

Supplemental Material

Supplemental Table 1. Adjusted mean changes of uric acid levels (mg/dL) over time (on-treatment) in the Empagliflozin (pooled) vs. Placebo group

Week (n/o patients analyzed)	UA level change Empagliflozin (n=4516)	UA level change Placebo (n=2260)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo	p-value
Baseline mean (SD)	5.93 (0.02)	6.01 (0.03)	-	-
Week 12 (n=6728)	-0.32 (0.02)	0.03 (0.02)	-0.35 (-0.40, -0.30)	<0.0001
Week 28 (n=6506)	-0.34 (0.02)	0.06 (0.02)	-0.40 (-0.45, -0.34)	<0.0001
Week 52 (n=6226)	-0.34 (0.02)	0.02 (0.02)	-0.37 (-0.42, -0.31)	<0.0001
Week 66 (n=6055)	-0.30 (0.02)	0.04 (0.02)	-0.34 (-0.40, -0.28)	<0.0001
Week 80 (n=5885)	-0.28 (0.02)	0.03 (0.03)	-0.31 (-0.37, -0.25)	<0.0001
Week 94 (n=5731)	-0.31 (0.02)	0.04 (0.03)	-0.35 (-0.41, -0.29)	<0.0001
Week 108 (n=5067)	-0.29 (0.02)	0.06 (0.03)	-0.35 (-0.41, -0.28)	<0.0001
Week 122 (n=4243)	-0.26 (0.02)	0.08 (0.03)	-0.34 (-0.41, -0.27)	<0.0001
Week 136 (n=3627)	-0.28 (0.02)	0.03 (0.03)	-0.31 (-0.38, -0.23)	<0.0001
Week 150 (n=3218)	-0.30 (0.02)	0.02 (0.03)	-0.32 (-0.39, -0.24)	<0.0001
Week 164 (n=2800)	-0.29 (0.02)	0.03 (0.04)	-0.32 (-0.41, -0.24)	<0.0001
Week 178 (n=2049)	-0.31 (0.03)	-0.02 (0.04)	-0.30 (-0.39, -0.20)	<0.0001
Week 192 (n=1272)	-0.33 (0.03)	-0.10 (0.05)	-0.24 (-0.34, -0.13)	<0.0001
Week 206 (n=463)	-0.31 (0.05)	0.10 (0.07)	-0.42 (-0.59, -0.24)	<0.0001

UA level changes are presented as adjusted mean (SE) changes from baseline based on MMRM analyses, that included continuous fixed effects of baseline uric acid and baseline HbA1c at each visit and discrete fixed effects for treatment at each visit, region, baseline eGFR, baseline BMI and last projected visit.

BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; UA=uric acid.

Supplemental Table 2. Adjusted mean changes of uric acid levels (mg/dL) over time (on-treatment) in the Empagliflozin (10 mg and 25 mg separately) vs. Placebo group

Week (n/o patients analyzed)	UA level change Empagliflozin 10 mg (n=2266)	UA level change Empagliflozin 25 mg (n=2250)	UA level change Placebo (n=2260)	Adjusted mean (95%-CI) treatment difference Empagliflozin 10mg vs. Placebo	Adjusted mean (95%-CI) treatment difference Empagliflozin 25 mg vs. Placebo
Baseline mean (SD)	5.91 (0.03)	5.96 (0.03)	6.01 (0.03)	-	-
Week 12 (n=6728)	-0.32 (0.02)	-0.32 (0.02)	0.03 (0.02)	-0.35 (-0.41, -0.29)	-0.36 (-0.41, -0.30)
Week 28 (n=6506)	-0.32 (0.02)	-0.35 (0.02)	0.06 (0.02)	-0.38 (-0.44, -0.32)	-0.41 (-0.47, -0.35)
Week 52 (n=6226)	-0.35 (0.02)	-0.33 (0.02)	0.02 (0.02)	-0.38 (-0.44, -0.31)	-0.35 (-0.42, -0.29)
Week 66 (n=6055)	-0.28 (0.02)	-0.32 (0.02)	0.04 (0.02)	-0.32 (-0.39, -0.25)	-0.35 (-0.42, -0.29)
Week 80 (n=5885)	-0.29 (0.03)	-0.27 (0.03)	0.03 (0.03)	-0.33 (-0.40, -0.26)	-0.30 (-0.37, -0.23)
Week 94 (n=5731)	-0.31 (0.03)	-0.31 (0.03)	0.04 (0.03)	-0.34 (-0.41, -0.27)	-0.35 (-0.42, -0.28)
Week 108 (n=5067)	-0.28 (0.03)	-0.30 (0.03)	0.06 (0.03)	-0.33 (-0.41, -0.26)	-0.36 (-0.43, -0.29)
Week 122 (n=4243)	-0.28 (0.03)	-0.24 (0.03)	0.08 (0.03)	-0.36 (-0.44, -0.28)	-0.32 (-0.40, -0.24)
Week 136 (n=3627)	-0.30 (0.03)	-0.27 (0.03)	0.03 (0.03)	-0.32 (-0.41, -0.24)	-0.29 (-0.38, -0.21)
Week 150 (n=3218)	-0.31 (0.03)	-0.29 (0.03)	0.02 (0.03)	-0.33 (-0.42, -0.24)	-0.31 (-0.39, -0.22)
Week 164 (n=2800)	-0.29 (0.03)	-0.29 (0.03)	0.03 (0.04)	-0.32 (-0.42, -0.23)	-0.33 (-0.42, -0.23)
Week 178 (n=2049)	-0.32 (0.04)	-0.31 (0.04)	-0.02 (0.04)	-0.30 (-0.41, -0.20)	-0.29 (-0.40, -0.18)
Week 192 (n=1272)	-0.38 (0.04)	-0.29 (0.04)	-0.10 (0.05)	-0.29 (-0.41, -0.16)	-0.19 (-0.31, -0.07)
Week 206 (n=463)	-0.36 (0.07)	-0.27 (0.06)	0.10 (0.07)	-0.47 (-0.66, -0.27)	-0.38 (-0.57, -0.18)

