGFR (ml/min/1.73 m2) | N | Baseline | At last observation | Change from baseline | 95% CI |
| Body weight (kg) | ≥90  60 to <90  45 to <60  30 to <45 | 1,869  3,073  682  97 | 78.53 (18.08)  75.05 (15.59)  73.59 (14.77)  72.64 (15.88) | 75.92 (17.92)  72.43 (15.18)  71.09 (14.47)  70.32 (15.57) | –2.61 (4.95)  –2.62 (4.10)  –2.50 (4.19)  –2.32 (3.60) | –2.83, –2.38  –2.76, –2.47  –2.81, –2.18  –3.04, –1.59 |
| eGFR (ml/min/1.73 m2) | ≥90  60 to <90  45 to <60  30 to <45 | 1,454  2,487  598  82 | 108.09 (23.89)  75.00 (8.39)  53.26 (4.19)  39.48 (4.24) | 98.50 (20.67)  74.70 (14.10)  53.90 (10.57)  38.95 (7.42) | –9.58 (23.62)  –0.30 (12.16)  0.65 (9.52)  –0.53 (5.96) | –10.80, –8.37  –0.78, 0.18  –0.12, 1.41  –1.84, 0.78 |

CI: confidence interval. eGFR: estimated glomerular filtration rate. SD: standard deviation.

\*Data are mean (SD) unless otherwise stated.

**Supplemental Figure S1.** Patient disposition. \*Indicates there is duplication. eCRF: electronic case report form. FPG: fasting plasma glucose. HbA1c: glycosylated hemoglobin A1c.

