Studies pools

The analyses were done in the pooled population of the long-term studies 1245.25, 1245.110, and 1245.121 (SAF-M1), in the pooled population of studies 1245.110 and 1245.121 (SAF-M2), and in each of the 3 studies separately.

Patients and study size, baseline characteristics

The SAF-M1 population included 16,731 treated patients and the SAF-M2 population included 9711 treated patients.

In the SAF-M1 population, the median duration of exposure to study drug was 24.20 (interquartile range [IQR] 14.93-34.53) months and was slightly longer in the overall empagliflozin treatment group (all empagliflozin) (median 25.17; IQR 15.63-35.27 months) than in the placebo group (median 22.40; IQR 14.03-31.77 months). Total exposure was 19813.9 yrs for empagliflozin and 13539.1 yrs for placebo (difference between placebo and empagliflozin due to the additional empagliflozin treatment arm in study 1245.25). In the SAF-M2 population, the median duration of exposure to study drug was 19.03 months overall, and was comparable in the empagliflozin and placebo groups (empagliflozin: median 19.00; IQR 12.13-27.33; placebo: median 19.13; IQR 12.13-27.40), as was total exposure (empagliflozin: 7834.0 yrs; placebo: 7792.0 yrs).

The treatment groups within the randomised controlled trials were well balanced with regard to demographic and other baseline characteristics, medical history, and use of concomitant medications. In the meta-analysis, approximately three quarters of all patients in SAF-M1 were White, and almost 20% were of Asian race, the mean age was 67.1 [standard deviation (SD) 10.2] years. About 40% of patients were living in Europe, and about 40% in North America and Latin America (note, this category also included patients in Australia and New Zealand).

All patients in study 1245.25 had type 2 diabetes mellitus (T2DM) and approximately 50% of patients in the heart failure (HF) studies had T2DM, giving an overall population of around 70% of patients with diabetes mellitus. More than half of the patients had documented coronary artery disease, and almost 90% of patients had hypertension. All patients in studies 1245.110 and 1245.121 had HF, as did 10% of patients in study 1245.25, giving an overall population of approximately 60% of patients with HF. The frequencies of lower limb amputations (LLA), osteomyelitis, and gangrene in patients' medical history were low (note that this specific information was available for patients in studies 1245.110 and 1245.121 only). Nephropathy was reported for almost 20% of patients. Peripheral artery obstructive disease was reported for almost 15% of the SAF-M1 population.

Primary outcome

In general, the frequencies of LLAs were low and similar for both the empagliflozin and placebo treatment groups (see a summary by analysis population and study in Table 1, below). Most patients with LLAs hadonly a single episode of LLA (SAF-M1: empagliflozin: 68/95 patients with LLAs; placebo: 46/55 patients with LLAs). In the analysis of the primary outcome (LLAs), in both the SAF-M1 and SAF-M2 populations, the results did not indicate an increased risk of LLAs in patients treated with empagliflozin. The findings in the individual studies were consistent with those from the overall populations of SAFM1 and SAF-M2. A summary of patients with LLAs on treatment, incidence rates for LLAs on treatment, and hazard ratios (HRs) for empagliflozin vs. placebo is tabulated below for the primary outcome in SAF-M1, SAF-M2, and the individual studies. Adjusting for death as a competing risk, the HR for LLAs for empagliflozin vs. placebo was almost unchanged from the primary analysis: HR 1.02 (95% confidence interval [CI]: 0.73, 1.43; p = 0.9017). There

were also no clinically meaningful differences in findings when the analyses were conducted on an intention-to-treat (ITT) basis, including LLAs to the last follow-up. In the ITT analysis of the SAF-M1 population the HR for LLAs for empagliflozin vs. placebo was almost unchanged from the primary analysis: HR 0.96 (95% CI: 0.72, 1.29; p = 0.7985). For SAF-M2, the HR was 0.89 (95% CI: 0.54, 1.46; p = 0.6314).

Considering the potential differences in patient populations, subgroup analyses by demographics, baseline medical conditions, and baseline therapies were carried out to assess any potential impact of these differences on the results. In subgroup analyses there were no patterns identified to suggest a substantial impact of empagliflozin on risk of LLAs, also including in subgroups of patients with a higher risk of LLA.

Table 1: Summary of primary outcome analyses; Cox regression for time to first LLA – on treatment (by analysis population / individual study)

Population / study	Placebo	Empagliflozin
SAF-M1		
Number of patients analysed, N	7185	9546
Patients with LLA events, N (%)	55 (0.8)	95 (1.0)
Incidence rate[1] (95% CI)	0.40 (0.30, 0.52)	0.48 (0.39, 0.58)
HR (95% CI); p value[2]	1.02 (0.73, 1.42); 0.9276	
SAF-M2		
Number of patients analysed, N	4852	4859
Patients with LLA events, N (%)	21 (0.4)	18 (0.4)
Incidence rate[1] (95% CI)	0.27 (0.17, 0.39)	0.23 (0.13, 0.34)
HR (95% CI); p value[2]	0.85 (0.45, 1.60); 0.6205	
1245.25		
Number of patients analysed, N	2333	4687
Patients with LLA events, N (%)	34 (1.5)	77 (1.6)
Incidence rate[1] (95% CI)	0.59 (0.41, 0.81)	0.64 (0.51, 0.79)
HR (95% CI); p value[2]	1.09 (0.73, 1.63); 0.6768	
1245.110		
Number of patients analysed, N	2989	2996
Patients with LLA events, N (%)	15 (0.5)	11 (0.4)
Incidence rate[1] (95% CI)	0.27 (0.15, 0.42)	0.20 (0.10, 0.33)
HR (95% CI); p value[2]	0.73 (0.34, 1.59); 0.4294	
1245.121		
Number of patients analysed, N	1863	1863
Patients with LLA events, N (%)	6 (0.3)	7 (0.4)
Incidence rate[1] (95% CI)	0.27 (0.10, 0.52)	0.31 (0.12, 0.58)
HR (95% CI); p value[2]	1.17 (0.39, 3.47); 0.7826	