Adjusted mean (SE) changes from baseline based on MMRM analyses, that included continuous fixed effects of baseline uric acid and baseline HbA1c at each visit and discrete fixed effects for treatment at each visit, region, baseline eGFR, baseline BMI and last projected visit.

BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; UA=uric acid

Supplemental Table 3. Adjusted mean changes of uric acid levels (mg/dL) over time (on-treatment) in the Empagliflozin (10 mg and 25 mg pooled) vs. Placebo group in patients with UA levels < vs. ≥6.0 mg/dL and < vs. ≥7.0 mg/dL at baseline and by prevalent CKD at baseline

Week (n/o patients analyzed)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo in participants with UA level <6.0 mg/dL at BL (n=3679)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo in participants with UA level ≥6.0 mg/dL at BL (n=3097)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo in participants with UA level <7.0 mg/dL at BL (n=5218)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo in participants with UA level ≥7.0 mg/dL at BL (n=1558)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo in participants without prevalent CKD at BL (n=4580)	Adjusted mean (95%-CI) treatment difference Empagliflozin vs. Placebo in participants with prevalent CKD at BL (n=2146)
Week 12	-0.26 (-0.34, -0.19)	-0.45 (-0.53, -0.37)	-0.31 (-0.37, -0.25)	-0.48 (-0.59; -0.37)	-0.41 (-0.47, -0.35)	-0.23 (-0.32, -0.14)
Week 28	-0.28 (-0.36, -0.21)	-0.52 (-0.60, -0.44)	-0.33 (-0.39, -0.26)	-0.61 (-0.72; -0.50)	-0.44 (-0.50, -0.37)	-0.32 (-0.42, -0.23)
Week 52	-0.28 (-0.36, -0.20)	-0.46 (-0.55, -0.38)	-0.30 (-0.37, -0.24)	-0.56 (-0.68; -0.43)	-0.38 (-0.45, -0.31)	-0.34 (-0.44, -0.23)
Week 66	-0.24 (-0.33, -0.16)	-0.44 (-0.53, -0.35)	-0.28 (-0.35, -0.21)	-0.51 (-0.63, -0.38)	-0.37 (-0.44, -0.30)	-0.28 (-0.38, -0.17)
Week 80	-0.25 (-0.33, -0.16)	-0.38 (-0.47, -0.29)	-0.27 (-0.34, -0.19)	-0.45 (-0.58, -0.32)	-0.33 (-0.41, -0.26)	-0.28 (-0.39, -0.17)
Week 94	-0.26 (-0.35, -0.18)	-0.44 (-0.54, -0.35)	-0.30 (-0.38, -0.23)	-0.47 (-0.61, -0.34)	-0.33 (-0.41, -0.26)	-0.40 (-0.52, -0.29)
Week 108	-0.28 (-0.38, -0.19)	-0.41 (-0.51, -0.31)	-0.31 (-0.38, -0.23)	-0.46 (-0.59, -0.32)	-0.36 (-0.44, -0.28)	-0.34 (-0.45, -0.22)
Week 122	-0.23 (-0.33, -0.13)	-0.46 (-0.57, -0.35)	-0.28 (-0.37, -0.20)	-0.51 (-0.66, -0.36)	-0.35 (-0.43, -0.26)	-0.32 (-0.45, -0.20)
Week 136	-0.24 (-0.34, -0.13)	-0.38 (-0.49, -0.27)	-0.28 (-0.37, -0.20)	-0.37 (-0.52, -0.21)	-0.34 (-0.42, -0.25)	-0.25 (-0.39, -0.12)
Week 150	-0.29 (-0.40, -0.18)	-0.34 (-0.45, -0.22)	-0.30 (-0.38, -0.21)	-0.37 (-0.53, -0.20)	-0.33 (-0.42, -0.24)	-0.29 (-0.43, -0.15)
Week 164	-0.32 (-0.44, -0.20)	-0.31 (-0.44, -0.18)	-0.32 (-0.42, -0.22)	-0.30 (-0.49, -0.12)	-0.34 (-0.44, -0.24)	-0.30 (-0.46, -0.15)
Week 178	-0.24 (-0.37, -0.11)	-0.35 (-0.49, -0.21)	-0.26 (-0.36, -0.15)	-0.43 (-0.63, -0.22)	-0.32 (-0.43, -0.21)	-0.24 (-0.42, -0.07)
Week 192	-0.23 (-0.37, -0.08)	-0.23 (-0.39, -0.07)	-0.21 (-0.33, -0.09)	-0.30 (-0.53, -0.07)	-0.25 (-0.37, -0.12)	-0.22 (-0.42, -0.03)
Week 206	-0.39 (-0.63, -0.14)	-0.43 (-0.67, -0.19)	-0.40 (-0.60, -0.20)	-0.42 (-0.78, -0.07)	-0.48 (-0.69, -0.27)	-0.25 (-0.56, 0.05)

