SUPPLEMENTAL DATA

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

|  |  |
| --- | --- |
|  | All patientsn (%) |
| Duration of treatment (days) N Mean (SD) MedianInitial dose 10 mg 25 mg OtherLast dose 10 mg 25 mg OtherAny 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 medicationsStatin | 7,618 (100)688.4 (294.1)748.07,227 (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)01 (0.1)2 (0.3)01 (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)038 (5.4)6 (0.9)01 (0.1)NA4 (0.6) | 113 (16.1)2 (0.3)1 (0.1)001 (0.1)15 (2.1)13 (1.8)1 (0.1)13 (1.8)011 (1.6)28 (4.0)1 (0.1)06 (0.9)042 (6.0)3 (0.4)02 (0.3)NA1 (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 (%) | TotalN = 7,618 | <65 years oldN = 4,828 | ≥65 to <75 years oldN = 1,988 | ≥75 years oldN = 802 |
| Total serious ADRsSerious 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)03 (0.04)02 (0.03)26 (0.34)01 (0.01)2 (0.03)12 (0.16)01 (0.01)02 (0.03) | 34 (0.70)000013 (0.27)01 (0.02)1 (0.02)2 (0.04)01 (0.02)01 (0.02) | 27 (1.36)02 (0.10)02 (0.10)8 (0.40)0009 (0.45)0001 (0.05) | 13 (1.62)01 (0.12)005 (0.62)001 (0.12)1 (0.12)0000 |

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 (%) | ≥9060 to <9045 to <6030 to <45 | 2,0353,268755106 | 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)  | ≥9060 to <9045 to <6030 to <45 | 6861,05323528 | 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) | ≥9060 to <9045 to <6030 to <45 | 1,8693,07368297 | 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) | ≥9060 to <9045 to <6030 to <45 | 1,4542,48759882 | 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.