Secondary outcomes

A summary of frequencies of vascular disorders, diabetic-foot-related events, infections potentially related to LLAs, wound/infections, nervous system disorders, and volume depletion events prior to an LLA, incidence rates, HRs (95%) CIs, and p values for these AEs are provided below (Table 2 and Table 3 for SAF-M1 and SAF-M2, respectively).

In subgroup analyses there were no patterns identified to suggest a substantial impact of empagliflozin on risk of the secondary outcomes in subgroups of patients compared with the overall population.

Table 2 Summary of secondary outcome analyses – AEs potentially related to LLAs (occurring before an LLA) – SAF-M1 - on treatment

AEs	Placebo	Empagliflozin
Number of patients analysed, N	7185	9546
Vascular AEs		
Patients with LLA events, N (%)	198 (2.8)	306 (3.2)
Incidence rate[1] (95% CI)	1.48 (1.28, 1.69)	1.57 (1.40, 1.75)
HR (95% CI); p value[2]	1.00 (0.83, 1.20); 0.9946	
Diabetic-foot-related AEs		
Patients with LLA events, N (%)	68 (0.9)	127 (1.3)
Incidence rate[1] (95% CI)	0.50 (0.39, 0.63)	0.64 (0.53, 0.76)
HR (95% CI); p value[2]	1.15 (0.85, 1.55); 0.3612	
Infections potentially related to LLAs		
Patients with LLA events, N (%)	290 (4.0)	396 (4.1)
Incidence rate[1] (95% CI)	2.19 (1.94, 2.44)	2.04 (1.85, 2.25)
HR (95% CI); p value[2]	0.89 (0.77, 1.04); 0.1526	
Wound infections		
Patients with LLA events, N (%)	115 (1.6)	168 (1.8)
Incidence rate[1] (95% CI)	0.86 (0.71, 1.02)	0.86 (0.73, 0.99)
HR (95% CI); p value[2]	0.89 (0.70, 1.13); 0.3396	
Nervous system disorders		
Patients with LLA events, N (%)	205 (2.9)	349 (3.7)
Incidence rate[1] (95% CI)	1.54 (1.34, 1.76)	1.81 (1.62, 2.00)
HR (95% CI); p value[2]	1.00 (0.84, 1.19); 0.9992	
Volume depletion		
Patients with LLA events, N (%)	90 (1.3)	129 (1.4)
Incidence rate[1] (95% CI)	0.67 (0.54, 0.81)	0.65 (0.54, 0.77)
HR (95% CI); p value[2]	1.21 (0.92, 1.58); 0.1765	

Table 3 Summary of secondary outcome analyses – AEs potentially related to LLAs (occurring before an LLA) – SAF-M2 - on treatment

AEs	Placebo	Empagliflozin
Number of patients analysed, N	4852	4859
Vascular AEs		
Patients with LLA events, N (%)	99 (2.0)	95 (2.0)
Incidence rate[1] (95% CI)	1.27 (1.03, 1.54)	1.21 (0.98, 1.47)
HR (95% CI); p value[2]	0.95 (0.72, 1.27); 0.7474	
Diabetic-foot-related AEs		
Patients with LLA events, N (%)	25 (0.5)	36 (0.7)
Incidence rate[1] (95% CI)	0.32 (0.21, 0.46)	0.46 (0.32, 0.62)
HR (95% CI); p value[2]	1.44 (0.86, 2.40); 0.1610	
Infections potentially related to LLAs		
Patients with LLA events, N (%)	143 (2.9)	139 (2.9)
Incidence rate[1] (95% CI)	1.85 (1.56, 2.17)	1.78 (1.50, 2.09)
HR (95% CI); p value[2]	0.96 (0.76, 1.21); 0.7430	
Wound infections		
Patients with LLA events, N (%)	51 (1.1)	36 (0.7)
Incidence rate[1] (95% CI)	0.65 (0.49, 0.84)	0.46 (0.32, 0.62)
HR (95% CI); p value[2]	0.70 (0.46, 1.08); 0.1050	
Nervous system disorders		
Patients with LLA events, N (%)	66 (1.4)	72 (1.5)
Incidence rate[1] (95% CI)	0.85 (0.66, 1.07)	0.92 (0.72, 1.14)
HR (95% CI); p value[2]	1.09 (0.78, 1.52); 0.6274	
Volume depletion		
Patients with LLA events, N (%)	74 (1.5)	91 (1.9)
Incidence rate[1] (95% CI)	0.95 (0.75, 1.18)	1.16 (0.94, 1.41)
HR (95% CI); p value[2]	1.22 (0.90, 1.66); 0.1978	

Conclusion

In this evaluation of LLAs and adverse events related to amputation in patients treated with empagliflozin compared with placebo in a pooled population of 3 long-term, randomised, controlled trials including patients with T2DM and heart failure with reduced and preserved ejection fraction, the frequencies of LLAs were low and comparable in patients treated with empagliflozin and placebo. There was also no increased risk of adverse events potentially related to LLAs. Based on the results of this meta-analysis, there is no change in the benefit-risk profile for empagliflozin.