Adjusted mean treatment difference based on MMRM analyses, that included continuous fixed effects of baseline uric acid (only if not subgroup) and baseline HbA1c at each visit and discrete fixed effects for treatment at each visit, region, baseline eGFR (only if not subgroup), baseline BMI, last projected visit and subgroup-by-treatment-by visit interaction. Prevalent CKD defined by an eGFR <60 ml/min/1.73m² or UACR >300 mg/g creatinine at baseline.

BMI=body-mass-index; BL=baseline; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; UA=uric acid; UACR=urinary-albumin-creatinine ratio

Supplemental Table 4. Effects of empagliflozin on new onset of gout or initiation of anti-gout medication during follow-up (on-treatment) by baseline UA level

	UA <6.0 mg/dL at baseline					UA ≥6.0 mg/dL at baseline					Interac tion P value
	Placebo		Empagliflozin (10 and 25 mg pooled)			Placebo		Empagliflozin (10 and 25 mg pooled)			
	n/N (%)	Rate	n/N (%)	Rate	HR (95%CI)	n/N (%)	Rate	n/N (%)	Rate	HR (95%CI)	
New onset of gout or initiation of anti-gout medication [†]	16/1172 (1.4)	5.5	28/2440 (1.1)	4.4	0.82 (0.44, 1.51)	98/1015 (9.7)	41.8	129/1977 (6.5)	26.9	0.66 (0.51, 0.86)	0.5282
New onset of gout [‡]	1/1231 (0.1)	0.3	9/2565 (0.4)	1.3	NC	46/1100 (4.2)	17.4	68/2121 (3.2)	12.9	NC	-
Initiation of anti-gout medication [†]	16/1172 (1.4)	5.5	26/2440 (1.1)	4.1	0.76 (0.41, 1.41)	88/1015 (8.7)	37.3	109/1977 (5.5)	22.6	0.62 (0.47, 0.82)	0.5621
	UA <7.0 mg/dL at baseline					UA ≥7.0 mg/dL at baseline					Interac tion P value
	Placebo		Empagliflozin (10 and 25 mg pooled)			Placebo		Empagliflozin (10 and 25 mg pooled)			
	n/N (%)	Rate	n/N (%)	Rate	HR (95%CI)	n/N (%)	Rate	n/N (%)	Rate	HR (95%CI)	
New onset of gout or initiation of anti-gout medication [†]	36/1678 (2.1)	8.7	50/3444 (1.5)	5.6	0.66 (0.43, 1.02)	78/509 (15.3)	7.05	107/973 (11.0)	48.3	0.68 (0.51, 0.91)	0.9377
New onset of gout [‡]	9/1768 (0.5)	2.0	22/3630 (0.6)	2.3	1.18 (0.54, 2.56)	38 /563 (6.7)	29.1	55/1056 (5.2)	21.8	0.73 (0.48, 1.11)	0.2905
Initiation of anti-gout medication [†]	33/1678 (2.0)	7.9	43/3444 (1.2)	4.8	0.62 (0.40, 0.98)	71/509 (13.9)	63.6	92/973 (9.5)	41.1	0.64 (0.47, 0.88)	0.9127

Rate is expressed in events per 1000 person-years. [†]Analysis performed in patients not on anti-gout medication at baseline (n=6607); [‡]Analysis performed in all patients (n=7020). HR for pooled empagliflozin versus placebo based on Cox proportional hazards regression analysis adjusting for baseline age, HbA1c, eGFR, sex, BMI, geographic region, treatment group, subgroup and treatment-by-subgroup interaction.

NC=not calculated due to <14 number of patients with events in one subgroup; UA=uric acid; HR=Hazard Ratio, CI=Confidence Interval

Supplemental Table 5. Mediation analysis to study the influence of new initiation of diuretics on the treatment effect of empagliflozin on new onset of gout or initiation of anti-gout medication during follow-up (on-treatment)

Time to new onset of gout or initiation of anti-gout medication	HR (95% CI) for use of diuretics (yes vs. no)	HR (95%CI) for empagliflozin (10 and 25 mg pooled) vs. placebo	% of treatment effect mediated by diuretic use
Cox regression model		0.67 (0.53,0.85)	-
Cox regression model with additional covariate for time-dependent use of loop diuretics	2.52 (1.95,3.26)	0.70 (0.55,0.89)	10.9%
Cox regression model with additional covariate for time-dependent use of thiazide diuretics	1.27 (0.98,1.65)	0.67 (0.53,0.86)	0.0%
Cox regression model with additional covariate for time-dependent use of loop or thiazide diuretics	2.14 (1.66,2.76)	0.69 (0.54,0.88)	7.3%

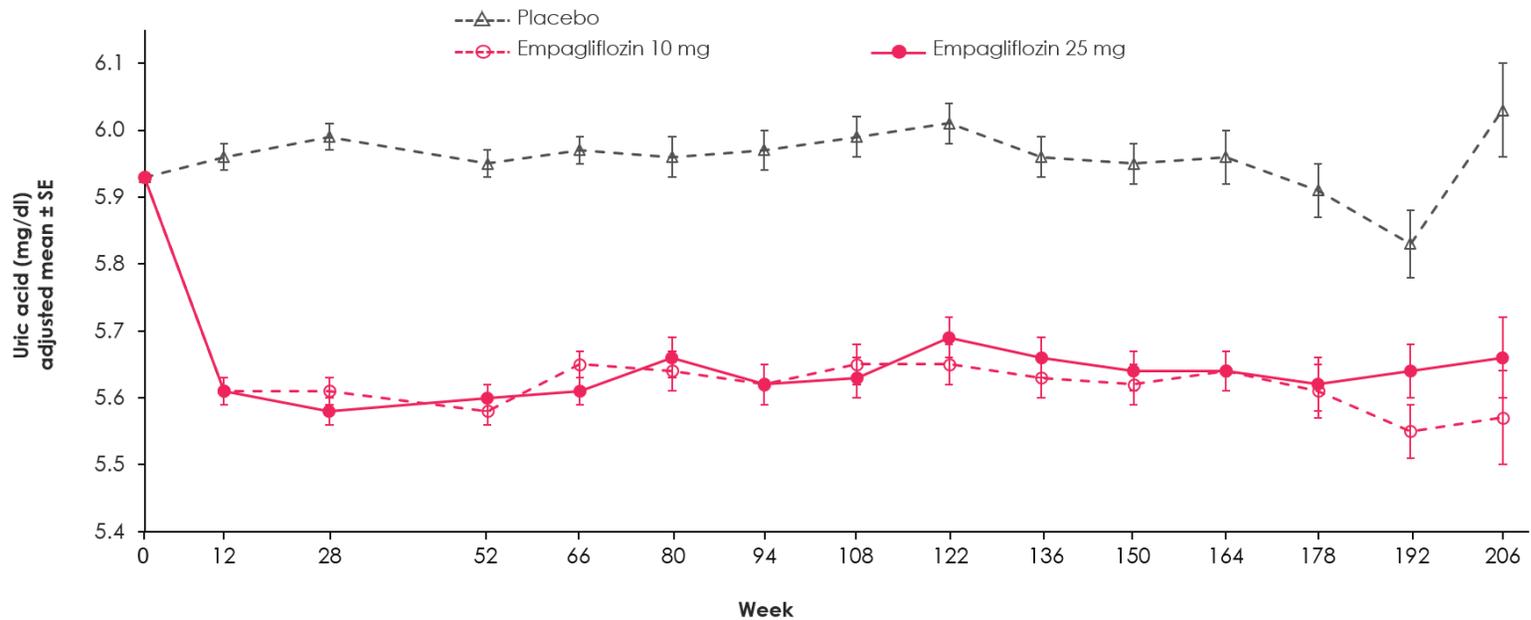
Analysis performed in patients not on anti-gout medication at baseline (n=6607). Hazard ratio (95 % CI) based on Cox proportional hazards regression analysis (primary model) adjusting for baseline age, HbA1c, eGFR, sex, BMI, geographic region and treatment group without and with time-dependent covariate for loop/thiazide diuretics use, respectively.

Percentage mediation was estimated as $(\ln(\text{HR}) - \ln(\text{HR}_c)) / \ln(\text{HR}) * 100\%$, where HR is the HR for the comparison of the treatment groups in the primary model, and HR_c is the HR for the comparison of the treatment groups in the model adjusting for the time-dependent covariate of diuretics.

Time to new onset of loop diuretics on-treatment in empa vs. placebo: HR 0.56, 95% CI (0.46,0.67), Time to new onset of thiazides on-treatment in empa vs. placebo: HR 0.65, 95% CI (0.52,0.81), both in patients not on anti-gout medication at baseline and not on loop diuretics resp. thiazides at baseline.

BMI=Body-mass-index; eGFR=estimated glomerular filtration rate; HR=Hazard Ratio, CI=Confidence Interval.

Supplemental Figure 1. Effect of Empagliflozin (10 and 25 mg) vs. placebo on uric acid levels (mg/dl) over time (on-treatment)

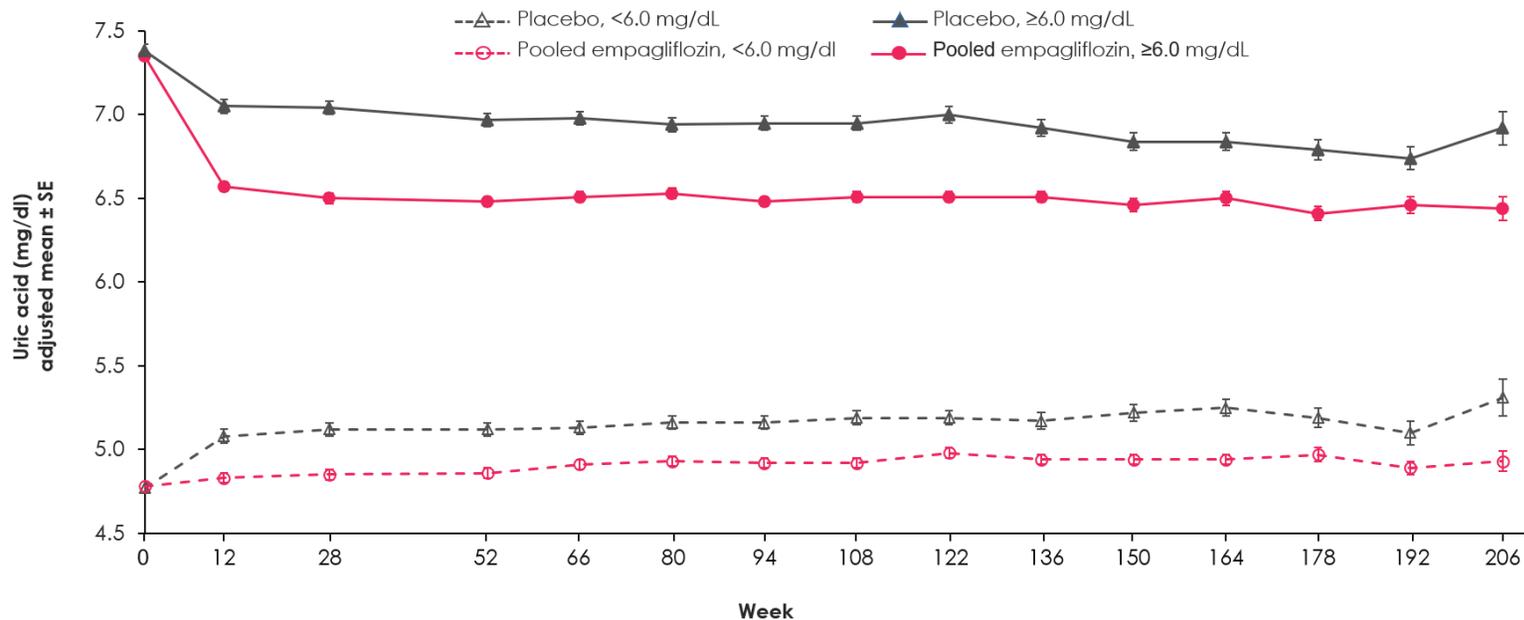


Patients with data at visit

Placebo	2260	2246	2155	2045	1977	1907	1847	1635	1360	1150	1013	878	623	365	129
Empagliflozin 10 mg	2266	2242	2190	2100	2046	1988	1944	1703	1428	1230	1087	947	693	447	152
Empagliflozin 25 mg	2250	2240	2161	2081	2032	1990	1940	1729	1455	1247	1118	975	733	460	182

Legend: MMRM analyses, that included continuous fixed effects of baseline uric acid and baseline HbA1c at each visit and discrete fixed effects for treatment at each visit, region, baseline eGFR, baseline BMI and last projected visit. BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; HR=hazard ratio; CI=confidence interval.

Supplemental Figure 2. Effect of Empagliflozin (10 and 25 mg pooled) vs. placebo on uric acid levels (mg/dl) over time (on-treatment) in participants with baseline UA ≥ 6.0 mg/dL vs. < 6.0 mg/dL

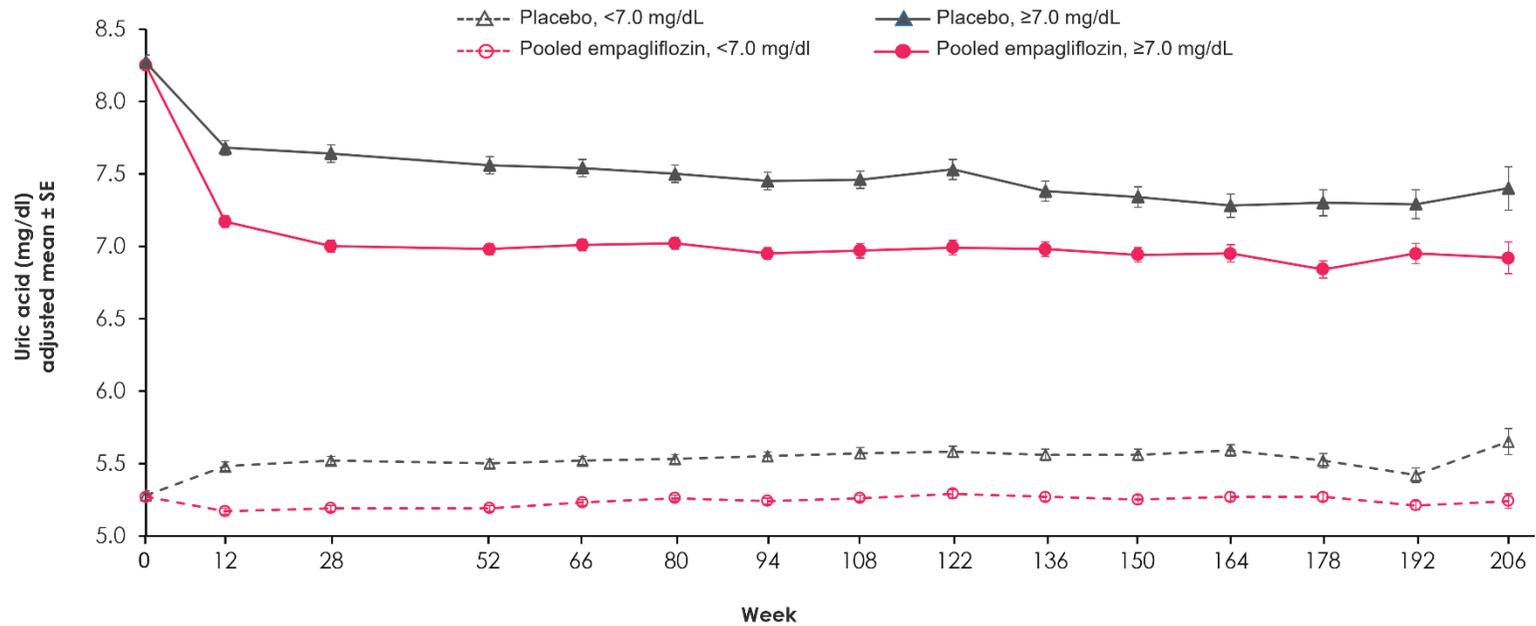


Patients with data at visit

Placebo, <6.0	1186	1178	1141	1077	1053	1020	988	877	731	626	551	475	350	196	58
Pooled empagliflozin, <6.0	2493	2474	2403	2307	2267	2217	2166	1913	1570	1362	1210	1084	809	523	195
Placebo, ≥ 6.0	1074	1068	1014	968	924	887	859	758	629	524	462	403	273	169	71
Pooled empagliflozin, ≥ 6.0	2023	2008	1948	1874	1811	1761	1718	1519	1313	1115	995	838	617	384	139

Legend: MMRM analyses, that included continuous fixed effects of baseline HbA1c at each visit and discrete fixed effects for treatment at each visit, region, baseline eGFR, baseline BMI, last projected visit and subgroup-by-treatment-by visit interaction. BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; HR=hazard ratio; CI=confidence interval.

Supplemental Figure 3. Effect of Empagliflozin (10 and 25 mg pooled) vs. placebo on uric acid levels (mg/dl) over time (on-treatment) in participants with baseline UA ≥ 7.0 mg/dL vs. < 7.0 mg/dL



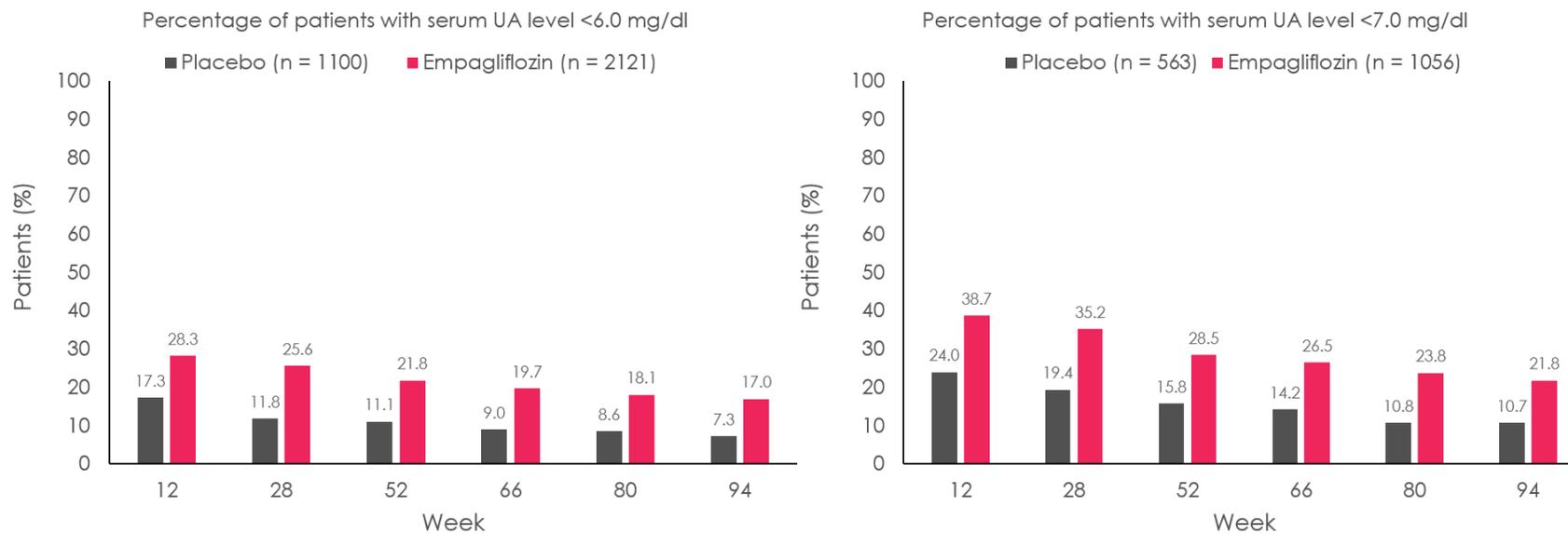
Patients with data at visit

Placebo, <7.0	1708	1698	1644	1559	1513	1467	1425	1260	1057	896	782	673	481	277	95
Pooled empagliflozin, <7.0	3510	3483	3387	3254	3187	3113	3043	2701	2255	1952	1742	1534	1144	745	270
Placebo, ≥ 7.0	552	548	511	486	464	440	422	375	303	254	231	205	142	88	34
Pooled empagliflozin, ≥ 7.0	1006	999	964	927	891	865	841	731	628	525	463	388	282	162	64

Legend: MMRM analyses, that included continuous fixed effects of baseline HbA1c at each visit and discrete fixed effects for treatment at each visit, region, baseline eGFR, baseline BMI, last projected visit and subgroup-by-treatment-by-visit interaction.

BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; HR=hazard ratio; CI=confidence interval.

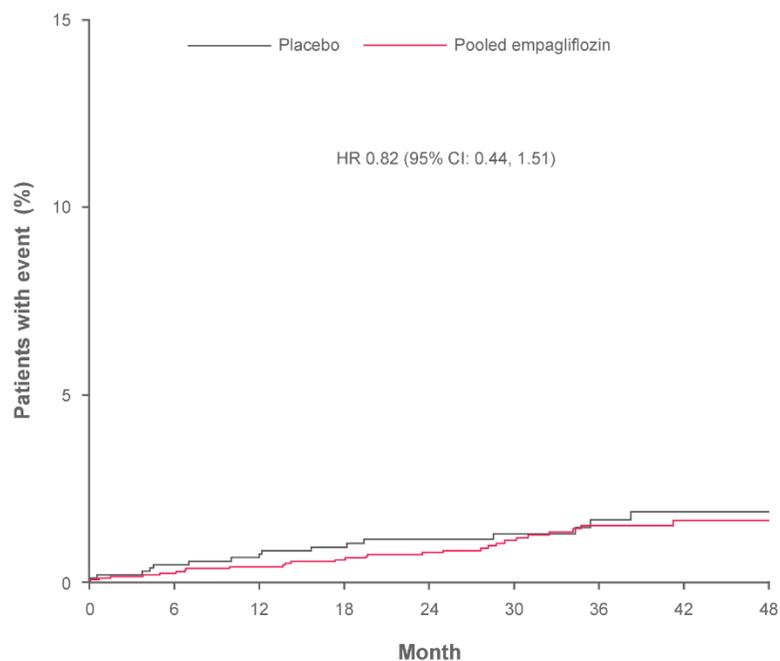
Supplemental Figure 4. Proportion of patients with serum uric acid levels <6.0 mg/dl (left panel) and <7.0 mg/dl (right panel) during on treatment phase



Legend: Data are presented up to week 94 visit, which could be reached by all patients. Patients with missing serum UA are considered not meeting the criterion. UA=uric acid.

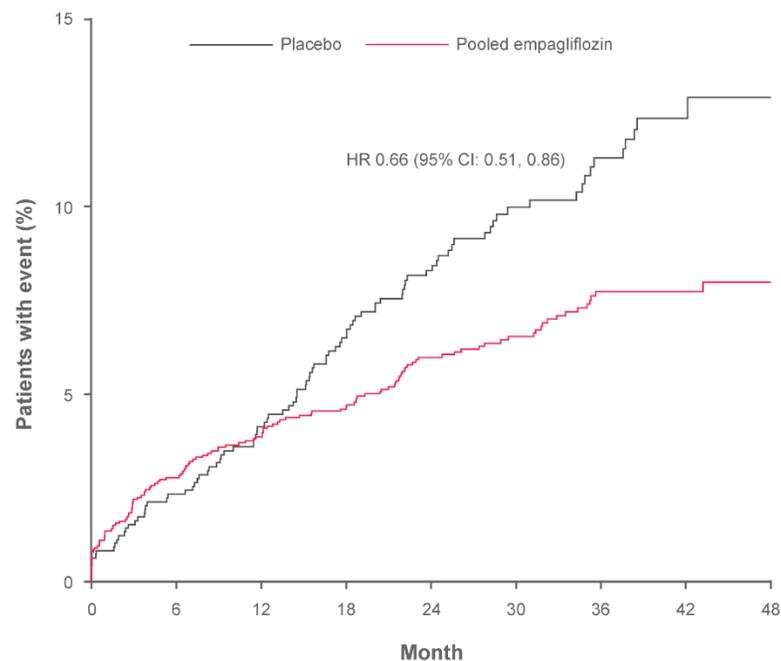
Supplemental Figure 5. Time to new onset of gout or anti-gout medication during on-treatment phase (for patients not on anti-gout medication at baseline) in patients with UA levels < vs. ≥6.0 mg/dL at baseline

Baseline uric acid: <6.0 mg/dL (N=3796)



Patients at risk, n		0	6	12	18	24	30	36	42	48
Placebo		1172	1101	1039	988	847	606	464	218	48
Empagliflozin		2440	2315	2230	2136	1855	1330	1044	559	150

Baseline uric acid: ≥6.0 mg/dL (N=3221)

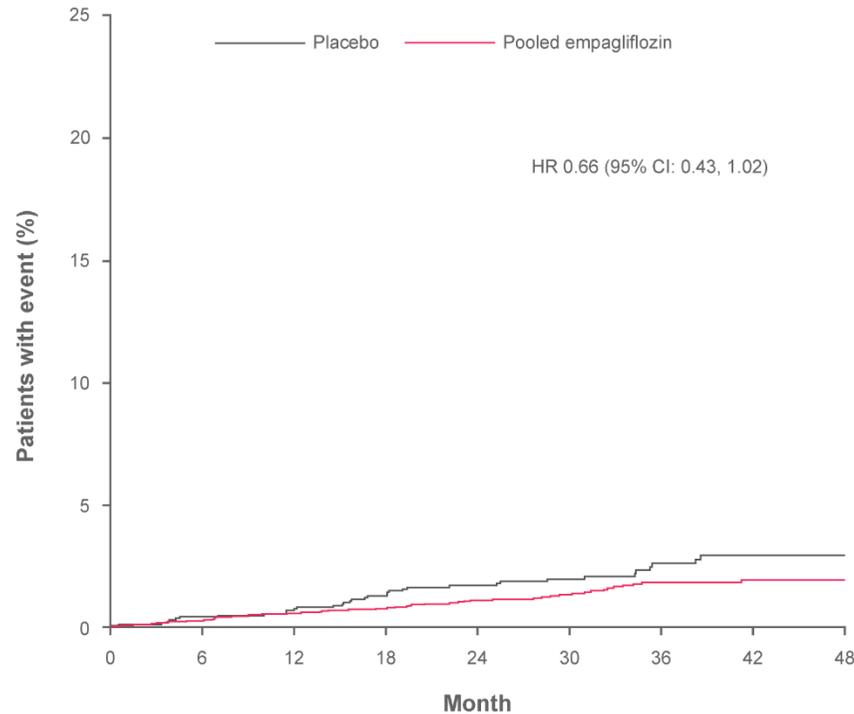


Patients at risk, n		0	6	12	18	24	30	36	42	48
Placebo		1015	935	868	786	659	454	347	155	48
Empagliflozin		1977	1796	1699	1602	1372	1014	749	363	100

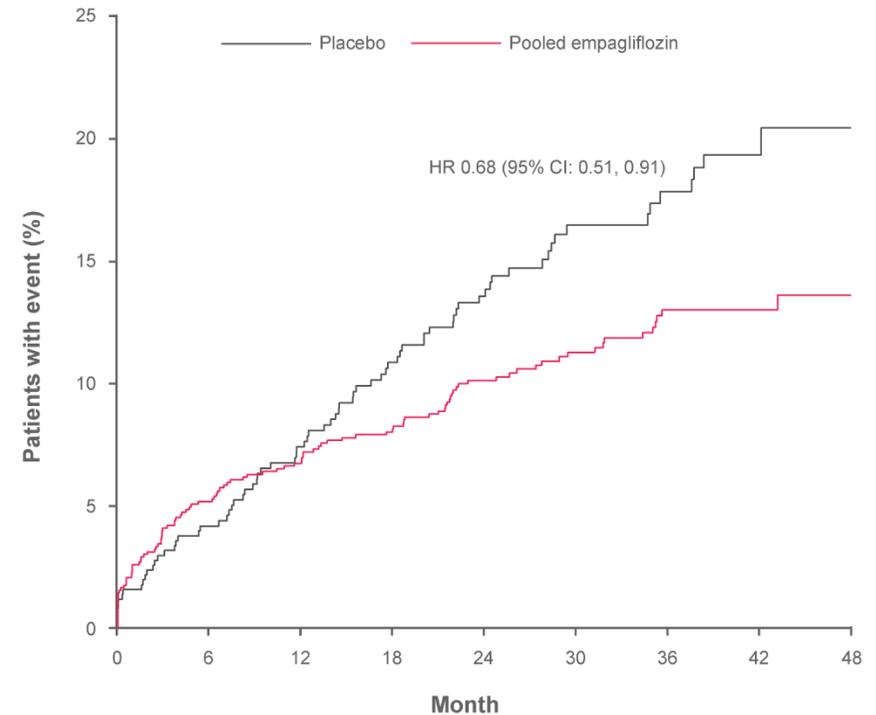
Legend: Cox proportional hazards models with terms for age, sex, geographic region, baseline HbA1c, baseline eGFR, baseline BMI, treatment, subgroups of participants based on baseline UA level < vs. ≥6 mg/dL and subgroup-by-treatment interaction (p=0.5282). BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c, HR=hazard ratio, CI=confidence interval.

Supplemental Figure 6. Time to new onset of gout or anti-gout medication during on-treatment phase (for patients not on anti-gout medication at baseline) in patients with UA levels < vs. \geq 7.0 mg/dL at baseline

Baseline uric acid: <7.0 mg/dL (N=5398)



Baseline uric acid: \geq 7.0 mg/dL (N=1619)



Patients at risk, n

Placebo	1678	1579	1491	1406	1203	858	651	301	76
Empagliflozin	3444	3250	3125	2990	2598	1890	1470	783	208

Patients at risk, n

Placebo	509	457	416	368	303	202	160	72	20
Empagliflozin	973	861	804	748	629	454	323	139	42

Legend: Cox proportional hazards models with terms for age, sex, geographic region, baseline HbA1c, baseline eGFR, baseline BMI, treatment, subgroups of participants based on baseline UA level < vs. \geq 7 mg/dL and subgroup-by-treatment interaction (p=0.9377). BMI=body-mass-index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin A1c; HR=Hazard Ratio, CI=Confidence Interval.